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THE EFFECT OF EXERCISE TRAINING ON THE AUTONOMIC FUNCTION, DISEASE ACTIVITY AND FUNCTIONAL CAPACITY IN FEMALES SUFFERING FROM RHEUMATOID ARTHRITIS

by

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MD

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DEDICATION

This dissertation is dedicated to all Rheumatoid Arthritis sufferers

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SYNOPSIS

Title	**The effect of exercise training on the autonomic function, disease activity and functional capacity in females suffering from rheumatoid arthritis**
Candidate	**Dr DC Janse van Rensburg**
Supervisor	**Prof JA Ker**
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Rheumatoid Arthritis (RA) is a chronic disease and one of the more common auto-immune diseases. It generally occurs more amongst females than males. Patients with RA rely almost solely on pharmaceutical intervention to manage the disease. This study firstly compared the autonomic function of RA females to that of healthy females, whereupon the emphasis shifted to the effect of exercise intervention on the following three aspects relating to the effects of RA:

- Autonomic function (as measured by heart rate variability)
- Disease activity (as measured by Disease Activity Score, Visual Analogue Scale and Health Activity Questionnaire)
- Functional capacity (as measured by strength, flexibility and aerobic capacity)

After a 3 month intervention period it was found that exposing Rheumatoid Arthritis patients to exercise had a meaningful effect on their autonomic function, disease activity and functional capacity.

Key words: autonomic nervous system dysfunction / impairment, rheumatoid arthritis, heart rate variability, exercise, disease activity, functional outcome

ABSTRACT

Introduction: Rheumatoid arthritis (RA) is a chronic disease and one of the more common auto-immune diseases. Patients with RA rely almost solely on pharmaceutical intervention to manage the disease. Autonomic impairment has been proven in previous studies on patients with RA. The positive effect of exercise on autonomic impairment has also previously been demonstrated, but not in the RA population. The purpose of this study was firstly to confirm autonomic impairment in a South African based female population with RA and secondly to evaluate the effect of exercise on the autonomic cardiac function (as measured by short-term heart rate variability), disease activity and functional capacity.

Methods: The study was conducted at the University of Pretoria during 2009 and 2010. In the first phase of the study female RA patients were recruited from all rheumatology practices in Pretoria and healthy controls were recruited from family and friends of the research team and of the RA group. Cardiac autonomic function was compared between the two groups by means of short-term heart rate variability. Three techniques were used: time domain, frequency domain and Poincare plot analysis.

In the second phase of the study, females with confirmed RA were randomly assigned to an exercise group and a control group. The exercise group was requested to train under supervision two to three times per week for a period of twelve weeks, while the control group continued with their sedentary lifestyle. At study completion the two groups were compared for the effect of exercise intervention on the following three aspects:

- Autonomic function (as measured by heart rate variability)
- Disease activity (as measured by Disease Activity Score, Visual Analogue Scale and Health Activity Questionnaire)

- Functional capacity (as measured by strength, flexibility and aerobic capacity)

Results: In the first phase of the study comparing females with RA (n=45) to healthy females (n=39), the basal heart rate was significantly higher in the RA group. In the supine position significant differences existed between the RA group and the control group ($p \leq 0.01$). Indicators of parasympathetic activity showed significantly lower variation in the RA group [RMSSD=14.70, pNN50=0.50, SD1=10.50, HF(ms^2)=31] compared to the control group [RMSSD=29.40, pNN50=7.8, SD1=20.9, HF(ms^2)=141.00]. Indicators of sympathetic variation were also significantly lower in the RA Group [SD2=36.70, LF(ms^2)=65) compared to the Control group (SD2=49.50, LF(ms^2)=175]. In the standing position 8 variables indicated autonomic impairment by significant differences ($p \leq 0.01$) between the 2 groups. The response of the RA Group to an orthostatic stressor showed less vagal withdrawal, [p-values for RMSSD=0.038, pNN50=0.022, SD1=0.043 and HF(ms^2)=0.008 respectively]; and lower sympathetic response [p-values for SD2=0.001 and LF(ms^2)<0.001] when compared to the Control group.

In the second phase of the study, comparing an RA exercise group to a RA sedentary group, three aspects were evaluated:

1. Heart rate variability

   At baseline the control group (n=18) had significantly higher variability compared to the exercise group (n=19) for most heart rate variability (HRV) indicators. At study completion the variables showing significant changes (p=0.01 to 0.05) favoured the exercise group in all instances. Wilcoxon signed rank tests were performed to assess changes within groups from start to end. The exercise group showed significant improvement for most of the standing variables, including measurements of combined autonomic influence e.g. SDRR (p=0.002) and variables indicating only vagal influence e.g. pNN50 (p=0.014). The control group mostly deteriorated with emphasis on variables measuring vagal influence [RMSSD, pNN50, SD1 and HF(ms^2)].

2. Disease activity

At baseline the two groups were comparable. At the end of the intervention, the exercise group had significant improvement for the tender joint count (p=0.015), swollen joint count (p=<0.001), physician global assessment (p=0.003) and DAS score (p=0.003) compared to the control group. To assess changes that happened within each group from start to end, Wilcoxon signed rank tests were performed. The exercise group improved significantly with regards to tender joint count (p=0.002), swollen joint count (p=0.001), physician global assessment (p=0.001), DAS score (0.001) and the visual analogue scale (p=0.032). The sedentary group improved significantly only in the health assessment questionnaire (p=0.032).

3. Functional capacity

Comparing the groups at baseline the exercise group had better knee- and hip flexion on the left hand side but it took them longer to complete the arm curl test. At study completion the exercise group was mostly favoured with regards to flexibility (significant p-values ranging between 0.001 – 0.049), strength (handgrip right p<0.001, leg strength p=0.035, arm curl test p=0.010, sit to stand test p=0.025) and aerobic fitness (1 mile walk test p<0.001 and VO_2 max p=0.007). Changes within each group were assessed by Wilcoxon signed rank tests. The exercise groups showed significant changes for many parameters in the three categories, i.e. flexibility (8 of 18), strength (5 of 5), and aerobic fitness (4 of 8). The control group mostly deteriorated in flexibility, while their strength also improved, but not to the same extent as for the exercise group. Their aerobic fitness did not change.

Discussion: In the first phase of this study, using standardised methods to measure short-term HRV, females with RA showed less variability compared to a healthy age- and sex matched control group. An inability of the autonomic nervous system to efficiently compensate to internal and external environmental changes may predispose RA patients to arrhythmias thereby increasing cardiovascular mortality.

All 3 methods used showed the same outcome, implying decreased HRV and thus an increased risk for arrhythmias in RA patients. Evaluating the autonomic nervous system might be critical in planning management of RA.

In the second phase study results indicated that twelve weeks of exercise intervention, had a positive effect on cardiac autonomic function as measured by short-term HRV, in females with RA. Several of the standing variables indicated improved vagal influence on the heart rate. Exercise can thus potentially be used as an instrument to improve cardiac health in a patient group known for increased cardiac morbidity.

The exercise programme was also effective in decreasing perception of pain as well as disease activity in female RA patients. Given our findings it seems warranted to include physical exercise as part of the treatment prescription of patients with class I and II RA.

Lastly this research has shown that regular, controlled exercise for RA patients with controlled disease can decrease joint stiffness and improve joint mobility, strength and aerobic capacity without exacerbating pain or disease activity. Also, if one observes the decline in the sedentary group for many parameters, it is important to note that this happened over a relative short time period and that even a small change may have a detrimental impact on the RA patient.

The current report supports previous literature on autonomic impairment in patients suffering from RA as well as the meaningful positive effect of exercise on disease activity and functional capacity. It is the only study on the effect of an exercise intervention on the cardiac autonomic function of RA patients.

Future research in this field should aim for larger study samples, longer intervention periods and perhaps add analysis of blood pressure variability to support results obtained by HRV analysis.

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Publications

1 Efficacy of an exercise program on the functional capacity and disease activity in females with Rheumatoid Arthritis.
South African Orthopaedic Journal Vol 9(2) 2010: 34-42

2 Land- and water-based exercises in Rheumatoid Arthritis.
South African Journal of Sports Medicine Vol 23(3) 2011: 84-88

3 Autonomic dysfunction in Rheumatoid Arthritis.
Article accepted for publication in International Journal of Rheumatic Diseases

4 Effect of exercise on cardiac autonomic function in female Rheumatoid Arthritis patients.
Article accepted for publication in Clinical Rheumatology

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5 Efficacy of an endurance exercise program on the functional capacity and disease activity in females suffering from Rheumatoid Arthritis: pilot study.
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11 Effect of exercise on cardiac autonomic function in female Rheumatoid Arthritis patients.
International e-Conference on Kinesiology and Integrated Physiology 2011(University of Houston)

CHAPTER ONE: INTRODUCTION

1.1 RHEUMATOID ARTHRITIS BACKGROUND

Rheumatoid arthritis (RA) is a chronic, systemic, inflammatory disease with articular- and extra-articular manifestations. Females are affected twice as common as males and approximately 1% of the world's population suffers from RA[1-3]. The joint disease is characterized by inflammation of the synovium in a symmetrical fashion. Any joint can be affected, large or small, but the small joints are mostly involved in early disease[3,4]. Ultimately, inflammation and pannus formation (pathological proliferation of the synovium) leads to tissue destruction, including: cartilage, bone, ligaments, tendons and blood vessels[5].

Rheumatoid arthritis leads to various physical impairments in those suffering from the disease. Inhibition of muscle contraction as a result of joint effusion, muscle atrophy secondary to decreased activity levels, loss of joint motion, and reduced aerobic capacity due to systemic disease account for the main reasons[6,7]. Extra-articular disease imparts a further burden on these patients with compromised health and almost any organ can be affected by RA[3].

1.2 MORBIDITY AND MORTALITY IN RA

Morbidity and mortality are increased due to joint and systemic involvement[8,9]. Cerebrovascular incidents and myocardial infarctions (as a result of accelerated cerebrovascular- and coronary artery atherosclerosis) top the list for increased mortality[8,10,11]. Meune et al, in their study on trends in cardiovascular mortality in patients with RA, concluded that reducing cardiovascular mortality should remain a major consideration in RA management[11]. Studies have shown the relationship between HRV, which is a way to measure cardiac autonomic function, and well-known cardiac risk factors[12-16]. HRV, for example, is lower in persons with hypertension and diabetes compared to healthy individuals. HRV can therefore be used to predict the development of hypertension and diabetes, as it was shown to be an independent risk factor[17-20].

1.3 AUTONOMIC DYSFUNCTION IN RA

Autonomic dysfunction has been suggested to exist in RA patients[21-44]. Abnormalities in autonomic nervous system (ANS) function in this group could bring about an increased disrhythmogenic potential contributing to increased cardiovascular morbidity/ mortality[44,45].

Quantification of the ANS functions as measured by HRV offer insight into the health of the autonomic cardiovascular control system[46,47]. In order to maintain internal homeostasis, the ANS adjust heart rate (HR) via the sympathetic and parasympathetic (vagal nerve) branches. Low variability in HR implies poor or inhibited ability to maintain internal homeostasis. Generally sympathetic system influence, increases HR (tachycardia response) and lowers variability of the HR, while parasympathetic input slows the HR (bradycardia response) and increases the variability. This finely tuned interaction between these systems leads to

minute changes in HR. It is then possible to quantify this effect on the HR via time domain-, frequency domain- and non-linear Poincare analysis[48-51].

1.4 EXERCISE AS INTERVENTION

Exercise intervention studies in patients with cardiac diseases showed positive changes in their cardiovascular functioning, such as increased HRV, parasympathetic activity and baroreflex sensitivity[52,53]. However, no studies have been done on the possible helpful effect of exercise on HRV, reflecting autonomic activity, in patients suffering from RA. Improving their vagal function by exercise may improve their risk profile.

Although there is no cure for RA, much can be done to manage the condition. Four major treatment approaches are recognized in the management of RA[54]:

1. Medication
2. Physical exercise
3. Joint protection and lifestyle changes
4. Surgical intervention

The use of exercise as part of the management of RA has been widely debated. The concept of total bed-rest was the standard of care since the late 1800's. Only in 1948 the undesirable effects of prolonged bed-rest were described, and exercise then resumed its role as part of RA treatment and rehabilitation[55].

According to the American College of Sports Medicine the primary objectives of exercise therapy in patients with RA are to:

1. Preserve or restore range of motion (ROM) and flexibility around affected joints
2. Increase muscle strength and endurance to build joint stability
3. Increase aerobic capacity in order to enhance psychological state and decrease the risk of cardiovascular disease[56].

Previous studies have reported a decrease in muscle strength, muscle endurance, aerobic capacity as well as postural control in RA patients compared to healthy subjects[57,58]. Reasons why RA patients tend to limit their physical activity include the perceived danger of eliciting pain or damaging their joints[58,59]. However, previous studies have reported improvement in functional parameters, pain levels, quality of life and disease activity scores in RA patients participating in training programs[60-67].

A comprehensive exercise program for RA patients is said to include aerobic exercises at a moderate intensity for 3-5 days a week, isometric and/or isotonic strength training exercises 3 days a week and stretching exercise once daily[68].

1.5 RELEVANCE OF THE STUDY: ROLE OF EXERCISE

The most prominent manifestation in patients with RA is joint disease, but extra-articular manifestations are very common[3,69]. Recently concern has been expressed on the observation that mortality is increased in RA patients[11]. Autonomic dysfunction has been described in patients with RA. Unfortunately, only a few studies have been done and different measurements of autonomic function that are difficult to compare have been utilized[21-44,70-72]. It is widely accepted that autonomic dysfunction leads to higher mortality, because the sympathetic-parasympathetic control of the heart is of vital importance for normal cardiac rhythm[48]. It therefore seems feasible that abnormalities in ANS function in this group could underlie an increased disrhythmogenic potential contributing to increased cardiovascular morbidity or mortality.

Exercise training has shown positive changes in cardiovascular functioning, such as increased parasympathetic- and decreased sympathetic activity[52,53,73]. However, no studies have been done to assess the effect of exercise on the autonomic dysfunction in RA.

Several studies have suggested that exercise may improve functional capacity (fitness parameters; quality of life) as well as disease activity, but a review by Hurkmans et al has reported limited to moderate evidence[74].

1.6 RESEARCH QUESTIONS

1) Is there a difference in cardiac autonomic function, as measured by short-term HRV, between female patients with RA and healthy female subjects?

2) Will exercise have an influence on the cardiac autonomic function, functional capacity and disease activity of females suffering from RA?

1.7 STUDY AIMS AND OBJECTIVES

This study has a number of aims and objectives.

1.7.1 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).

1.7.2 PHASE 2

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

1.7.2.1 Objective 1

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

1.7.2.2 Objective 2

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

1.7.2.3 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.

1.7.2.4 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 sit and reach test.

1.8 HYPOTHESES

1.8.1 PHASE 1

The Null Hypothesis has been stated that there is no difference in the cardiac autonomic function as measured by short-term HRV parameters between healthy subjects and female 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 female patients with RA.

1.8.2 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.

1.9 POSSIBLE LIMITATIONS OF THE STUDY

It will be difficult to get large numbers of participants for the study. Most of the participants will be recruited from my own private practice, but it is expected to have limited success in sourcing patients from other Rheumatology practices in the city of Pretoria.

It is expected that there will be logistical challenges to get the participants to train three times per week for a period of three months. Patients who are working will have to fit the practice session in after work, which will compromise on their family time. Patients who fall ill during this period will have to interrupt their programme for a while.

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CHAPTER TWO: LITERATURE REVIEW

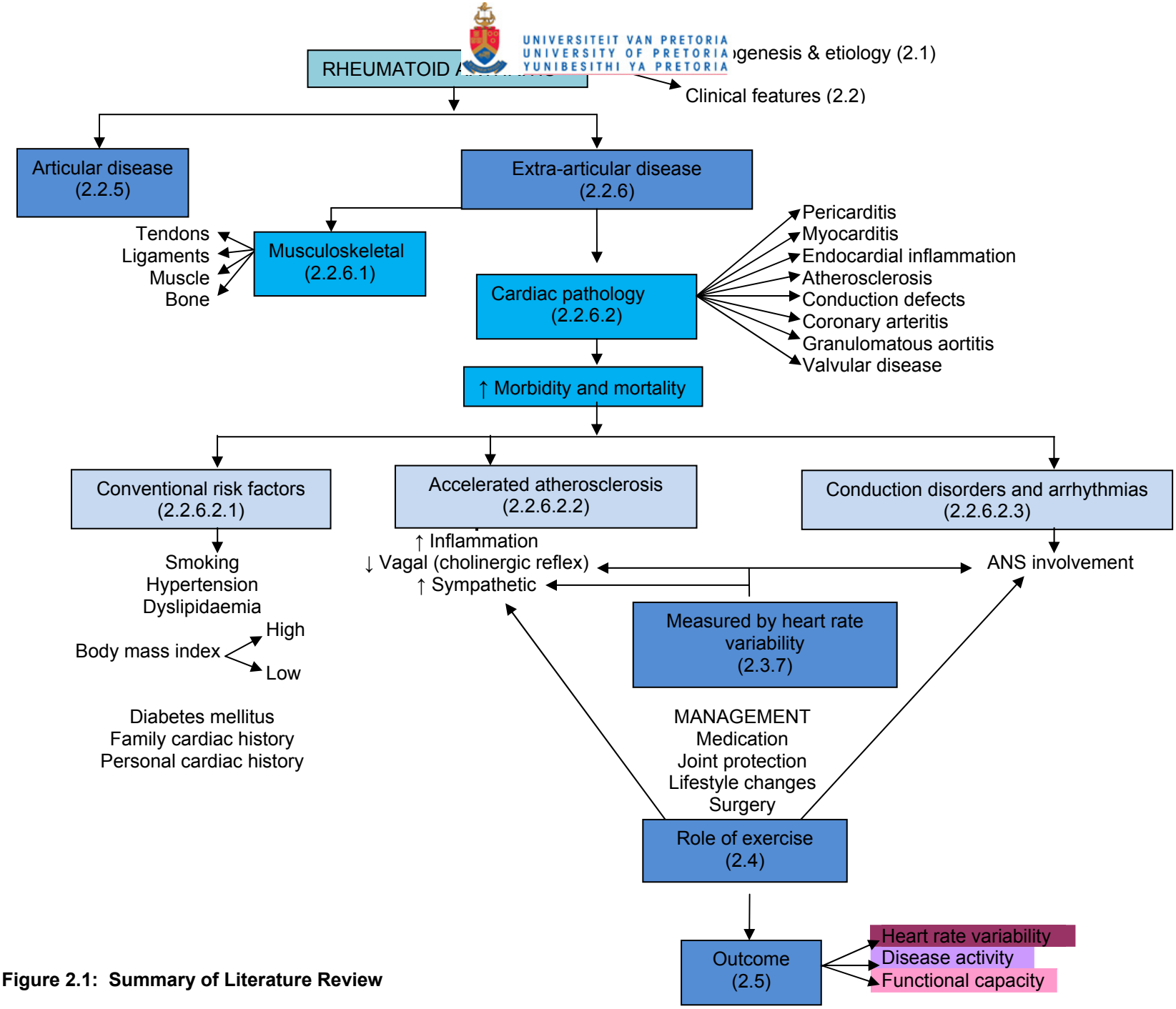

Figure 2.1: Summary of Literature Review

RHEUMATOID ARTHRITIS

Rheumatoid arthritis is a chronic, inflammatory disease of unknown cause affecting 0.5%-1% of the world population. It is the most common inflammatory arthritis. Although considered a disease of the joints, a variety of extra-articular manifestations are caused by abnormal immune responses. The etiology of RA is still unknown and why the synovium is the primary target remains a mystery. The synovial cells can act like a localized tumor; invading and destroying articular cartilage, subchondral bone, ligaments and tendons. Early intervention to reduce synovitis has an important impact on morbidity and mortality[1].

2.1 PATHOGENESIS AND ETIOLOGY

There are a number of factors that may play a role in the pathogenesis and etiology.

2.1.1 ROLE OF IMMUNITY

Both the adaptive and innate immune responses are part of the initiation, propagation and maintenance of the auto-immune process of RA.

The immune mechanisms are complex and numerous. All cell types, including dendritic cells, macrophages, fibroblasts, T-cells and B-cells are involved.

Cytokine pathways show abnormal production and regulation in RA, with macrophages and synovial fibroblasts being the main producers of pro-inflammatory cytokines e.g. tumor necrosis factor (TNF)-alpha and interleukin-1.

High serum levels of autoantibodies like rheumatoid factor (RF) and anti-citrullinated peptide antibodies (ACPA) are evident of the role of auto-immunity. It is suggested that synovial macrophages and fibroblasts may lose responsiveness to T-cells, thus becoming autonomous leading to pannus formation and ultimately destruction of cartilage and bone[1-3]. Figure 2.2 shows a schematic diagram of the immune mechanisms that likely play a role in RA.

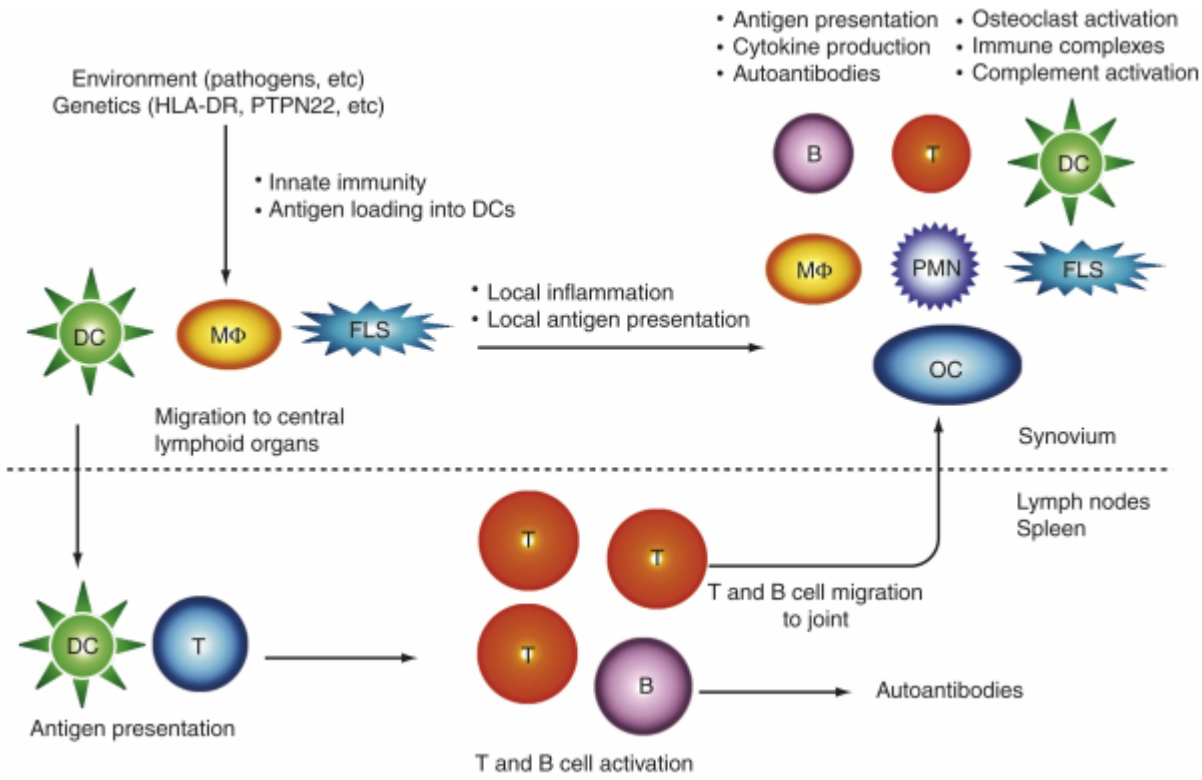

Figure 2.2: Immune mechanisms possibly playing a role in RA[1]

Schematic diagram of disease mechanisms that likely occur in rheumatoid arthritis. Innate immunity activates fibroblast-like synoviocytes (FLS), dendritic cells (DC), and macrophages (MΦ) in the earliest phases in individuals with underlying immune hyperreactivity as evidenced by the production of autoantibodies. The genetic makeup of an individual, including the presence of certain polymorphisms in genes that regulate immune responses, and environmental exposures are required. DC can migrate to the central lymphoid organs to present antigen and activate T cells, which can activate B cells. These lymphocytes can migrate back to the synovium and enhance adaptive immune responses in the target organ. In addition, repeated activation of innate immunity can lead directly to chronic inflammation and possibly antigen presentation in the synovium. In the latter phases of disease, many cell types activate osteoclasts (OC) through the receptor activator of nuclear factor κB (NFκB)/receptor activator of NFκB ligand (RANK/RANKL) system, although FLS and T cells likely provide the greatest stimulus. Autonomous activation of FLS also might contribute to this process.

2.1.2 GENDER (HORMONAL)

As with many other auto-immune diseases, RA has a predominance in women. The female to male ratio is 2:1 to 3:1. The specific mechanisms for this are not clear, but exposure to estradiol seems to make autoantibody producing B-cells more resistant to apoptosis. The effect on the T-cells are more difficult to explain, because estrogen tends to favour T-lymphocyte differentiation towards T-helper type 2 cells which produces anti-inflammatory cytokines[1]. Various methods have been utilized to explore the role of

estrogens[4]. RA has a reduced incidence in women on contraceptives and it appears to be less active during pregnancy with recurrence in the post-partum period

2.1.3 TOBACCO

The best defined environmental risk factor for RA is smoking. In susceptible individuals this can possibly provide a stimulus for generation of anti-cyclic citrullinated peptide antibodies (anti-CCP)[5].The enzymatic conversion of protein-contained arginase residues to citrulline is the process of citrullination. The enzyme responsible for citrullination is peptidyl arginie deaminase (PADI). Citrullination of relevant self-proteins may induce autoantibody production. Also, it has been reported that environmental factors (e.g. smoking) may cause enhanced cell apoptosis and that citrullination occurs in dying cells. Therefore smoking may result in high cittrulline levels in broncho-alveolar lavage fluids[6]. Citrullinated peptides have been found in broncho-alveolar lavage samples of smokers.

2.1.4 INFECTION

The first clear description of RA in Europe appears to be that of Landré-Beauvais (1772-1840). He believed that it was a variant of gout. No convincing evidence of RA could be detected in ancient skeletal remains from Europe, in contrast to those of Native Americans. A current line of thought suggests that an undefined environmental exposure (possibly an infectious agent) could cause RA in susceptible Europeans as genetic admixture at that time was relatively limited[1,7]. Table 2.1 gives a summary of the possible infectious agents that may play a role in the pathogenesis.

Table 2.1: Possible infectious causes of rheumatoid arthritis[1]

Infectious Agent	Potential Pathogenic Mechanisms
Mycoplasma	Direct synovial infection; superantigens
Parvovirus B19	Direct synovial infection
Retroviruses	Direct synovial infection
Enteric bacteria	Molecular mimicry (QKRAA)
Mycobacterium	Molecular mimicry (proteoglycans, QKRAA), immunostimulatory DNA
Epstein-Barr virus	Molecular mimicry (QKRAA)
Bacterial cell walls	Macrophage activation

2.1.5 GENETICS

A shared epitope of the HLA-DR_4 cluster (HLA-DR beta *0401, 0404, or 0405) is carried by approximately 60% of patients with RA in the United States. HLA-DR_1 (HLA-DR beta *0101) also carries this shared epitope[3]. Polymorphisms on many other non-HLA genes e.g. the ones associated with PADI are currently under investigation[1].

2.2. CLINICAL FEATURES

2.2.1 PREVALENCE AND INCIDENCE

RA is the most prevalent chronic inflammatory arthritis affecting 0.5-1% of the world population. All races are affected, although some, like the Chinese to a lesser extent (0.3%) and others like the Pima Indians (5%), more so. A prevalence of 0.9% has been reported in an urban black South African (SA) population. However, some rural areas in SA reported hardly any cases[8,9]. Females are affected more commonly with estimated incidences based on European and North American studies being 24-60 / 100 000 for females and 15-26 / 100 000 for males[10]. RA can occur at any age, but the incidence increases with age[11,12].

2.2.2 PATTERNS OF ONSET

2.2.2.1 Insidious onset

In 55-65% of cases the onset is slow over weeks to months. Initial symptoms can either be systemic or articular. Morning stiffness (lasting at least 30-45 minutes) can be the first symptom and is an important sign of inflammatory arthritis.

2.2.2.2 Acute onset

8-15% of patients have an acute onset of disease. Symptoms peak within a few days. Fever can be a prominent sign and vasculitis or sepsis must be ruled out.

2.2.2.3 Intermediate onset

Symptoms develop over days to weeks in 15-20% of cases. Systemic complaints are more on the foreground than in insidious type of onset[13].

2.2.2.4 Unusual patterns (variants) of disease[14]

2.2.2.4.1 Palindromic

Symptoms include pain, swelling and erythema of joints or peri-articular tissues that worsen over hours to a few days. In reverse sequence, symptoms resolve without leaving residual effects. 50% of patients will continue to develop RA.

2.2.2.4.2 Rheumatoid Nodulosis

A variant disorder with subcutaneous nodules, recurrent pain and swelling in different joints, and subchondral bone cysts on imaging.

2.2.2.4.3 Arthritis Robustus

More common in men, with proliferative synovitis and deformity, but with little pain and even less disability.

2.2.2.4.4 RA and Paralysis

In patients with strokes, cerebral palsy, poliomyelitis etc, joints are spared on the paralysed side.

2.2.3 CLASSIFICATION

In 1987 classification criteria were developed by the American College of Rheumatology (ACR) to distinguish non-RA from established RA[15]. Table 2.2 gives a summary of the 1987 revised criteria.

Table 2.2: The 1987 revised criteria for the classification of rheumatoid arthritis (traditional format)*

Criterion	Definition
1. Morning stiffness	Morning stiffness in and around the joints, lasting at least 1 hour before maximal improvement.
2. Arthritis of 3 or more joint areas	At least 3 joint areas simultaneously have had soft tissue swelling or fluid (not bony overgrowth alone) observed by a physician. The 14 possible areas are right or left PIP, MCP, wrist, elbow, knee, ankle, and MTP joints.
3. Arthritis of hand joints	At least 1 area swollen (as defined above) in a wrist, MCP, or PIP joint
4. Symmetric arthritis	Simultaneous involvement of the same joint areas (as defined in 2) on both sides of the body (bilateral involvement of PIPs, MCPs, or MTPs is acceptable without absolute symmetry).
5. Rheumatoid nodules	Subcutaneous nodules, over bony prominences, or extensor surfaces, or in juxta-articular regions, observed by a physician.
6. Serum rheumatoid factor	Demonstration of abnormal amounts of serum rheumatoid factor by any method for which the result has been positive in <5% of normal control subjects
7. Radiographic changes	Radiographic changes typical of RA on postero-anterior hand and wrist radiographs, which must include erosions or unequivocal bony decalcification localised in or most marked adjacent to the involved joints (osteoarthritis changes alone do not qualify)

*For classification purposes, a patient shall be said to have RA if he/she has satisfied at least 4 of these 7 criteria. Criteria 1 through 4 must have been present for at least 6 weeks. Patients with 2 clinical diagnoses are not excluded. Designation as classic, definite, or probable RA is *not* to be made.

PIP Proximal interphalangeal joint
MCP Metacarpophalangeal joint
MTP Metatarsophalangeal joint

Reprinted from Arthritis Rheum. 1988 Mar;31(3):315-324. Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Copyright notice 2011. With permission from John Wiley and Sons

If at least 4 of the 7 criteria are present for at least 6 weeks it is 77-95% sensitive and 85-98% specific for RA. It is however important not to exclude the diagnosis on this alone as it is not a diagnostic tool for early disease[11]. More recently the 2010 ACR-EULAR classification criteria for RA was published[16].

2.2.4 CONSTITUTIONAL SYMPTOMS

Patients often present with constitutional symptoms including malaise, weight loss, loss of appetite, fever, fatigue and myalgia[11].

2.2.5 JOINT INVOLVEMENT

Joint involvement is the characteristic feature of RA. Well-documented descriptions of specific joint involvement were mostly reported in the decades before 1980. Stress put on individual joints by the patient as well as the intensity of the disease and its chronicity determines the effect of synovitis on joints[14].

The disease usually affects the joints in a symmetrical pattern, but an asymmetrical pattern does not exclude the diagnosis. Small joints of the hands and feet are most commonly affected with larger joints becoming involved at a later stage[11,17]. Table 2.3 gives an overview on the joint distribution in acute flare-ups.

Table 2.3: Distribution of joints involved in attacks based on a cumulative experience with 227 patients[14]

Joint Involvement	% Patients (Mean)	% Patients (Range)
MCP, PIP	91	74-100
Wrists	78	54-82
Knees	64	41-94
Shoulders	65	33-75
Ankles	50	10-67
Feet	43	15-73
Elbows	38	13-60
Hips	17	0-40
Temporomandibular	8	0-28
Spine	4	0-11
Sternoclavicular	2	0-6
Para-articular sites	27	20-29

MCP Metacarpophalangeal
PIP Proximal interphalangeal

Affected joints show inflammation with warmth, swelling, tenderness and decreased range of motion (ROM). RA results in characteristic deformities if inflammation is not controlled, including:

- boutonniere and swan-neck deformities
- ulnar deviation
- hammer toes
- joint ankylosis

2.2.6 EXTRA-ARTICULAR MANIFESTATIONS

The severity and duration of the disease in general determines the number and severity of extra-articular features. These are associated with excess mortality[11,18]. A summary of these extra-articular features is found in Table 2.4.

Table 2.4: Extra-articular features of rheumatoid arthritis

Pulmonary	On post-mortem up to 75 %
Pleural effusions/pleurisy	Most common. Often asymptomatic, small effusions. Unilateral or bilateral. Usually exudates - mixed cell counts, high LDH, low glucose. Presence of multi-nucleated giant cells highly specific.
Nodules	Mainly seropositive patients with widespread synovitis and nodules. Usually asymptomatic. Peripheral or pleural in location.
Pulmonary Fibrosis	Up to 6% of patients develop systematic fibrosis within 10 years of RA onset. Men >women. Association with nodules. Usually bibasal. May be asymmetrical. Larger proportion may be asymptomatic. Contribution of methotrexate therapy debated.
Obstructive airways disease	Associated with inflammation, constrictive bronchiolitis, crico-arytenoid joint involvement. Up to 50% bronchiectasis on CT scan.
Bronchiolitis oblite-rans organizing pneumonia (BOOP)	Associated with fever and constitutional symptoms.
Shrinking lung syndrome, pulmonary arteritis and primary pulmonary hypertension are very rare.	
	On post-mortem up to 50%.
Cardiac	
Coronary artery disease	RA is an independent risk factor, particularly with persistently elevated ESR/CRP. Increased risk of cardiovascular death - myocardial infarction.
Pericarditis	Mainly seropositive patients with widespread nodules. Usually asymptomatic.
Valvular abnormalities, myocarditis and arteritis/aortitis are rare.	
Heamatological	
Anaemia	Correlates with disease activity. Abnormal iron utilization. Inhibition of erythropoiesis.
Thrombocytosis	Correlates with disease activity
Leucopenia	Felty's syndrome - in association with splenomegaly. May also have thrombocytopenia. Variant may have neutropenia without splenomegaly. Increased risk infection and lymphoproliferative disease including malignancies.
Lymphadenopathy	Common with active disease, can be associated with splenomegaly.
Neurological	
Mononeuritis multiplex/sensory neuropathy	Associated with RA vasculitis (<1%)
Nerve impingement	Secondary to joint inflammation and destruction. Peripheral nerves and nerve roots.
Cervical cord compression	Secondary to atlanto-axial or sub-axial subluxation due to erosive/destructive disease of the spine. Less commonly seen with aggressive early treatment of active RA. Important to consider pre-procedures requiring sedation where the neck may be subjected to extension (e.g. intubation, endoscopy).
Vasculitis (<1%)	Typically affecting smaller vessels with skin manifestations; leucocytoclastic vasculitis, capillaritis, chronic skin ulcers, infarcts (nail-fold infarct in up to 5%, does not seem to be associated with poorer outcome). Vasculitis can affect larger vessels and is more common with Felty's syndrome. Joint disease may not be active. Contributes to renal, neurological, cardiac and gastrointestinal complications. Associated with high RF levels and cryoglobulins.
Liver	Elevated liver function tests are not uncommon and parallel disease activity. Can be difficult to distinguish from drug effects (NSAIDs or DMARDs). Generally is due to drug treatment liver function should improve with discontinuation of the drug. Hepatomegaly can occur with Felty's syndrome. Rarely nodular regenerative hyperplasia can occur.
Renal	Renal abnormalities more commonly secondary to drug effects (NSAIDs, some DMARDs). Rarely low-grade membranous nephropathy, glomerulitis or vasculitis can occur with RA. Nephrotic syndrome is seen with secondary amyloidosis - less common now with adequate inflammation control.
Ocular	Keratoconjunctivitis sicca is most common, associated with xerostomia from secondary Sjögren's syndrome in up to 10% of patients. Episcleritis can occur with active RA. Scleritis indicates associated vasculitis and if persistent can result in scleromalacia, though seen less commonly with adequate inflammation control. Glaucoma and cataracts can occur as a result of drug therapy corticosteroids.

CT, computed tomography; DMARDs, disease-modifying antirheumatic drugs; LDH, lactate dehydrogenase; NSAIDs, non-steroidal anti-inflammatory drugs; RA, rheumatoid arthritis; RF, rheumatoid factor

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2.2.6.1 Muskuloskeletal involvement

RA causes various physical impairments in those suffering from the disease, including:

- inhibition of muscle contraction secondary to joint effusion
- muscle atrophy due to decreased activity levels, leading to a further decline in muscle strength and contributing to limitations in function, fatigue and deformities
- loss of joint motion
- reduced aerobic capacity as a result of systemic disease and decreased activity levels[19].

Most patients have muscle weakness, but only a few have muscle tenderness with elevated muscle enzymes[14]. Recent studies have described at least 5 different types of muscle involvement in RA:

1. Chronic myopathy (probably the end stage of inflammatory myositis)
2. Active myositis and muscle necrosis
3. Peripheral neuromyopathy
4. Atrophy of Type II fibers with diminution of muscle bulk
5. Steroid myopathy.

Other commonly described musculoskeletal manifestations include tenosynovitis and associated tendon rupture as well as carpal tunnel syndrome[3].

A further problem is bone loss due to systemic disease and/or glucocorticosteroid treatment, increasing the risk for stress fractures, fractures and generalized osteoporosis[20].

2.2.6.2 Cardiac involvement

RA can affect the cardiac system in many ways and many of these features are only found at post-mortem[11]. All structures can be involved, e.g. the pericardium (pericarditis), myocardium (myocarditis) and the endocardium (endocardial inflammation, valvular disease). Some other recognized cardiovascular (CV) diseases include:

- Atherosclerosis

- Conduction defects
- Coronary arteritis
- Aortitis[14].

Alamanos et al in their research made the statement that people with RA die prematurely[21]. Meune et al reported a 60% increase in risk of CV death in RA patients compared to the general population[22], while Aviña-Zubieta et al, after doing an observational meta-analysis reported that the increased mortality risk in RA patients are largely due to the higher rate of CV death[23].

There is thus a growing body of evidence recognizing the excess cardiovascular risk in patients suffering from RA[24-27]. Figure 2.3 illustrates the complex interactions between RA characteristics, CV risk factors and other determinants in developing CV disease.

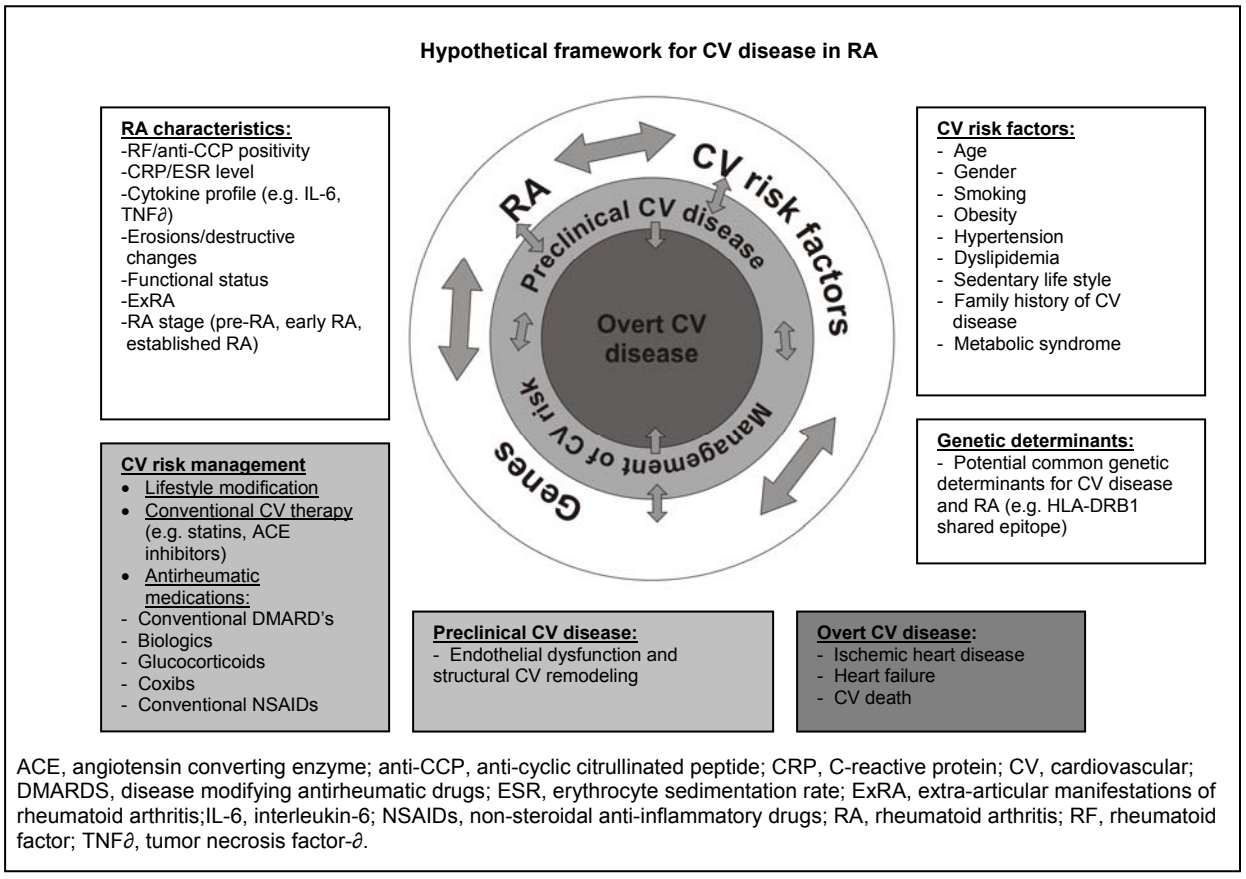

Figure 2.3: The complex interactions between RA characteristics, cardiovascular risk factors, genetic determinants and therapies on the development of preclinical and overt cardiovascular disease in RA[28].

Myasedova E, Gabriel SE, Cardiovascular disease in rheumatoid arthritis: a step forward. Current Opinion in Rheumatology 2010, 22:342-347

Some of the hypotheses that have been generated to explain an increased risk of CV events are:

- Conventional risk factors
- Accelerated atherosclerosis and chronic inflammation
- Conduction disorders and arrhythmias

2.2.6.2.1 Conventional Cardiovascular Risk Factors

Gabriel in a recently published study evaluated the prevalence of traditional risk factors between RA and non-RA subjects. The prevalence did not appear to differ significantly at disease onset. Over the follow-up period when comparing RA and non-RA subjects for hypertension, high body mass index (BMI) or diabetes mellitus, there was also no significant difference. However, low BMI was significantly more common and hyperlipidaemia significantly less common comparing RA with non-RA subjects over time[27]. In Table 2.5 the prevalence of traditional risk factors are compared between RA (at disease onset) and non-RA patients:

Table 2.5: Prevalence of traditional cardiovascular risk factors at RA incidence in RA and non-RA patients[27]

Cardiovascular risk factor	RA Patients N%	Non-RA Patients N%	P Value
Cigarette smoking			<0.001
Never	285 (47)	341 (57)	
Former	148 (25)	118 (19)	
Current	170 (28)	144 (24)	
Hypertension	312 (52)	298 (49)	0.42
Dyslipidaemia	163 (49)	169 (52)	0.45
High BMI (>30 kg/m2)	71 (13)	68 (13)	0.98
Low BMI (<20 kg/m2)	73 (13)	63 (12)	0.50
Diabetes mellitus	44 (7)	41 (7)	0.74
Family cardiac history	287 (48)	284 (47)	0.86
Personal cardiac history	77 (13)	72 (12)	0.66

BMI, body mass index; RA, rheumatoid arthritis

The authors next examined the impact of conventional risk factors on cardiovascular outcome, which was defined as a combined endpoint including heart failure, myocardial infarction and cardiovascular (CV) death. Interestingly, a threefold increased risk of CV

death was associated with a low BMI among RA patients. Lipids appeared to have a paradoxical effect, while the relative impact of the other risk factors (gender, smoking, personal- or family cardiac history, hypertension and diabetes mellitus) appeared to be significantly less in RA patients compared to non-RA patients (Figure 2.4).

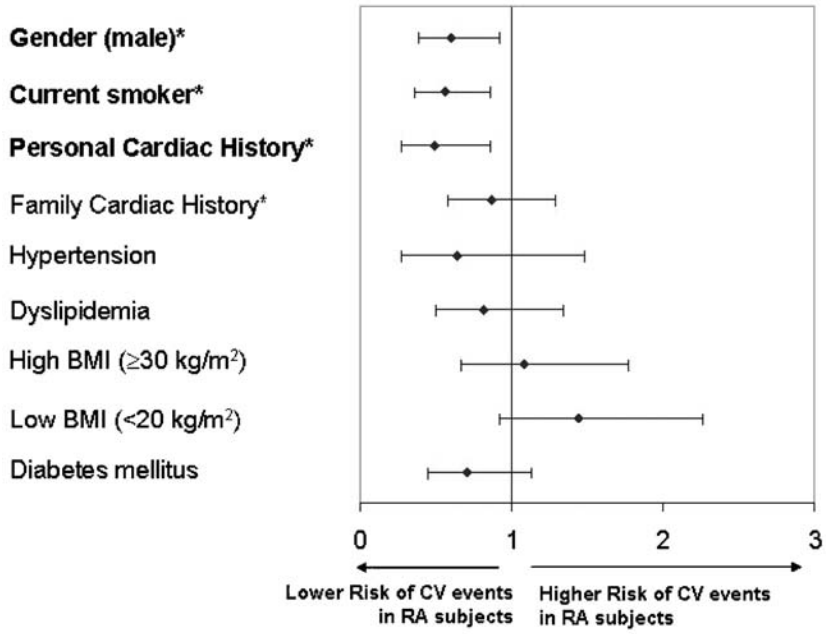

Figure 2.4: Relative impact of traditional CV risk factors on combined CV endpoint in RA and non-RA subjects[27]

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The above findings were noted by other authors like Kitas and Avina-Zubieta, as well as Maradit-Kremers et al who in their study concluded that "the risk of CV disease in RA precedes the American College of Rheumatology (ACR) criteria-based diagnosis of RA, and the risk cannot be explained by an increased incidence of traditional CV disease risk factors in RA patients", [23,29,30]. Myasoedova commented that RA not only represents an important modifier of conventional CV risk factors, but also has a role to play as an independent risk factor[28].

2.2.6.2.2 Accelerated atherosclerosis and chronic inflammation

There is compelling evidence that chronic inflammation has a pivotal role in the etiopathogenesis of atherosclerosis[31]. Several recent studies demonstrated the independent association of inflammatory indicators and RA towards an increased risk for CV disease[27,32-35]. RA activity and severity, high C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), rheumatoid factor (RF), ACPA and HLA DRB_1 gene are statistically significantly associated with increased risk of CV events[33,34,36-39].

The Autonomic Nervous System (ANS) is one of a variety of neuronal pathways that have been implicated in modulating inflammation[40]. The "cholinergic anti-inflammatory pathway" is a well studied mechanism where signals transmitted via the vagus nerve control the release of cytokines, reducing the production of pro-inflammatory cytokines by an α-7 nicotinic acetylcholine receptor (α7nAChR) dependent mechanism, and therefore ameliorating inflammatory disease[41-43].

Recent studies have shown improved survival in animal models of inflammation by stimulation of the vagus nerve via electrical or pharmacological methods[42,44-46]. Goldstein et al in a prospective observational study found that RA patients had an increase in high mobility group box-1 ($HMGB_1$) – a pro-inflammatory cytokine – and a decrease in cholinergic anti-inflammatory pathway activity as measured by heart rate variability (HRV). They postulated that it would be interesting to consider if subclinical CV disease is the result of increased inflammation secondary to decreased vagus nerve activity[47].

2.2.6.2.3 Conduction disorders and Arrhythmias

Conduction disturbances arise through impaired conduction or abnormalities of intrinsic automaticity[48]. As the heart is richly innervated by efferent and afferent sympathetic and vagal fibers, it is highly susceptible to autonomic influences[49]. Zipes et al had already in 1995 described the autonomic modulation of cardiac arrhythmias. Electrophysiological mechanisms underlying disrhythmogenesis are influenced by increased sympathetic and decreased vagal tone[50,51].

2.3 AUTONOMIC DYSFUNCTION IN RA

Autonomic dysfunction in patients with RA, has been studied. The literature was reviewed by searching different databases and consulting standard textbook references. The search was conducted to cover a period of 48 years (1963-2011). Databases included Ovid Medline, Pubmed, Scopus, Google Scholar. Textbooks consulted included Kelly Harris' Textbook of Rheumatology, Dieppe's Rheumatology, Mathias CJ Bannister's Autonomic failure: a textbook of clinical disorder of the autonomic nervous system (1999) and E Oribe's Testing autonomic function, from Handbook of clinical neurology, 1999, p595-647. Figure 2.5 shows the route that was followed for the literature review.

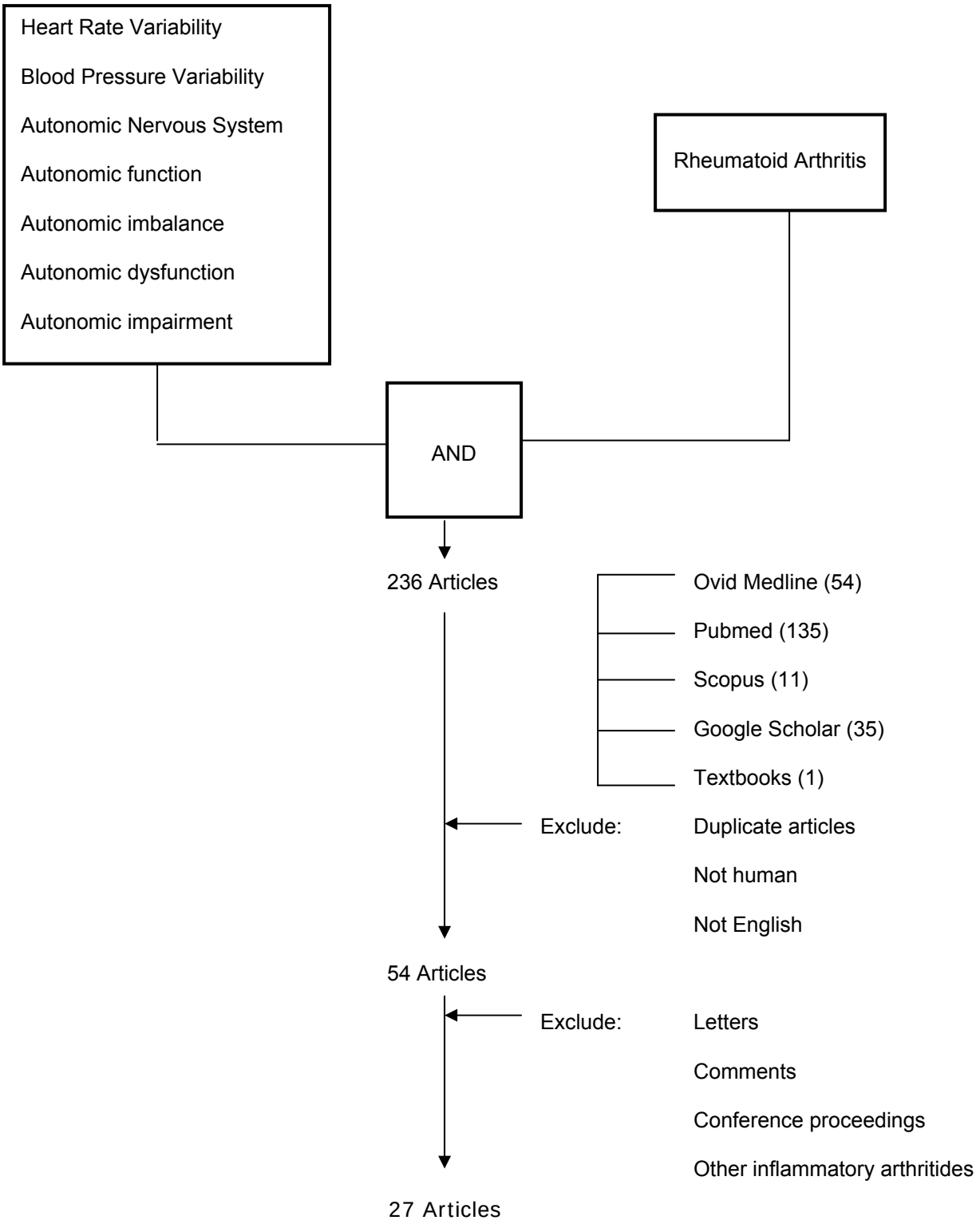

Figure 2.5: Database Search (1963-February 2011)

The 27 articles will now be discussed. The measurements utilized and background of each article is summarized in Table 2.7 which can be found at the end of the chapter.

2.3.1 SWEAT RESPONSES (SYMPATHETIC INVOLVEMENT)

In 1965 Bennett undertook a study to determine the presence, extent and location of autonomic nerve involvement in adult subjects with RA. He studied 18 RA patients with peripheral neuropathy, 8 patients with uncomplicated RA and 13 non-RA subjects. The thermo-regulatory sweating response to warm water immersion and the local sweating response to intradermal injection of acetyl choline and faradic stimulation were tested. In the Control Group (CG), areas of deficient sweating were small and symmetrical. In the uncomplicated RA group 6 of the 8 patients showed sweat responses similar to the CG, with 2 patients showing larger areas of sweat loss. In the RA group with peripheral neuropathy there was sweat loss in areas corresponding to those of cutaneous sensory impairment. It was concluded that clinical sensory neuropathy in RA is usually accompanied by an autonomic neuropathy of postganglionic type[52]. Kalliomaki et al performed axon reflex sweating tests in 100 RA patients and 100 non-RA patients with mental disorders. The number of patients reacting negatively to the test was significantly higher ($p<0.01$) in the RA group. These findings were only found in the female patients and the authors wrote that their observations suggested impaired axon reflex sweating (i.e. sympathetic involvement) in females suffering from RA[53].

2.3.2 CARDIOVASCULAR REFLEX TESTS (CRT)

Ewing described a test battery to evaluate cardiac autonomic function[54-56]. This battery tested the parasympathetic nerve function as follows:

i. Heart rate response to Valsalva manoeuvre
ii. Heart rate variation during deep breathing
iii. Immediate heart rate response to standing

and the sympathetic nerve function:

i. Blood pressure response to standing
ii. Blood pressure response to sustained handgrip.

These measurements were adopted by some authors to test for autonomic dysfunction in RA patients[57-59] while other used shorter or modified versions[60-68].

In 1979 Edmonds published his findings of autonomic neuropathy in RA. They investigated the cardiovascular reflexes, only using the tests described for parasympathetic nerve function. The conclusion was that significantly more patients with RA had abnormal autonomic function when compared to the control groups. They also felt that these abnormal cardiovascular reflexes could not be ascribed by other cardiac abnormalities found in RA patients (like pericarditis) and that autonomic neuropathy on its own might be a complicating factor leading to increased morbidity and mortality in RA[62]. Leden in 1983 assessed autonomic nerve function in RA of varying severity by means of deep breathing and an orthostatic test. Irrespective of disease severity all RA patients had increased resting heart rates. Only patients with severe RA showed significant abnormal responses to orthostatic stress, suggesting autonomic neuropathy[63].

Observing only parasymphatic nerve function, Piha could not show abnormalities in the cardiovascular reflexes of RA patients comparing 34 of them to 76 diabetes patients and 67 healthy controls. They suggested that the elevated resting heart rate in RA patients could be due to physical deconditioning and concluded that their data indicated that the parasympathetic pathway mediating cardiovascular reflexes via the vagus nerve is intact in RA[67]. Toussirot also only reported on parasympathetic involvement. A significant difference was found for Valsalva manoeuvre comparing RA patients to healthy subjects ($p<0.01$), but there was no correlation with inflammatory markers, presence of RF, disease duration or degree of joint destruction[68].

Bekkelund in 1996 compared RA subjects (n 43) to controls (n 61). They used 4 of the 5 tests described by Ewing, including:

i. Heart rate response to Valsalva manoeuvre
ii. Heart rate variation during deep breathing
iii. Immediate heart rate response to standing
iv. Blood pressure response to standing.

Cardiovascular reflexes were equal in the 2 groups, contradicting some of the other reports. They suggested that the high variability in the assessments of ANS between studies may be due to non-standardised test procedures as well as the choice of the statistical test used[60]. Maule et al in their study using CRT wanted to assess autonomic nervous function in a group of patients with Systemic Lupus Erythmathosus (SLE), RA and a matched healthy population. At the same time they assessed for the presence of circulating autoantibodies directed against sympathetic and parasympathetic nervous structures. Similar to Toussirot, they did not find any correlation between autonomic dysfunction and disease duration. They did however confirm autonomic nervous function impairment in connective tissue disease and this was significantly associated with the presence of autoantibodies to autonomic nervous structures[65]. Like Maule, Louthrenoo included SLE, RA and healthy controls, and they correlated ANS function as measured by CRT, to clinical features. 47% of the RA patients had symptoms suggesting ANS dysfunction. They confirmed Maule and Toussirot's findings that there was no correlation between ANS dysfunction and disease duration, or raised ESR[64].

Sandhu used 5 tests as described by Ewing to investigate autonomic cardiovascular reflexes in RA patients with reference to age, presence of RF and disease duration. The RA group comprised of 62 and the healthy CG of 41 subjects. Compared to the CG the RA group had significantly lower values for the following:

i. Heart rate response to Valsalva manoeuvre
ii. Heart rate variation during deep breathing
iii. Immediate heart rate response to standing
iv. Blood pressure response to sustained handgrip.

When age was taken into account the group <60 years of age showed significant differences for the same measurements as for the whole group compared to the CG. The group >60 years of age showed a significant difference only for the blood pressure response to sustained handgrip. Contrary to previous authors' findings, Sandhu reported a positive correlation for ANS impairment and presence of RF as well as disease duration[57]. A further study was performed by Stojanovich, who evaluated cardiovascular ANS function in patients with SLE, RA, Sjögren syndrome, scleroderma

and Polymyalgia Rheumatica (PMR). They correlated the ANS function to clinical features. They reported that in all tests higher percentages of the different patient groups demonstrated abnormal results compared to the controls ($p < 0.05$). No correlation was found between ANS dysfunction and disease duration, clinical manifestations or disease activity[58].

Bidikar investigated sympathetic nervous system involvement in RA. 50 RA patients were compared to 50 healthy controls. Compared to the controls the RA patients had a significant higher resting HR and blood pressure (BP). Significant differences were also shown for the sympathetic autonomic function tests between the two groups[61].

2.3.3 FOUR TASKS INDICATING AUTONOMIC FUNCTION

Geenen et al investigated the responsiveness of the ANS in RA of recent onset. The two groups (RA 21; CG 20) were subjected to 4 tasks presented in a fixed order: film watching and mild physical exercise to assess the parasympathetic system; and cognitive discrimination and the Stroop test for sympathetic activation. The patients showed normal responses to film watching and mild physical exercise, but diminished responses to cognitive discrimination and the Stroop test. According to them this implies normal parasympathetic activity but diminished sympathetic activity. They concluded that already in early disease there is evidence for diminished autonomic responsiveness, while baseline ANS levels may only deteriorate in the course of the disease. Their patients (recent onset disease) had normal resting heart rate, but they commented on the hypothesis of Piha that elevated heart rate levels might be due to physical deconditioning and that this may be a reversible phenomenon that can be rectified by exercise[69].

2.3.4 PRE-EJECTION PERIOD AND RESPIRATORY SINUS ARRHYTHMIA

In 2004 Dekkers published results on autonomic nervous system involvement in recent onset RA. Subjects with RA (n 25) were compared to healthy controls (n 28). The pre-ejection period (reflecting sympathetic nerve activity) and respiratory sinus arrhythmia (reflecting para-sympathetic nerve activity) were measured. The findings were in agreement with those of Geenen with abnormal sympathetic nervous system activity but normal parasympathetic nervous system activity in RA of recent onset. They did comment however that the environment was not standardized and this could have influenced the sympathetic nervous system activity[70].

2.3.5 SYMPATHETIC SKIN RESPONSE AND RR-INTERVAL VARIATION

In 1993 Tan decided to investigate autonomic function in RA patients with methods previously described by Shahani[71,72]. Sympathetic skin response (SSR) is an indicator of sympathetic nervous system function and RR-interval variation (RRIV) tests vagal function. Both tests were normal in the healthy CG (n=30). The RA group (n=30) had abnormal SSR's in 6 patients and abnormal RRIV's in 8 patients. Only 5 patients had complaints of clinical dysautonomia, leading to their conclusion that ANS dysfunction is frequent in RA patients even in the absence of clinical dysautonomia[73]. Gozke took this a step further and examined RA patients without clinical dysautonomia. Using the same methods as Tan et al they could not prove sympathetic involvement, but in 50% of RA cases the RRIV values were decreased [74].

2.3.6 PUPILLOGRAPHY

By using an infrared light reflection method, one can measure both parasympathetic function (constriction latency and latency of maximum constriction velocity) and sympathetic function (dilatation latency). Barendregt used this method to study autonomic dysfunction in 18 RA patients with ocular dryness, 18 RA patients without ocular dryness and 33 healthy controls. Constriction latency and maximum constriction velocity latency were prolonged in RA patients with ocular dryness compared to the other two groups ($p < 0.05$). Dilation latency did not differ between the three groups, neither was any correlation found between pupillography and age, disease duration or DAS score[75]. Schwemmer et al used a combination of pupillography and cardiovascular reflex tests to assess the prevalence and the characteristics of autonomic dysfunction in RA. This was followed by a longitudinal study to investigate if disturbed autonomic function is linked to higher mortality. Autonomic dysfunction was demonstrated in 60% of patients, with the prevalence for pupillary autonomic dysfunction (PAD) 15 out of 30 (50%) and for cardiac autonomic dysfunction (CAD) 6 out of 30 (20%). During the longitudinal study (8 years observation), 4 out of 30 patients died. The non-survivors did not differ at baseline with regards to age, gender, disease duration, swollen joint count, tender joint count, Visual Analogue Scale (VAS) for pain, Physician's Global Assessment, or medicine from survivors. Both CAD and PAD were

more frequent in non-survivors, perhaps indicating that autonomic dysfunction might be linked to higher mortality [76].

2.3.7 HRV

HRV has previously been shown to be a practical, reproducible and non-invasive method to detect early ANS impairment. Already in 1965 quantitative markers for autonomic homeostasis by HRV were recognized as a meaningful measurement. Since then it has been used to determine ANS dysfunction in fetal distress, diabetic autonomic neuropathy and RA[77].

Rhythmic contributions from sympathetic and parasympathetic activity modulate the heart rate and it modulates the RR-intervals between the QRS complexes on an electrocardiograph (ECG). Sympathetic activity shortens the RR-interval (tachycardia response) while parasympathetic activity lengthens the RR-interval (bradycardia response)[77]. Low variability implies poor or inhibited ability to maintain internal homeostasis. Commonly used methods to evaluate HRV are time domain analysis, frequency domain analysis and non-linear Poincare analysis. A detailed description of each of these measurements will follow in the chapter on Methodology.

Evrengul was one of the first authors applying this method to assess the autonomic function in patients with RA. They used time domain and frequency domain analysis in 42 RA patients and 44 healthy subjects. Recordings were obtained over an hour. Results conflicted between time and frequency domain parameters, but they defended this by pointing out that frequency domain analysis are more precise than time domain analysis by referring to work done by Fei in1996 and Howorka in 1998[78,79]. They concluded that their data suggested “an increase in sympathetic control of the heart rate in patients with RA”. No correlation between HRV parameters and stage of RA, disease duration or ESR was found[80]. Anichkov followed suit and investigated HRV parameters in RA patients, however recordings were obtained over 24 hours. Compared with controls, all time domain and Poincare parameters were significantly lower in RA patients. Contrary to most other studies already discussed they found a positive correlation between autonomic dysfunction and disease activity[81].

$HMGB_1$ is a pro-inflammatory cytokine and increased expression in synovium of RA patients has been shown. The cholinergic anti-inflammatory reflex (vagus nerve dependent) inhibits the release of $HMGB_1$ in experimental disease models[82]. Goldstein

et al did a study in RA patients where the results indicated that elevated levels of $HMGB_1$ correlated with depressed levels of vagus nerve activity as measured by time domain and frequency domain analysis[47]. The same group in another study on RA patients hypothesized that cytokine release can be suppressed by adding cholinergic agonists to whole blood cultures stimulated with endotoxin, even if vagus nerve activity is significantly reduced. Although their results showed reduced vagus nerve activity in the RA group compared to the healthy group, there was a significant age difference ($p<0.05$) with the RA group being older than the CG. This might have affected the result favouring the RA group, but previous authors[57,81] did not find age in RA patients to be a confounding factor. In the second phase of the study they proved their hypothesis to be correct[83].

Aydemir published a study on the cardiac autonomic profile of RA and SLE patients. They utilized both cardiac reflex tests and heart rate variability parameters. The groups consisted of 36 RA, 38 SLE and 40 Control subjects. The results showed that autonomic dysfunction is common in patients compared to controls, with RA patients having abnormal results in 61-75% of cases. There was a significant association between the different methods utilised. They found no relation between autonomic dysfunction and autoantibody positivity, disease duration or disease activity, supporting other authors' findings [58,59,64,65,68,75,80]. Another author that made use of a combination of methods to assess ANS dysfunction in RA and SLE patients, is Milovanovic. They aimed to evaluate the presence and level of ANS dysfunction as well as to identify cardiovascular risk factors associated with sudden cardiac death. In all measurements abnormal findings were significantly higher in the patient groups, but prolonged QT's interval was only significant in SLE patients. Although both diseases were associated with depressed HRV, in the RA group vagal predominance was evident while in the SLE group it was mostly higher sympathetic activity. They pointed out that there are still great discrepancies regarding published data on autonomic nervous system function in immunologic disorders with findings ranging from normal to grossly abnormal[66].

Vlcek in a small study (8 RA and 8 Control subjects) aimed to assess symphatoneural and adrenomedullary reactivity to changes in body position. Blood samples for epinephrine, norepinephrine (NE) and a sympathetic co-transmitter Neuropeptide Y

(NPY) were drawn during the course of HRV measurements. Levels for epinephrine were lower at baseline (p 0.053) and to orthostatic response (p 0.079), while NE levels were higher at baseline (p 0.034) but with no difference to orthostatic response comparing the RA group with the controls. No difference was shown for NPY or HRV parameters between the two groups. The authors concluded that their study "showed increased basal sympathetic activity and a tendency toward smaller adrenomedullary response to orthostasis in RA patients"[84].

Holman conducted a study to predict anti-tumor necrosis factor treatment response by assessing the autonomic status of RA and psoriatic arthritis patients. Although the results suggested that autonomic status may influence outcome there are a few problems identified in this study:

i. Can response to treatment be compared between different diseases (i.e. pathogenesis differ)?
ii. HRV was measured by an assessment tool (Omegawave) not previously validated in pathological conditions[85].

2.3.8 HEART RATE TURBULENCE (HRT)

According to Avsar HRT has been considered to reflect cardiac autonomic activity. HRT is measured in two phases, namely:

i. Turbulence onset (TO) is a measure of the initial acceleration after a premature ventricular complex due to vagal inhibition.
ii. Turbulence slope (TS) measures the rate of sinus deceleration that follows sinus acceleration with both parasympathetic and sympathetic contribution.

The response of the sinus node to premature ventricular complexes is reflected by HRT, while HRV describes variations in both RR-intervals and instantaneous heart rate. In this study of 26 RA patients and 26 healthy controls TO and TS did not show significant differences between the two study groups[86].

2.3.9 SUMMARY OF LITERATURE ON AUTONOMIC DYSFUNCTION IN RA

In the 27 studies reviewed there were a total of 1232 subjects (males and females) in the patient group and 918 (males and females) in the control group. The mean age for the patient group was 51.8 years and for the control group 44.25 years. Although all studies aimed to assess autonomic dysfunction in patients with RA, different methods were utilized, including:

- Sweat response[52,53]
- Cardiovascular Reflex Tests[57-68]
- Divergent autonomic reactions to specific tasks[69]
- Pre-ejection period and respiratory sinus arrhythmia[70]
- Sympathetic skin response and RR-interval variation[73,74]
- Pupillography[75,76]
- Heart Rate Variability[47,59,66,80,81,83-85]
- Heart Rate Turbulance[86]

Autonomic dysfunction was reported by most authors, with only Piha, Bekkelund and Avsar reporting no difference between patients and healthy controls, and Vlcek observing only a trend (not statistically significant) of increased basal sympathetic activity. Authors concomitantly assessing disease activity, disease duration and presence of RF mostly agreed that these do not correlate with ANS dysfunction[58,59,64,65,68,75,80]. Sandhu and Anichkov reported a positive correlation[57,81].

Unfortunately due to different measurements used, one cannot compare one study to the next. Other problems identified include:

- All studies did not comment on exclusion criteria (i.e. co-morbid diseases like diabetes[56,87] and hypertension[88,89] as well as medications used e.g. anti-arrhythmics and β-blockers will influence autonomic function). Stojanovic even included patients with HT and DM.
- Environment was not stabilized in all studies[70].
- Male and female subjects were used in the same study. Previous studies showed differences in HRV between males and females[90-92].

- Different statistical methods were used, even for the same measurement e.g. heart rate variability.
- Large age differences between patients and controls, with the patients being older could have skewed data in favour of the patient group[93,94].

Measures of autonomic function as prognostic factor for treatment response to biologic drugs was only reported on by Holman, and Anichkov commented that prednisolone use did not affect their results. No substantial evidence could be found in the reviewed articles on possible impairment of ANS function due to use of disease modifying drugs. Furthermore, exercise intervention studies have shown positive changes in increased cardiovascular functioning as measured by HRV[95-97]. No such data could be found for RA patients, and Metsios et al in their published review in 2008 concluded that "surprisingly little has been investigated and published on the role of exercise as a means to control risk and manage CV disease in individuals with RA"[98].

2.4 ROLE OF EXERCISE

RA patients are usually sedentary, with patients tending to limit physical activity due to the perceived danger of eliciting pain or damaging their joints[99,100]. Although there is still no cure for RA, much can be done to manage the condition. High-grade systemic inflammation and its vascular and metabolic effects have received much attention. Despite compelling evidence that exercise can play a significant role in the physical and psychosocial health of the general population there were no studies found investigating exercise interventions in relation to CV disease in RA[98].

Metsios mentions that exercise has been identified as one of the most important behavioural strategies for CV disease prevention and that sedentary individuals (like RA sufferers) will benefit by just a slight increase in physical activity[98,101,102]. Up to now the main focus of exercise therapy has been to improve physical capacity and functional ability[99].

Studies on exercise intervention in RA patients used resistance training[99,103-111], or aerobic training[112-125], or a combination of strength and aerobic training[126-134]. Unfortunately training regimes, methodology and outcomes differ widely, making conclusions difficult[135]. In a review done by Hurkmans et al, published in the Cochrane Library, they only included 8 studies because methodological criteria differed so much[135].

Strength training on its own seems to have a positive effect on functional ability[136-138] and muscular strength[139]. Cycling, followed by aquatics, aerobic dancing and walking/running are most frequently used as the mode of exercise in aerobic training for RA patients[98]. Although weight-bearing (and therefore possible joint damage) is minimized due to buoyancy[113], Hurkmans et al in their review found that water-based training only showed limited evidence for a positive effect on aerobic capacity and muscle strength contrary to land-based exercise which showed moderate evidence[135].

No Randomised Control Trials (RCT) based on walking as the main focus have been conducted[98], while studies focusing on aquatics suggest improvement of aerobic

capacity[119,140,141], muscle strength[106,120] and psychological status[119]. Studies on combination training showed positive influence on both cardiorespiratory fitness and muscle strength[126,142].

Previous studies in non-RA groups demonstrated that endurance exercise will improve HRV (i.e. cardiac health)[143-149] while strength training can have the opposite effect[150]. Similar studies have not been done in the RA population.

Buccheit et al have shown that, in middle-aged subjects, moderate endurance exercise is associated with greater vagal tone while high intensity exercise is not[151]. This fact will be used in our study population because due to sore joints and stiffness, patients will comply better with moderate rather than high intensity exercise. Patients with late stage rheumatic disease and many joint deformities will not comply with an intense exercise programme. Therefore the study population for this study will be limited to class 1 and 2 disease according to the Classification of Global Functional Status of RA[152]. This classification can be viewed in Table 2.6.

Table 2.6: **Classification of global functional status in rheumatoid arthritis**

Class I	Completely able to perform usual activities of daily living (self-care, vocational, and avocational)
Class II	Able to perform usual self-care and vocational activities, but limited in avocational activities
Class III	Able to perform usual self-care activities, but limited in vocational and avocational activities
Class IV	Limited in ability to perform usual self-care, vocational, and avocational activities
Usual self-care activities include dressing, feeding, bathing, grooming, and toileting. Acovational (recreational and/or leisure) and vocational (work, school, homemaking) activities are patient-desired and age- and sex-specific.	

Reprinted from Arthritis Rheum, 1992 May:35(5):498-502. Hochberg MC, Chang RW, Dwosh I, Lindsey S, Pincus T, Wolfe F. The American College of Rheumatology 1991 revised criteria for the classification of global functional status in rheumatoid arthritis. Copyright notice 2011. With permission from John Wiley and Sons

Iversen has shown that rehabilitation started early in disease is more effective[153], and Geenen et al have shown diminished ANS responsiveness in patients with early RA disease[69]. These facts further strengthen the motivation to recruit patients with early disease (class 1 and 2 patients).

Stenstrom and Minor investigated the evidence for the benefit of aerobic and strengthening exercise in RA. They drew recommendations for exercise intervention from this evidence based approach. For aerobic exercise they concluded that in the light of the reviewed studies, the intensity level should be moderate to hard (60-85% of heart rate maximum) performed 3 times weekly for a duration of 30-60 minutes. Exercise can be land- or water based and progressive adjustment of the intensity was recommended. For resistance training they concluded that the load level of strengthening exercises should be moderate to hard (50-80% of a maximal voluntary contraction) and performed 2-3 times per week. Exercises can be static or dynamic and performed with various types of equipment or against body weight. A progressive adjustment of load was recommended[100].

A further suggestion made by them was that it is important to start documenting exercise response in terms of the individual's characteristics, as response criteria have been published for drug trials but those are not specifically applicable to exercise studies[100].

2.5 ASSESSMENT OF DISEASE ACTIVITY

As rightly stated by Stenstrom there are no specific response criteria to measure outcome following exercise intervention in patients with RA[100]. The major target of therapeutic interventions is reduction of disease activity, but for the patient the most relevant outcome is functional capacity. Current measurements have been developed and validated for the purpose of facilitating clinical trial reporting, but Aletaha and Smolen mention that it is reasonable to use these same measurements for clinical practice[154].

International bodies introduced the term “core set” comprising of tender and swollen joint counts, global assessments by the patient and the assessor (mostly the physician), pain assessment by the patient, acute-phase response and a functional element[154].

For the purpose of this study, it was decided to make use of the following previously validated measurements, in order to address all elements of the core set:

- DAS_{28}[155-157].
- Visual analogue scale (VAS)[158-160].
- Health assessment questionnaire (HAQ)[161,162].

All of the above will be discussed in detail in the chapter on Methodology.

2.6 CONCLUSION

The literature review has shown:

- There are extra-articular manifestations associated with increased mortality in patients with RA
- Patients with RA have cardiac involvement, and the autonomic nervous system (ANS) may play a role
- ANS dysfunction has been proven in patients with RA, but different measurements were used and there are still uncertainties left

- Exercise can improve ANS dysfunction in the general population, in cardiac patients with hypertension and ischemic heart disease as well as in patients with diabetes mellitus
- No previous exercise studies have been done in an RA population to measure the effect, if any, on autonomic function.

Table 2.7: Studies on autonomic nervous system function in rheumatoid arthritis patients

Assessment	Author	Study Title	Disease duration (Mean)	n		Gender		Age (mean)		Co-Morbidity	Aim
				EG	CG	Female	Male	EG	CG		
Film watching (P) Mild physical exercise (P) Cognitive discrimination (S) Stroop interference test (S)	Geenen (1996)	Diminished autonomic nervous system responsiveness in rheumatoid arthritis of recent onset	<1yr	21	20	EG 17 CG 16	4 4	55.7 (±16.5)	52.7 (±11.8)	Excluded - not specified	Responsiveness of ANS in RA of recent onset
Pre-ejection period (S) Respiratory Sinus Arrythmia (P)	Dekkers (2004)	Elevated sympathetic nervous system activity in patients with recently diagnosed rheumatoid arthritis with active disease	<2 yr	25	28	EG 19 CG 20	6 8	55.2 (±13.0)	55.8 (±11.3)	Excluded - not specified	1. Assess ANS activity 2. Association with - disease activity - symptoms of RA
Sympathetic skin response (S) RR-Interval variation (P)	Gozke (2003)	Sympathetic skin response and R-R interval variation in cases with rheumatoid arthritis	Not mentioned	10	14	EG 10 CG 14	0	48.7 (±11.6)	44.6 (±10.6)	Clinical dysautonomia excluded	Assess ANS involvement

ANS	Autonomic nervous system	P	Parasympathetic
CG	Control Group	RA	Rheumatoid arthritis
EG	Experimental Group	S	Sympathetic

Assessment	Author	Study Title	Disease duration (Mean)	n		Gender		Age (mean)		Co-Morbidity	Aim
				EG	CG	Female	Male	EG	CG		
Sympathetic skin response (S) RR-Interval variation (P)	Tan (1993)	Sympathetic skin response and R-R interval variation in rheumatoid arthritis. Two simple tests for the assessment of autonomic function	90.2 months (7.5 yr)	30	30	EG 27 CG 26	3 4	51.3	50.4	Dysautonomia not excluded in EG. Neurological disease excluded inCG.	Assess ANS neuropathy in presence or absence of clinical dysautonomia
Pupillography CL (P) MCV (P) DL (S)	Barendregt (1966)	Parasympathetic dysfunction in rheumatoid arthritis patients with ocular dryness	EG1 22yr EG2 10 yr	EG1 18 (Dryness of eyes or mouth) EG2 18 (No dryness of eyes or mouth)	33	EG1 18 EG2 18 CG 33	0	EG1 62 EG2 55	57	Excluded: Neurological disease Amyloidosis, Renal failure DM Other diseases known to interfere with ANS Drugs interfering with ANS	Is abnormal ANS function associated with oral and ocular dryness?
Pupillography (P and S) Cardiovascular reflex tests (P)	Schwemmer (2006)	Cardiovascular and pupillary autonomic nervous dysfunction in patients with rheumatoid arthritis - a cross-sectional and longitudinal study	EG1 6.7 yr EG2 6.4 yr EG3 8.6 yr	EG1 30 (All patients) EG2 26 (Survivors) EG3 4 (non-survivors)	0	EG1 17 EG2 16 EG3 1	13 10 3	EG1 52.2 (±1.9) EG2 51.6 (±2.1) EG3 56.5 (±2.2)	Not used	Excluded: CVD, Peripheralneuropathy Other diseases or drugs	1. Assess ANS dysfunction in RA patients. 2. Interview 8.3 years lateron mortality.

ANS	Autonomic nervous system	DL	Dilation latency	P	Parasympathetic
CG	Control Group	DM	Diabetes mellitus	RA	Rheumatoid arthritis
CL	Constriction latency	EG	Experimental Group	S	Sympathetic
CVD	Cardiovascular disease	MCV	Maximum constriction velocity		

Assessment	Author	Study Title	Disease duration (Mean)	n		Gender		Age (mean)		Co-Morbidity	Aim
				EG	CG	Female	Male	EG	CG		
Sweat response (S)	Bennett (1965)	Autonomic neuropathy in rheumatoid arthritis	Not mentioned	EG1 18 (RA neuro-pathy) EG2 8 (No RA-neuropathy)	13	EG1 10 EG2 7 CG 5	8 1 8			Neuropathy included	Determine ANS involvement in RA
Sweat response (S)	Kalliomaki (1963)	Axon reflex sweating in rheumatoid arthritis	Not mentioned	100	100	EG 70 CG 44	30 56	47.9	51.1	CG No somatic disease Psychiatric hospital patients	1) ANS involvement 2) Correlation with clinical signs of RA
Cardiovascular reflex tests P - Valsalva Deep breathing Orthostatic S - Orthostatic Handgrip	Sandhu (2004)	The effects of age, seropositivity and disease duration on autonomic cardiovascular reflexes in patients with rheumatoid arthritis	Not mentioned	62	41	EG 39 CG 21	23 20	RA 63	50	Excluded: DM CVD Co-pathology likely to interfere with ANS Drugs likely to interfere with ANS	To investigate ANS in RA with reference to - age group - disease duration - disease activity - RF status
Cardiovascular reflex tests P - Valsalva Deep breathing Orthostatic	Piha (1993)	Elevated resting heart rate in rheumatoid arthritis: possible role of physical deconditioning	15 (±9)	RA 34 DM 76	69	RA 34 DM 76 CG 69	0	RA 49 DM 43	43	Excluded: ANS conditions CVD	Assess ANS function i RA by comparing then to DM andControls

ANS	Autonomic nervous system	EG	Experimental Group	S	Sympathetic
CG	Control Group	P	Parasympathetic		
CVD	Cardiovascular disease	RA	Rheumatoid arthritis		
DM	Diabetes mellitus	RF	Rheumatoid factor		

Assessment	Author	Study Title	Disease duration (Mean)	n		Gender		Age (mean)		Co-Morbidity	Aim
				EG	CG	Female	Male	EG	CG		
Cardiovascular reflex tests P - Valsalva Deep breathing Orthostatic S - Orthostatic	Maule (1997)	Autonomic nervous dysfunction in systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA): possible pathogenic role of autoantibodies to autonomic nervous structures	9.3 (± 7.9)	RA 17 SLE 17	25	RA 17 SLE 17 CG 25	0	37 (±13.5)	31.9 (±11.2)	Excluded: DM Obesity Renal failure Chronic liver disease Arrhythmia Anaemia Anti-hypertensive treatment	1) Assess ANS functi in RA and SLE 2) Assess presence of Compliment fixing antibodies
Cardiovascular reflex tests P - Orthostatic Valsalva Deep breathing	Edmonds (1979)	Autonomic neuropathy in rheumatoid arthritis	Not mentioned	RA 27 OA 13	Old 13 Young 15			RA 54.6 OA 54.2	Old 51 Young 24.6	Exclude: Drugs influencing cardiovascular rhythm HT Anaemia Cardiac failure	Assessing integrity of ANS
Cardiovascular reflex tests (Tilt table) P - Deep breathing Orthostatic S - Orthostatic	Leden (1983)	Autonomic nerve function in rheumatoid arthritis of varying severity	20	17	24	EG 12 CG 8	5 16	56	53	Exclude: CVD Pulmonary disease Renal Disease	1) Assess ANS 2) Correlate ANS function with severity RA

ANS	Autonomic nervous system	EG	Experimental Group	RA	Rheumatoid arthritis
CG	Control Group	HT	Hypertension	S	Sympathetic
CVD	Cardiovascular disease	OA	Osteo-arthritis	SLE	Systemic lupus erythemathosus
DM	Diabetes mellitus	P	Parasympathetic		

Assessment	Author	Study Title	Disease duration (Mean)	n		Gender		Age (mean)		Co-Morbidity	Aim
				EG	CG	Female	Male	EG	CG		
Cardiovascular reflex tests P - Deep breathing Valsalva Orthostatic S - Orthostatic	Bekkelund (1996)	Autonomic nervous system function in rheumatoid arthritis. A controlled study.	13.6 (± 7.4)	43	61	EG 43 CG 61	0	44.4 (±8)	42.1 (±9.3)	Excluded: Somatic disease Psychiatric disease CTD Primary neurological disease Alcoholism Drugs interfering with ANS	1) Assess ANS 2) Pancreatic polypeptide (PP) association with abnormal ANS and disease activity
Cardiovascular reflex tests P - Deep Breathing Valsalva Orthostatic	Toussirot (1993)	Autonomic nervous system involvement in rheumatoid arthritis	6	50	82	EG 31 CG 49	19 33	55.6	47.2	Excluded: Dysautonomia Drugs interfering with ANS Anaemia Renal Disease DM Porphyria Parkinsons Polyneuropathy MS HIV infection Breathing failure Sympatectomy	Frequency of ANS dysfunction
Cardiovascular reflex test S - Orthostatic Handgrip Cold Press	Bidikar (2010)	Autonomic (sympathetic) nervous system involvement in rheumatoid arthritis patients	Not mentioned	50	50	Not mentioned	Not mentioned	20-60	20-60	History of dysauto-nomia. Treatment interfering with ANS.	To examine the frequency of sympathetic dysfunc in RA patients

ANS	Autonomic nervous system	DM	Diabetes mellitus	MS	Multiple sclerosis
CG	Control Group	EG	Experimental Group	P	Parasympathetic
CTD	Cardiac thoracic disease	HIV	Human immunodeficiency virus	S	Sympathetic

Assessment	Author	Study Title	Disease duration (Mean)	n		Gender		Age (mean)		Co-Morbidity	Aim
				EG	CG	Female	Male	EG	CG		
Cardiovascularreflex tests P - Orthostatic Valsalva Deep Breathing Insp : Exp S - Orthostatic Handgrip HRV Frequency domain	Aydemir (2010)	Cardiac autonomic profile in rheumatoid arthritis and systemic lupus erythematosus	RA 11.2 (±10) SLE 6.9 (± 5)	RA 36 SLE 38	40	RA 30 SLE 32 CG 31	RA 6 SLE 6 CG 9	RA 48.7 (±12.5) SLE 38.4 (±11.3)	HCG 42.5 (±12.5)	Excluded: Pregnancy DM Uraemia Hepatic failure Porphyria Amyloidosis Alcoholism Ishchemic Heart Disease Cardiomyopathy Arrhythmia Cardiovascular incident Parkinson's Disease Multiple sclerosis Drugs interfering with blood pressure and heart rate Fibromyalgia Vasculitis Secondary Sjögrens	To define the frequenc and spectrum of ANS dysfunction in patients with RA
Cardiovascular reflex tests P - Deep breathing Orthostatic S - Orthostatic Handgrip	Louthrenoo (1999)	Cardiovascular autonomic nervous system dysfunction in patients with rheumatoid arthritis and systemic lupus erythematosus	5.1	RA 34 SLE 37	62	RA 30 SLE 34 CG 50	4 3 12	RA 47.2 (±10.5) SLE 30.4 (±8.1)	47 (±10.6) 30.3 (±7.9)	Excluded: Hb<10 Pregnancy DM Renal disease Liver disease Parkinsons Amyloidosis CVD Neurological disease Drugs interfering with ANS	1) To evaluate cardiovascular ANS function in RA and SL 2) To correlate ANS function with clinical features

ANS	Autonomic nervous system	HCG	Healthy Control Group	S	Sympathetic
CG	Control Group	HRV	Heart rate variability	SLE	Systemic lupus erythemathesus
CVD	Cardiovascular disease	P	Parasympathetic	SSc	Systemic sclerosis
DM	Diabetes mellitus	RA	Rheumatoid arthritis		

Assessment	Author	Study Title	Disease duration (Mean)	n		Gender		Age (mean)		Co-Morbidity	Aim
				EG	CG	Female	Male	EG	CG		
Cardiovascular reflex tests P - Deep Breathing Valsalva Orthostatic S - Orthostatic Handgrip	Stojanovich (2007)	Cardiovascular autonomic dysfunction in systemic lupus, rheumatoid arthritis, primary Sjogren syndrome and other autoimmune diseases	9.5 (± 5.2)	RA 39 SLE 54 Sjö 20 PMR 8 SSc 4	35	RA 33 SLE 49 Sjö 19 PMR 6 SSc 3 CG 19	6 5 1 2 1 16	RA 58.1 (±12.2) SLE 46.3 (±12.50) Sjö 52.2 (± 12.4) PMR 68 (± 9.9) SSc 60 (±4.5)	52.3	Excluded: Pregnancy Renal insufficiency Liver Insufficiency Cardiac insufficiency Respiratory insufficiency Arrhythmia Acute thrombosis	1) Evaluate ANS function in RA/SLE/PMR/SSc/Sjö 2) Correlate ANS function with clinical features
Cardiovascular reflex tests P - Deep Breathing Valsalva Orthostatic S - Orthostatic HRV - Time domain - Frequency domain - Poincare analysis	Milovanovic (2010)	Cardiac autonomic dysfunction in patients with systemic lupus, rheumatoid arthritis and sudden death risk	Not mentioned	SLE 52 RA 38	41	SLE 46 RA 32 CG 17	6 6 23	SLE 43.3 (±22.8) RA 56.3 (±13.1)	HCG 37.4 (±14.6)	Excluded: Pregnancy Renal insufficiency Liver Insufficiency Cardiac insufficiency Respiratory insufficiency Arrhythmia Acute thrombosis	To evaluate the presence and level of ANS dysfunction in patients with SLE and RA and to identify cardiovascular risk factors associated with sudden cardiac death
HRV - Frequency domain	Vlcek (2008)	Sympathetic nervous system response to orthostatic stress in female patients with rheumatoid arthritis	7.5 (± 0.9)	8	8	RA 8 CG 8	0	30.5 (±2)	30.5 (±1.4)	Not mentioned	To evaluate autonomic activity in RA patients, namely sympathoneur and adreno-medullary reactivity in changes to body position

ANS	Autonomic nervous system	P	Parasympathetic	Sjö	Sjögrens
CG	Control Group	PMR	Polymyalgia rheumatica	SLE	Systemic lupus erythemathosus
HCG	Healthy Control Group	RA	Rheumatoid arthritis	SSc	Systemic sclerosis
HRV	Heart rate variability	S	Sympathetic		

Assessment	Author	Study Title	Disease duration (Mean)	n		Gender		Age (mean)		Co-Morbidity	Aim
				EG	CG	Female	Male	EG	CG		
HRV - Frequency domain	Holman (2008)	Heart rate variability predicts anti-tumor necrosis factor therapy response for inflammatory arthritis	7.6 (± 6.4)	RA 25 PsA 8		26	7	48 (±13.9)		Not mentioned	To consider autonomic status as a predictor o anti-tumour necrosis factor treatment response for inflammatory arthritis
HRV (24hr) - Time domain - Poincare	Anichkov (2007)	Heart rate variability is related to disease activity and smoking in rheumatoid arthritis patients	4	23	23	EG 23 CG 23	0 0	48 (±7)	47 (±7)	Excluded: HT DM Angina Pectoris Previous MI Previous stroke Congestive heart failure Peripheral neuropathy Drugs for CVD	1) Assess ANS involvement 2) Relationship with disease related characteristics
HRV - Frequency domain - rMSSD	Goldstein (2007)	Cholinergic anti-inflammatory pathway activity and high mobility group box-1 (HMGB1) serum levels in patients with rheumatoid arthritis	13 yr	RA 13	HCG 11	RA 9 HCG 6	4 5	52	38	Smoking	To consider whether decreased activity in th cholinergic anti-inflammatory pathway occur in patients with
HRV - Frequency domain - Time domain	Bruchfeld (2010)	Whole blood cytokine attenuation by cholinergic agonists ex vivo and relationship to vagus nerve activity in rheumatoid arthritis	13.2 yr	RA 13	HCG 10	RA 9 HCG 5	4 5	52	32	Not mentioned	Hypothesize that the addition of cholinergic agonists to whole bloo cultures stimulated wit endotoxin can attenua cytokine release, even RA patients with significantly reduced vagus nerve activity

ANS	Autonomic nervous system	DM	Diabetes mellitus	HRV	Heart rate variability	RA	Rheumatoid arthritis
CG	Control Group	EG	Experimental Group	HT	Hypertension	rMSSD	Root of the average squares of differences between neighbouring NN intervals
CVD	Cardiovascular disease	HCG	Healthy Control Group	PsA	Psoriatic arthritis		

Assessment	Author	Study Title	Disease duration (Mean)	n		Gender		Age (mean)		Co-Morbidity	Aim
				EG	CG	Female	Male	EG	CG		
HRV (1hr) - Time domain - Frequency domain	Evrengul (2004)	Heart rate variability in patients with rheumatoid arthritis	6.5	42	44	EG 31 CG 31	11 13	48 (±10.4)	45 (±8.4)	Excluded: ANS dysfunction Previous MI HT DM Pulmonary disease Drugs interfering with ANS	Assess ANS involvement
HRT	Avsar (2010)	Cardiac autonomic function in patients with rheumatoid arthritis: heart rate turbulence analysis	Not mentioned	RA 26	HCG 26	Not mentioned		56 (±10)	55 (±9)	Excluded: Angina Pectoris MI Heart failure HT DM Valvular heart disease Non-sinus rhythm Hyper thyroidism Left ventricular hypertophy Electrolyte disturbances Chronic renal failure Hepatic failure Smokers Cardio-active drug use	To determine if HRT changes in patients with RA in comparison with healthy controls
			TOTALS:	1232	918			51.79	44.28		

ANS	Autonomic nervous system	HCG	Healthy Control Group	HT	Hypertension
CG	Control Group	HRT	Heart rate turbulence	MI	Myocardial infarction
DM	Diabetes mellitus	HRV	Heart rate variability	RA	Rheumatoid arthritis
EG	Experimental Group				

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CHAPTER THREE: METHODOLOGY

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[1]

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[2].			
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[3,4]			
Strength	Exercises	Intensity	Repetitions (Sets)
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

Week 6-9	Chest press Bicep curls Lat pull downs Seated row Hip extension Leg presses Hamstring curls Hip abduction Calf raises	70-80% 1 RM	2 sets of 10 repetitions
Week 10-12	Chest press Bicep curls Lat pull downs Seated row Hip extension Leg presses Hamstring curls Hip abduction Calf raises	70-80% 1 RM	2 sets of 15 repetitions

1RM 1 Repetition maximum

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 gastro-intestinal 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

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


Figure 3.1: Anthropometer


Figure 3.2: Scale

Figure 3.3: Polar heart rate monitor

Figure 3.4: Sphygmomanometer

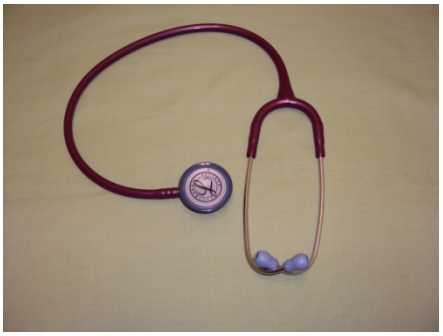

Figure 3.5: Stethoscope

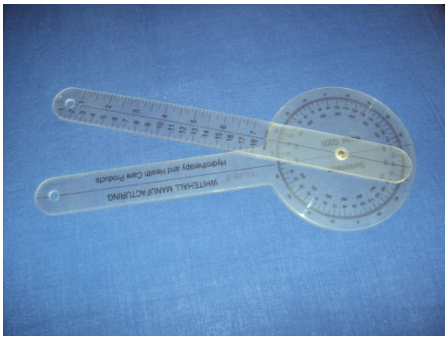

Figure 3.6: Goniometer

Figure 3.7: Tape measure

Figure 3.8: Ruler

Figure 3.9: Dynamometer

Figure 3.10: Leg dynamometer

Figure 3.11: Dumbbells

3.7 MEASUREMENTS

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

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

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].

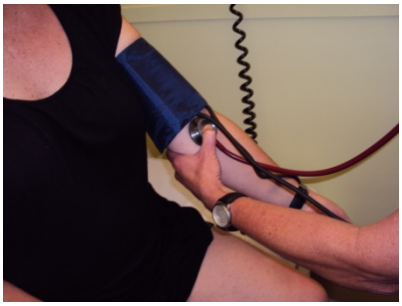

Figure 3.14: Measurement of blood pressure

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.

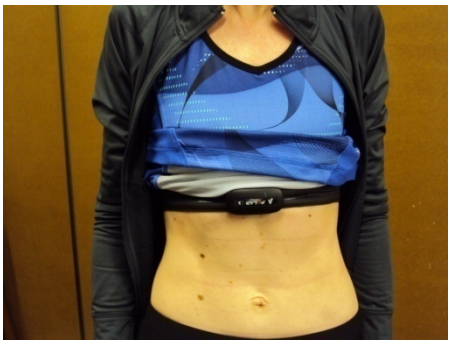

Fig 3.15: The Polar strap in position around the chest

Figure 3.16: Participants in the supine position

Figure 3.17: Participants in the standing (stress) position

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.

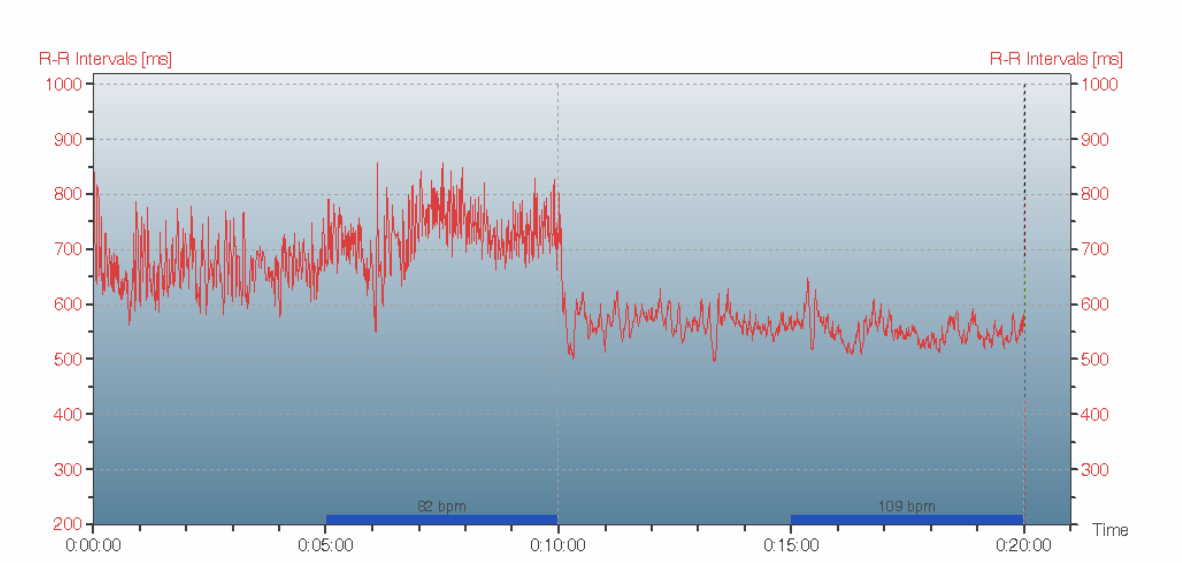

Fig 3.18: Example of a tachogram

Table 3.3: HRV techniques, HRV indicators and origins of variability

Time domain analysis	**RR(s)**	The mean of the intervals between successive QRS complexes, result of vagal and sympathetic influence on HRV.
	RRSD(s)	Standard deviation of intervals between successive QRS complexes, indicator of vagal and sympathetic influence on HRV (Overall HRV).
	RMSSD(ms)	Root mean square of the standard deviation between RR-intervals, indicator of vagal influence.
	pNN50(%)	The percentage of successive RR-interval differences larger than 50ms computed over the entire recording, indicator of vagal influence on HRV.
Poincarè plot analysis	**SD1(ms)**	Indicator of the standard deviation of the immediate RR variability due to parasympathetic efferent (vagal) influence on the sino-atrial node.
	SD2(ms)	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.
Frequency domain analysis	**LF(ms^2)**	Indicator of sympathetic influence, but also including a parasympathetic component.
	HF(ms^2)	Indicator of only parasympathetic influence.
	LF/HF	Indicator of autonomic balance.
	LF(nu)	LF (normalised units) represent the relative power of the LF component in proportion to the total power minus the VLF component, i.e. LF/(total power-VLF).
	HF(nu)	The HF (normalised units) represent the relative power of the HF component in proportion to the total power minus the VLF component, i.e. HF/(total power-VLF)

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.

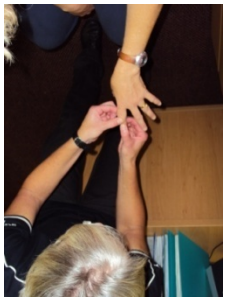

Figure 3.19 Examining of tender joints: hands

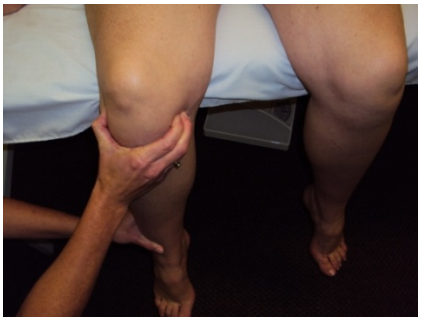

Figure 3.20: Examining of tender joints: knees

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.

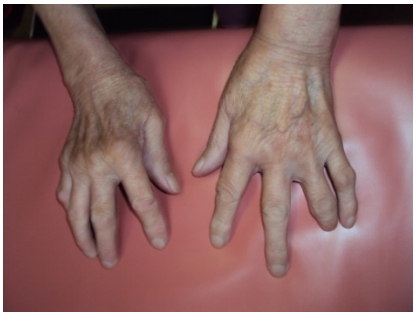

Figure 3.21: Swollen joints of the hands

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).

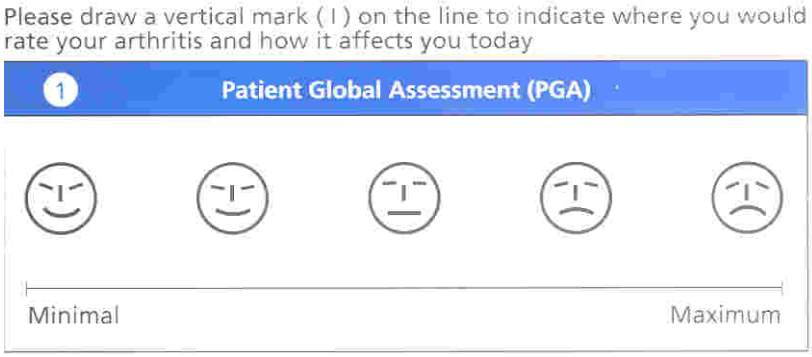

Figure 3.22: Scale for measuring Patient Global Assessment

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).

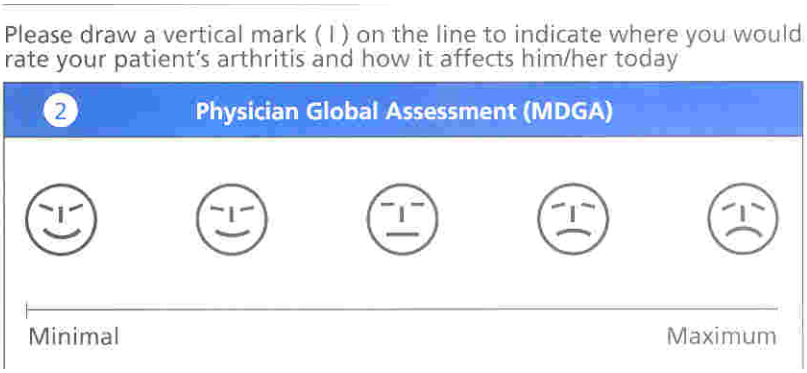

Figure 3.23: Scale for measuring Physician Global Assessment

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) (*Appendix 5*)[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[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).

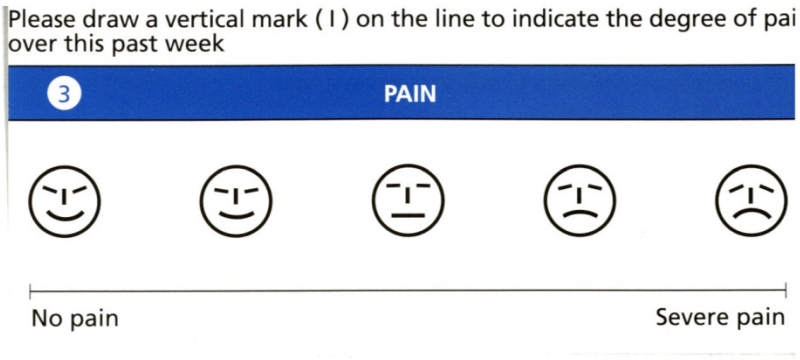

Figure 3.24: Scale for measuring pain

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[26]:

3.7.9.1.1 **Wrist flexion** (Figures 3.25-3.26)

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

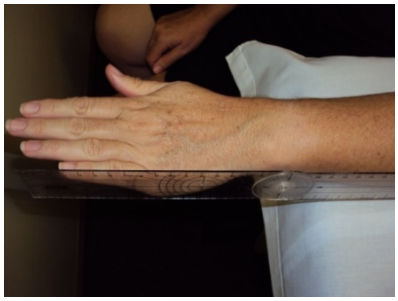

Figure 3.25 Wrist flexion: starting position

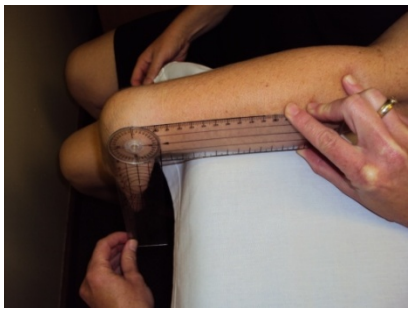

Figure 3.26: Wrist flexion: end position

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

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

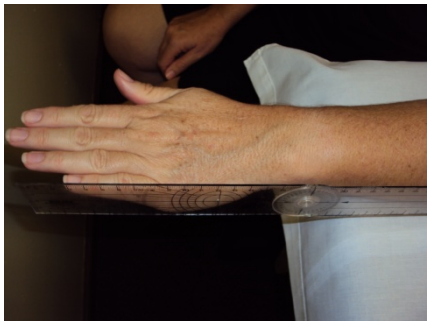

Figure 3.27: Wrist extension: starting position

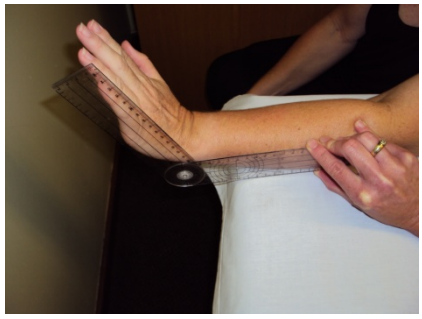

Figure 3.28: Wrist extension: end position

3.7.9.1.3 **Knee flexion** (Figures 3.29-3.30)

Body position	Axis of rotation	Stationary leg	Moving leg	Starting position	End position
Prone	Lateral epicondyle of the femur	Lateral midline of the femur	Lateral midline of the fibula and the lateral maleolus	Patient in prone position. Knee in extension	Knee flexed towards the back to the limit of motion[26]

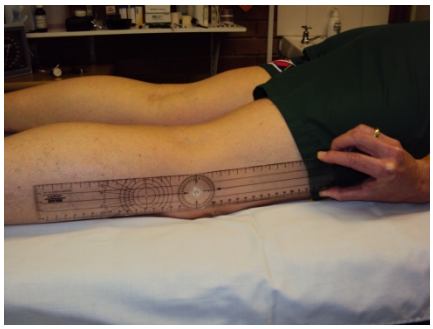

Figure 3.29: Knee flexion starting position: patient in prone position

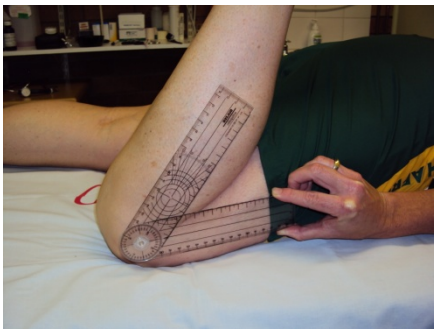

Figure 3.30: Knee flexion in end position

3.7.9.1.4 **Knee extension** (Figures 3.31-3.32)

Body position	Axis of rotation	Stationary leg	Moving leg	Starting position	End position
Supine	Lateral epicondyle of the femur	Lateral midline of the femur	Lateral midline of the fibula and the lateral maleolus	Patient supine with knee straight	Knee extended to limit of motion[26]

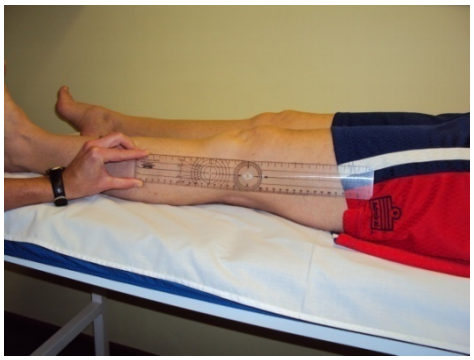

Figure 3.31: Knee extension starting position

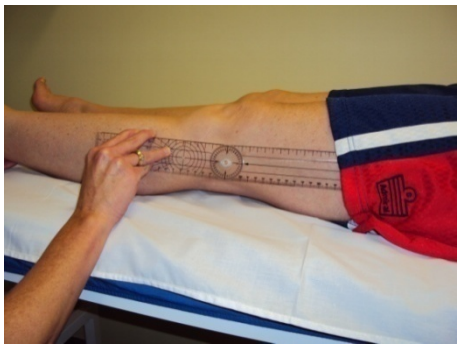

Figure 3.32: Knee extension in end position

3.7.9.1.5 **Hip flexion** (Figures 3.33-3.34)

Body position	Axis of rotation	Stationary leg	Moving leg	Starting position	End position
Supine	Greater trochanter	Lateral midline of the pelvis	Lateral midline of the femur	Patient in the supine position with hip in straight line	Hip flexed toward abdomen to limit of motion[26]

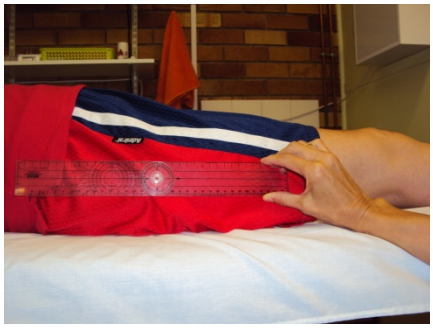

Figure 3.33: Hip flexion starting position

Figure 3.34: Hip in flexed position

3.7.9.1.6 **Hip extension** (Figures 3.35-3.36)

Body position	Axis of rotation	Stationary leg	Moving leg	Starting position	End position
Prone	Greater trochanter	Lateral midline of the pelvis	Lateral midline of the femur	Patient in prone position with hip in straight line	Hip extended upwards to limit of motion[26]

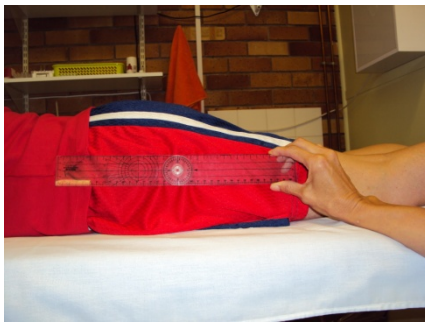

Figure 3.35: Hip extension starting position: patient in prone position

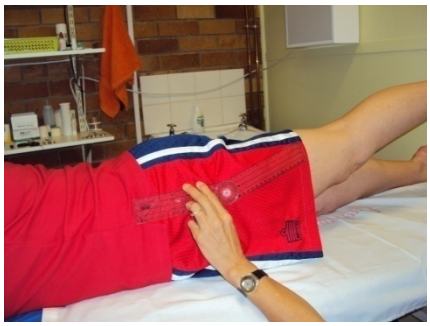

Figure 3.36: Hip in extended position

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].

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Figure 3.37: Lateral flexion

Figure 3.38: The distance of the hand from the floor is measured

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].

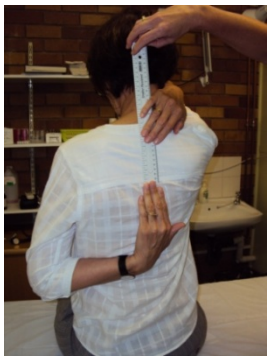

Figure 3.39: Back scratch test

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^{o}. 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)].

Figure 3.40: Chair sit and reach test

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

Figure 3.42: The dynamometer is squeezed as hard as possible

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].

Figure 3.44: Arm curl test

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].

Figure 3.45: Sit to stand test

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].

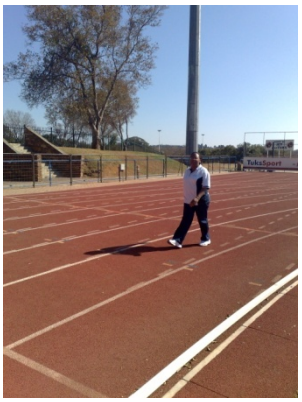

Figure 3.46: Walking the 1 mile

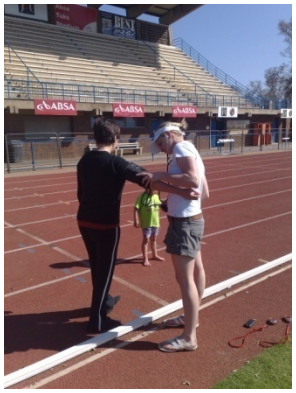

Figure 3.47: Patient's blood pressure was taken after completion of 1 mile walk

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(ms^2) (supine), HF(ms^2) (supine), HF(nu) (supine), LF/HF (supine), HR (stress), HRSD (stress), RMSSD (stress), pNN50 (stress), SD1 (stress), SD2 (stress), LF(ms^2) (stress), HF(ms^2) (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*

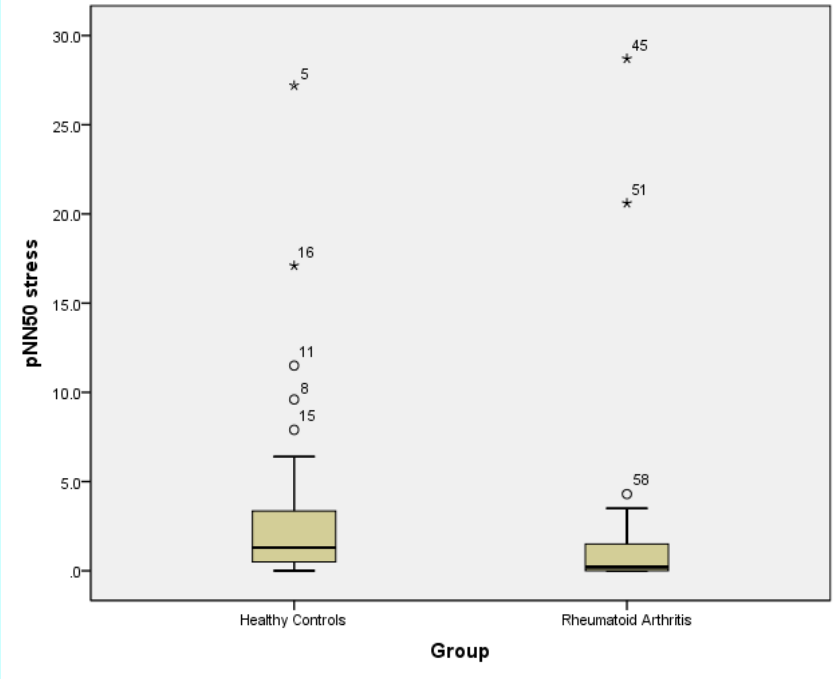

Figure 3.48: Clustered box plot of pNN50 (stress) demonstrating positive skewness

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[30]. 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.

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CHAPTER FOUR: RESULTS

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(ms^2), HF(ms^2), 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, VO_2 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 DAS_{28} 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 ** p<0.01
IQR Interquartile range

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 ln-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 ln-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

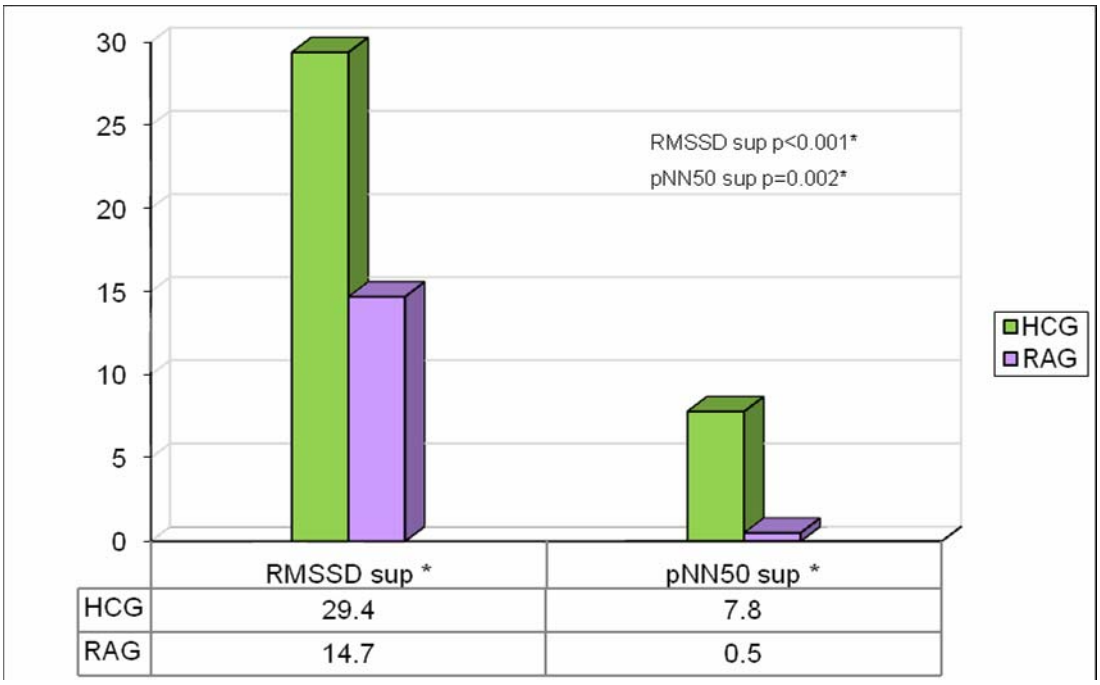
In Table 4.2 the mean, standard deviation of the mean, and median of the HRV indicator values in the supine position, for the HCG and the RAG, are reported. The level of significance of differences found between the HCG and RAG is also displayed. All indicators, except HRSD, showed significant differences ($p \leq 0.01$) 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**

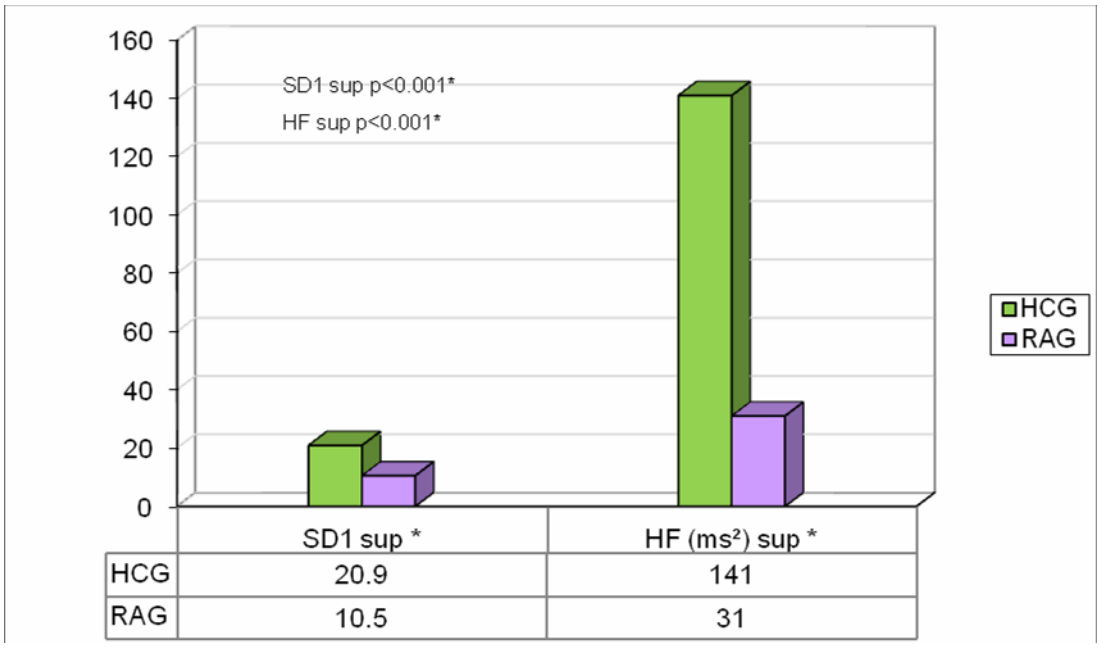
IQR Interquartile range; S seconds; bpm beats per minute; ms milliseconds; % percentage; ms^2 milliseconds, squared; nu normalised units; ** p≤0.01

In the supine position all variables assessing parasympathetic variability were significantly lower for the RAG [RMSSD, pNN50, SD1, HF(ms^2)] (Figures 4.1 and 4.2).



	RMSSD sup *	pNN50 sup *
HCG	29.4	7.8
RAG	14.7	0.5

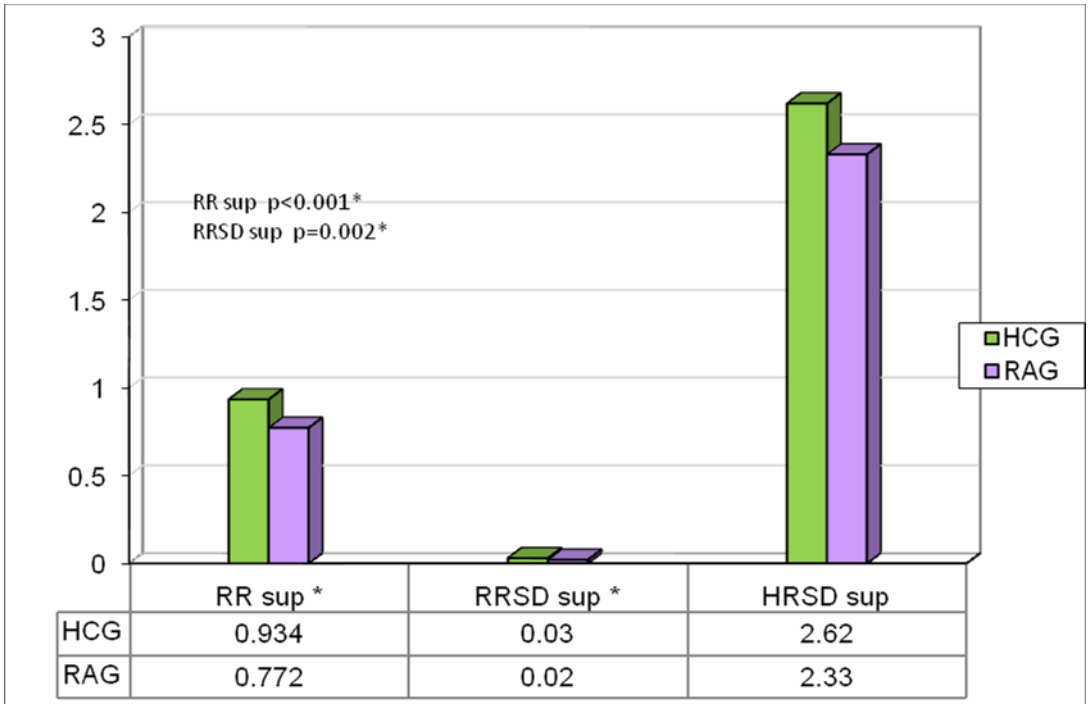
Figure 4.1: Medians of RMSSD supine and pNN50 supine in the HCG and RAG



	SD1 sup *	HF (ms^2) sup *
HCG	20.9	141
RAG	10.5	31

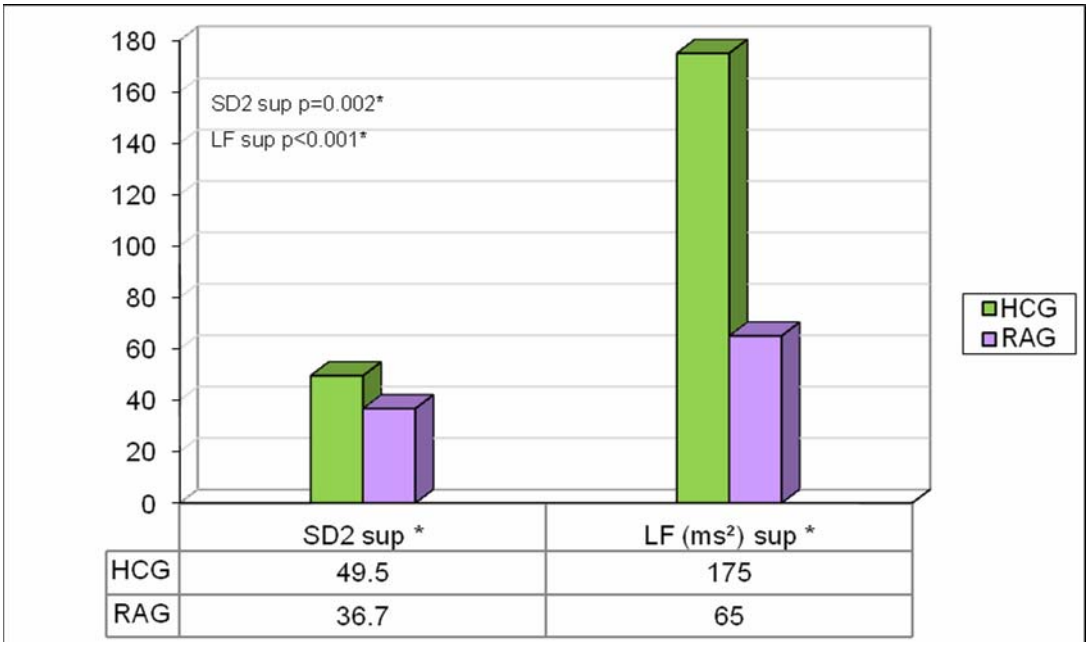
Figure 4.2: Medians of SD1 supine and HF(ms^2) supine in the HCG and RAG

Variables assessing HRV indicators influenced by both the sympathetic and parasympathetic branches of the autonomic nervous system [RR, RRSD, HRSD, SD2, LFms^2] also showed statistically significant lower values for the RAG, except for HRSD (Figures 4.3 and 4.4).



	RR sup *	RRSD sup *	HRSD sup
HCG	0.934	0.03	2.62
RAG	0.772	0.02	2.33

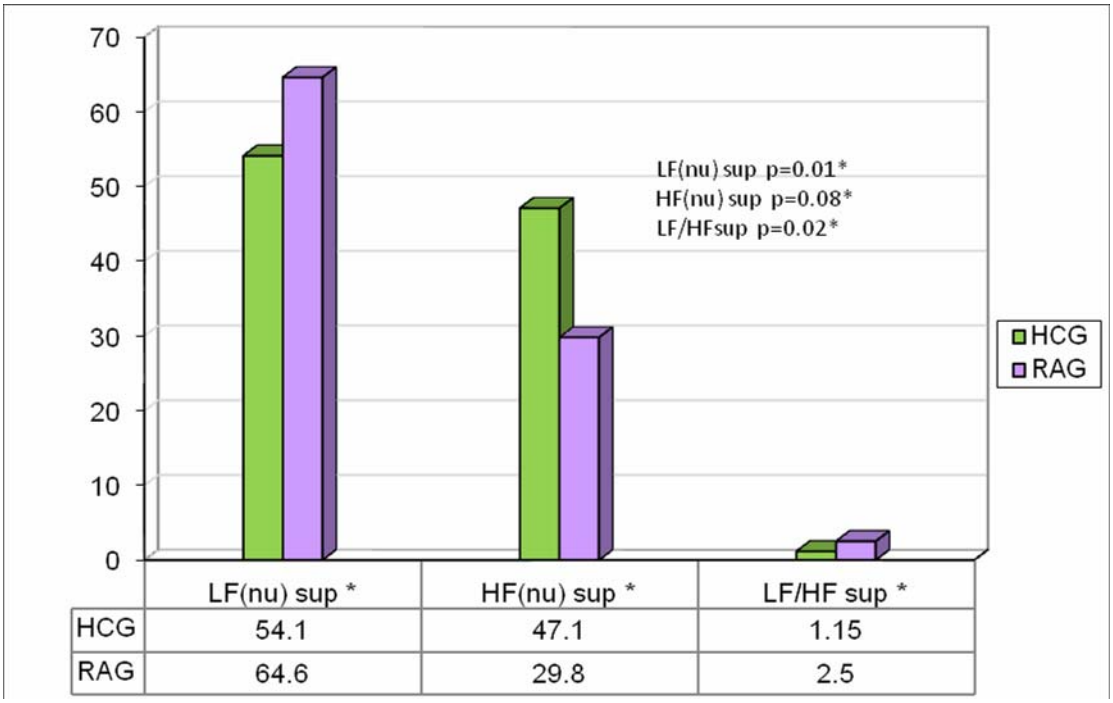
Figure 4.3: Medians of RR supine, RRSD supine and HRSD supine in the HCG and RAG



	SD2 sup *	LF (ms²) sup *
HCG	49.5	175
RAG	36.7	65

Figure 4.4: Medians of SD2 supine and LF(ms^2) 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).



	LF(nu) sup *	HF(nu) sup *	LF/HF sup *
HCG	54.1	47.1	1.15
RAG	64.6	29.8	2.5

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≤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(ms²)	544.59	552.91	333.00	450.00	145.02	177.47	88.00	155.00	<0.001**
HF(ms²)	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).

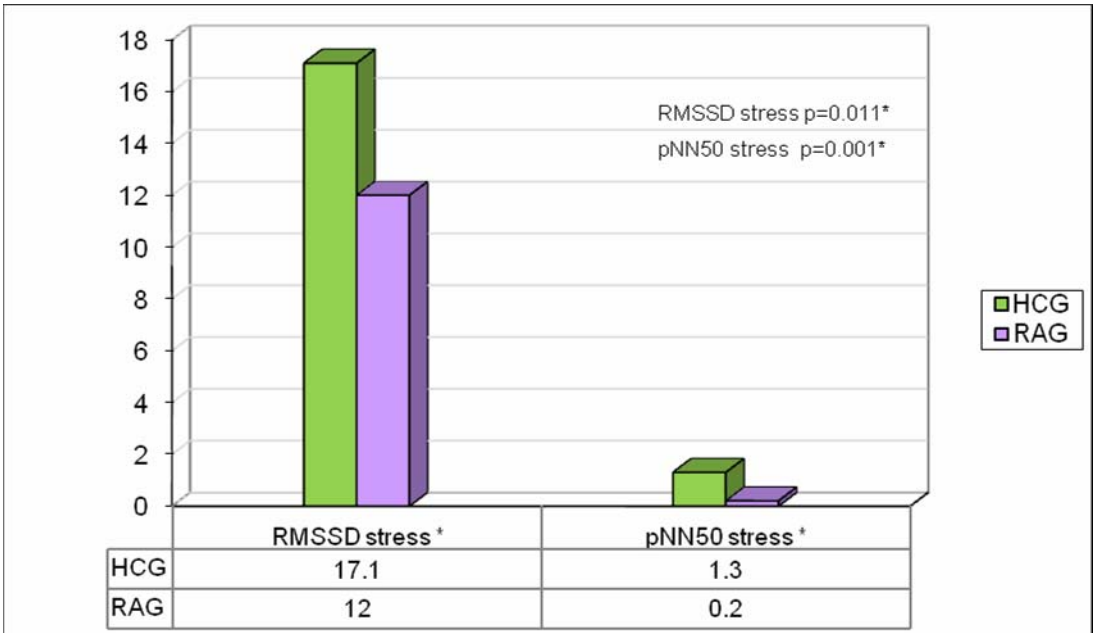


Figure 4.6: Medians of RMSSD stress and pNN50 stress in the HCG and RAG

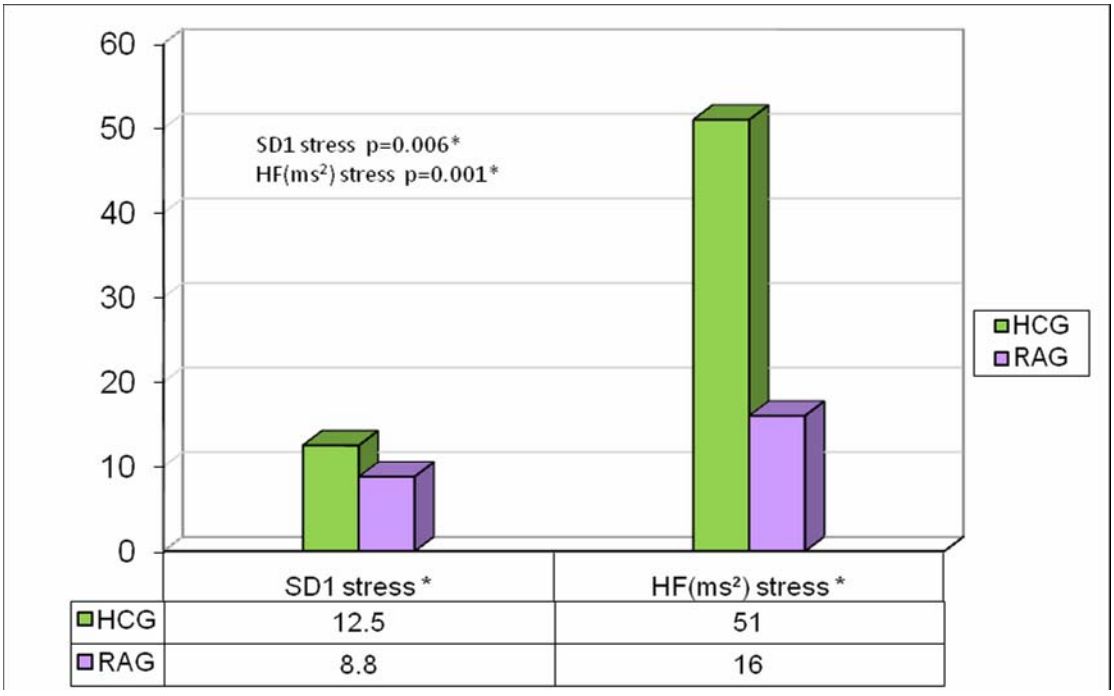
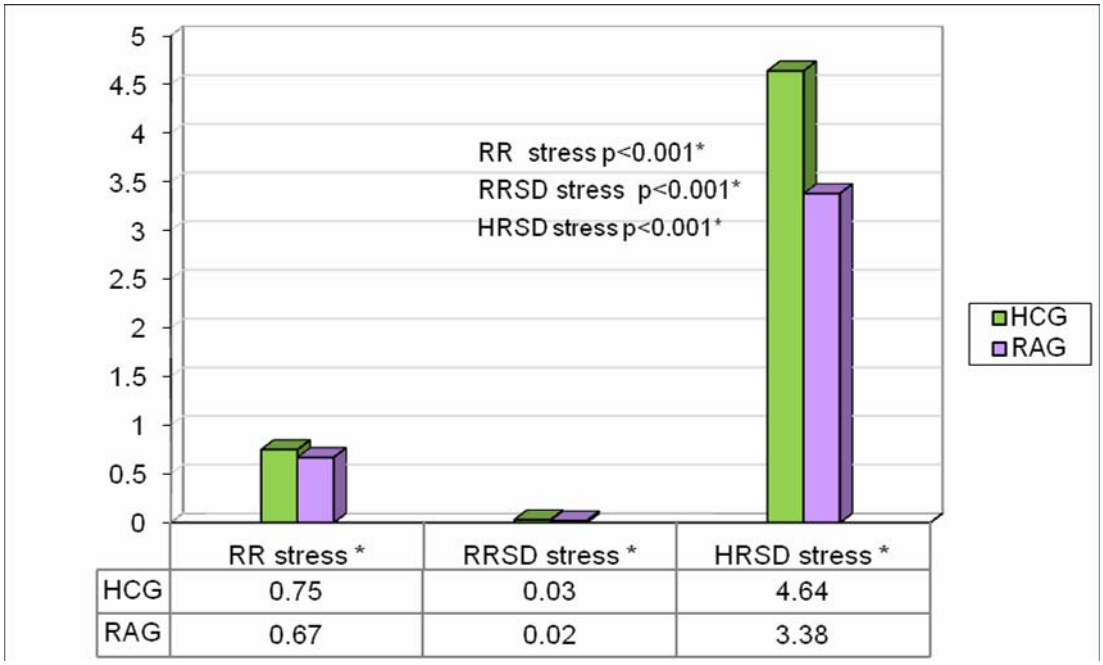


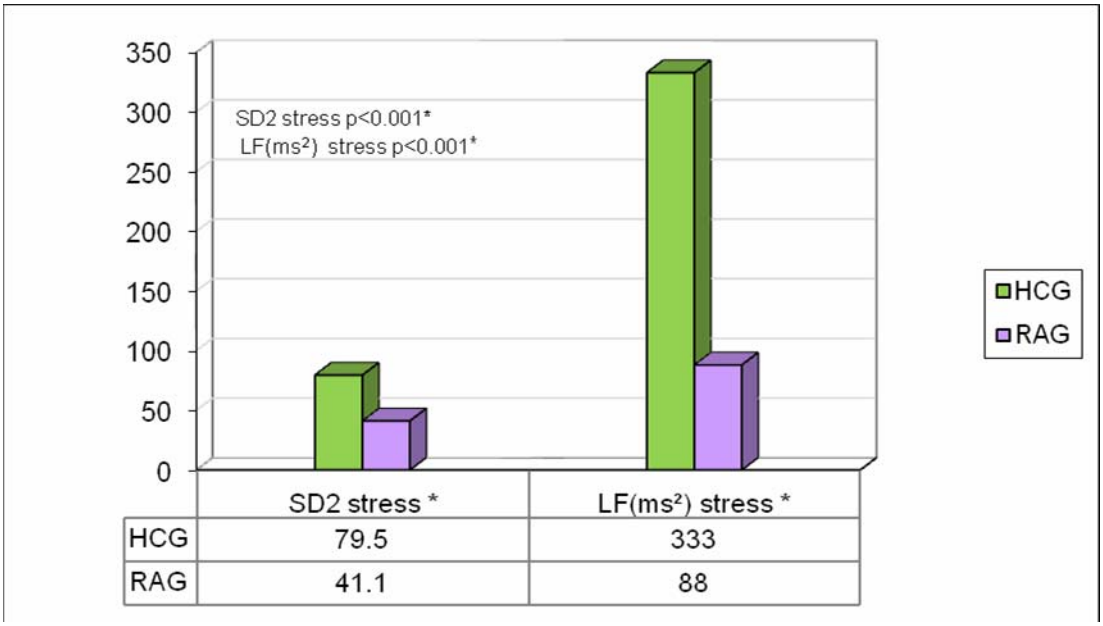
Figure 4.7: Medians of SD1 stress and HF(ms^2) stress in the HCG and RAG

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(ms^2)] (Figures 4.8 and 4.9).



	RR stress *	RRSD stress *	HRSD stress *
HCG	0.75	0.03	4.64
RAG	0.67	0.02	3.38

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



	SD2 stress *	LF(ms^2) stress *
HCG	79.5	333
RAG	41.1	88

Figure 4.9: Medians of SD2 stress and LF(ms^2) 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).

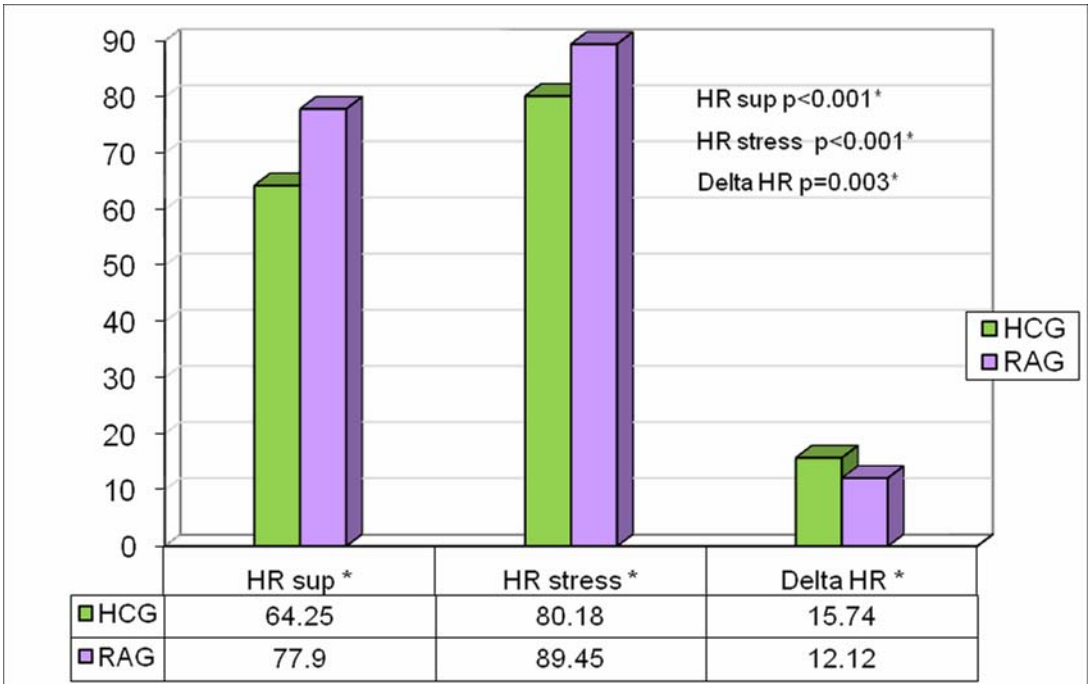
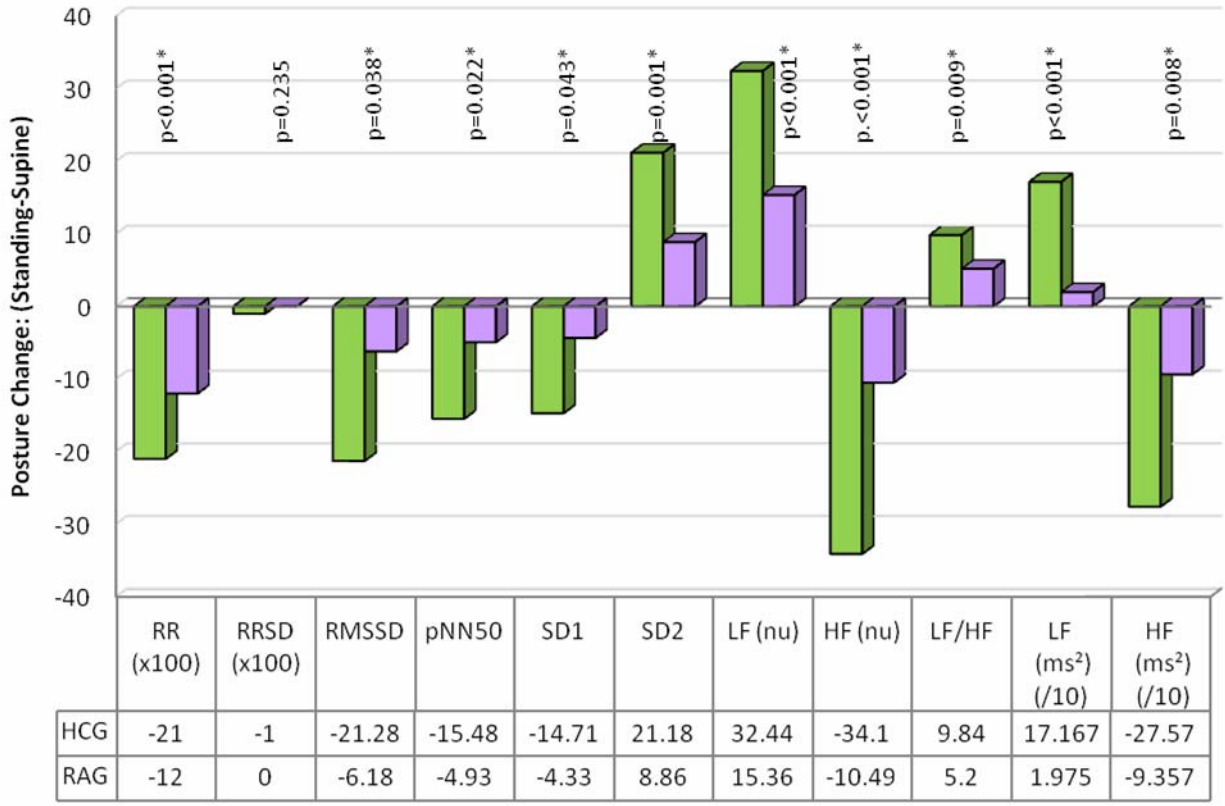


Figure 4.10: Medians of HR supine and stress in the HCG and RAG

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(ms^2) and HF(ms^2) were divided by 10.



	RR (x100)	RRSD (x100)	RMSSD	pNN50	SD1	SD2	LF (nu)	HF (nu)	LF/HF	LF (ms^2) (/10)	HF (ms^2) (/10)
HCG	-21	-1	-21.28	-15.48	-14.71	21.18	32.44	-34.1	9.84	17.167	-27.57
RAG	-12	0	-6.18	-4.93	-4.33	8.86	15.36	-10.49	5.2	1.975	-9.357

*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 (DAS_{28}) 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.

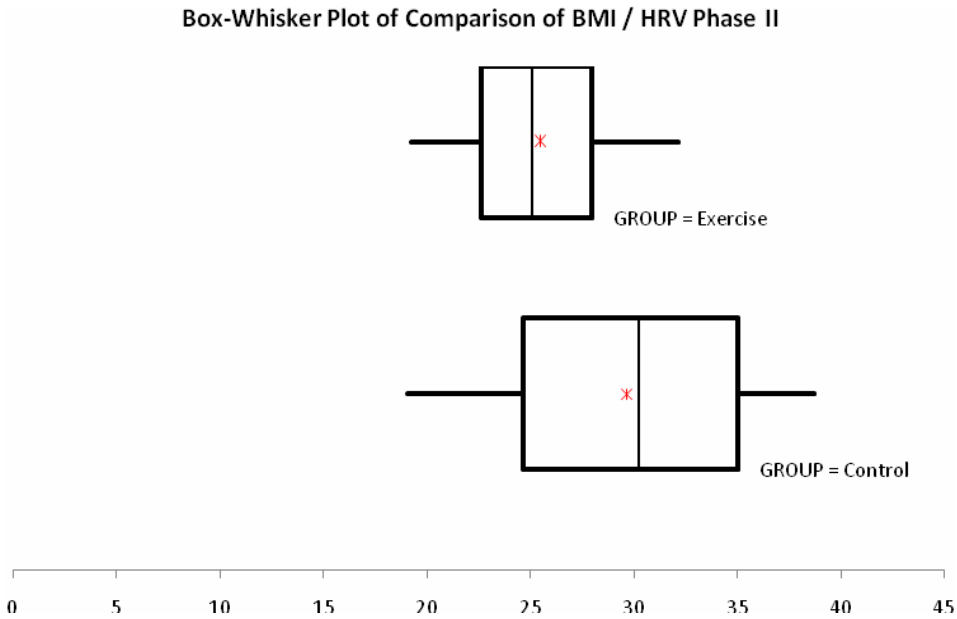


Figure 4.12: Box-Whisker plot of comparison of BMI

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

	RAE (n=19)				RAC (n=18)			
Indicator	**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(ms²)	60.41	49.58	46.00	56.00	207.33	202.01	147.50	182.00
HF(ms²)	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(ms²)	59.38	51.52	38.50	69.00	250.78	232.84	174.50	263.00
HF(ms²)	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

	RAE (n=19)				RAC (n=18)			
Indicator	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	01.8
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(ms²)	79.20	129.72	34.00	100.00	260.64	295.44	177.09	349.73
HF(ms²)	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(ms²)	101.23	94.97	86.50	137.00	229.43	175.89	194.00	226.00
HF(ms²)	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

	RAE				RAC					
Indicator	**Mean**	**SD**	**Median**	**IQR**	**Mean**	**SD**	**Median**	**IQR**	**p**	**Group favoured**
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(ms²)	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(ms²)	59.38	51.52	38.50	69.00	250.78	232.84	174.50	263.00	<0.001**	RAC
HF(ms²)	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(ms²)	59.38	101.23	41.85	↑	38.50	86.50	0.063°	0.40	↑	I

s seconds
bpm beats per minute
nu normalised units
ms milliseconds
ms^2 milliseconds, squared

** p<0.01
* p<0.05
° p<0.10

◆ Reflects true value where rounded off value could be misleading
I Improvement on median values
D Deterioration on median values

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

Indicator	Mean pre-value	Mean post-value	Mean diffe-rence	↑↓	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	*	p<0.05
ms	milliseconds	°	p<0.10
%	percentage	I	Improvement on median values
ms^2	milliseconds, squared	D	Deterioration on median values
nu	normalised units		

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

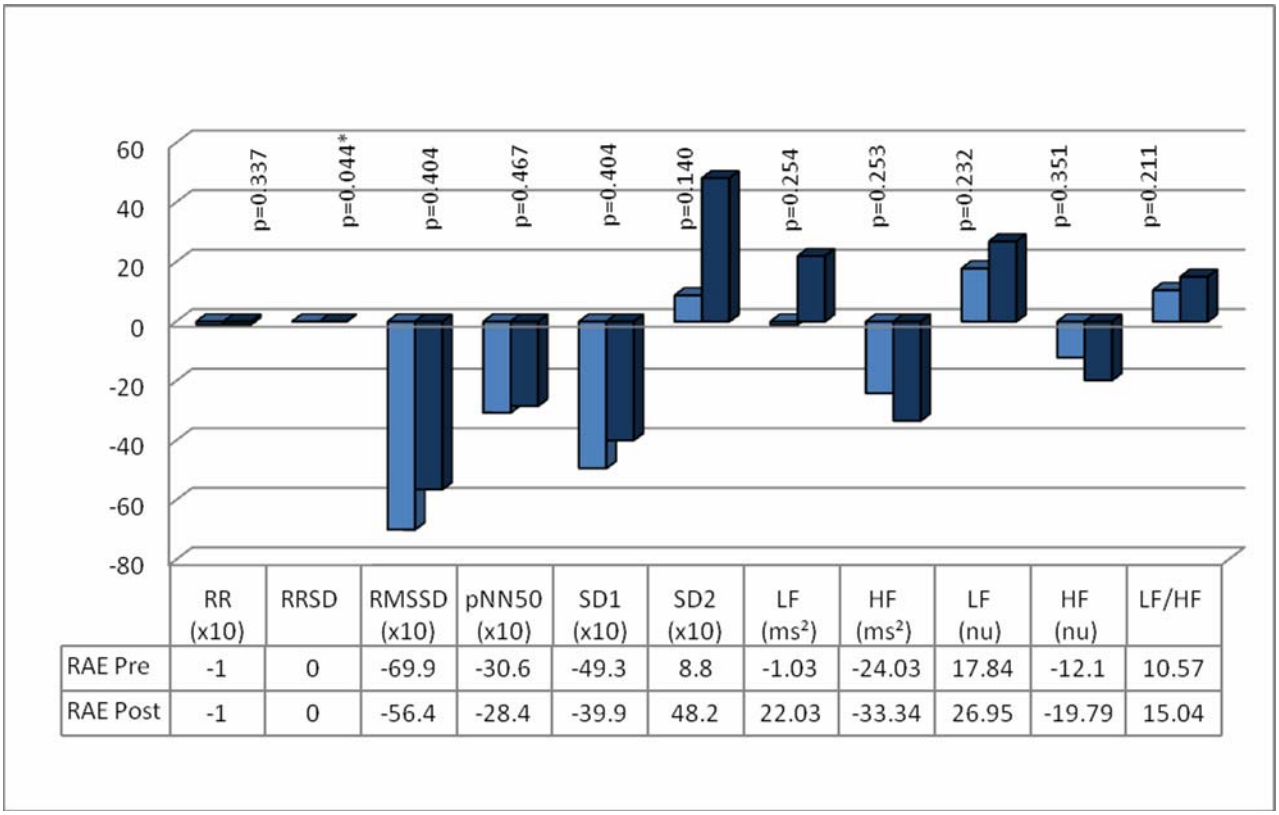
Indicator	Differences		p	Effect size	Group favoured
	RAE	RAC			
Supine (Resting)					
RR(s)	0.07	-0.01	0.022*	0.52	RAE
HR(bpm)	-6.79	1.47	0.029*	0.49	RAE
Stress (Standing)					
RR(s)	0.03	0.00	0.033*	0.47	RAE
HR(bpm)	-6.91	-0.31	0.021*	0.52	RAE
RMSSD(ms)	1.40	-3.90	0.012*	0.59	RAE
pNN50(%)	0.00	-0.20	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
bpm beats per minute
ms milliseconds
% percentage
** p<0.01
* 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(ms^2), HF(ms^2), 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).

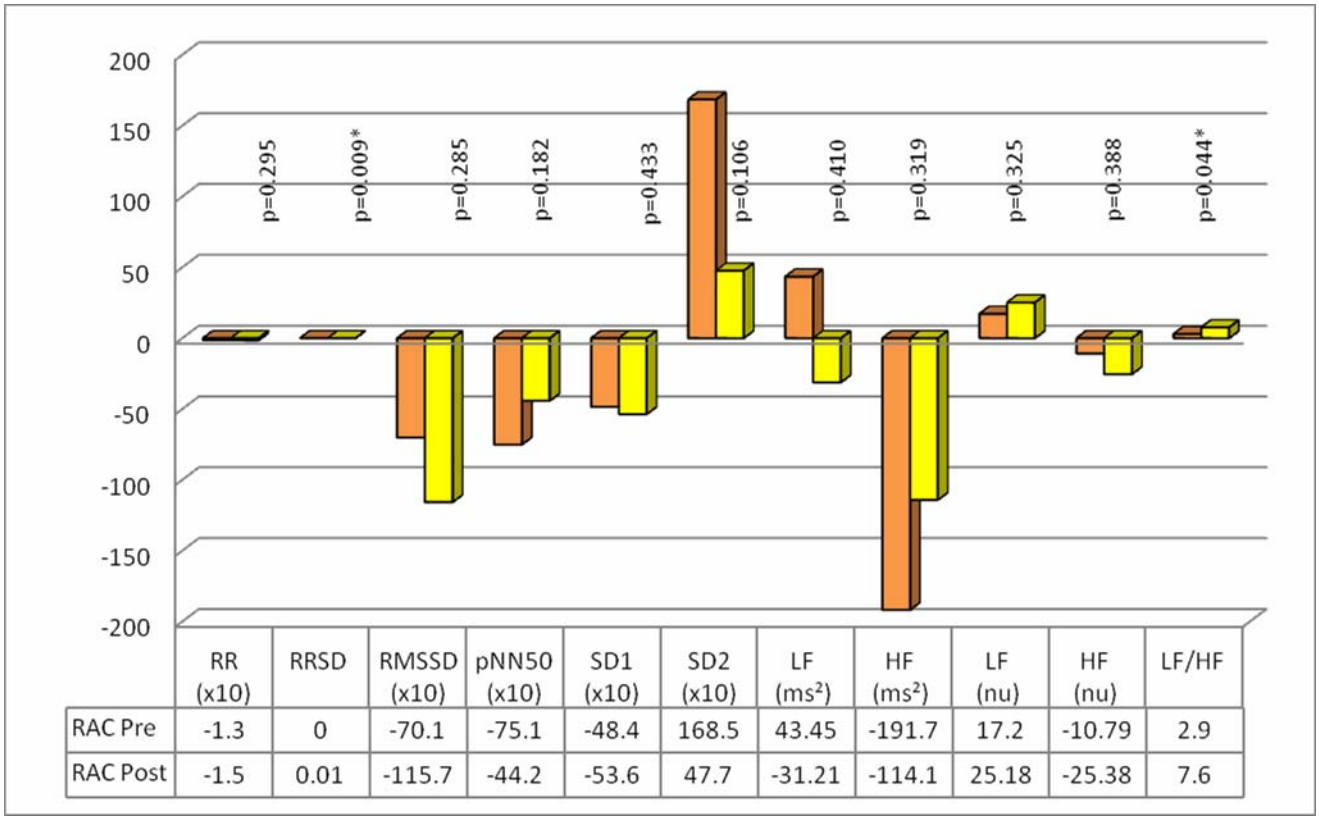


	RR (x10)	RRSD	RMSSD (x10)	pNN50 (x10)	SD1 (x10)	SD2 (x10)	LF (ms^2)	HF (ms^2)	LF (nu)	HF (nu)	LF/HF
RAE Pre	-1	0	-69.9	-30.6	-49.3	8.8	-1.03	-24.03	17.84	-12.1	10.57
RAE Post	-1	0	-56.4	-28.4	-39.9	48.2	22.03	-33.34	26.95	-19.79	15.04

*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(ms^2) and HF(ms^2) 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.



	RR (x10)	RRSD	RMSSD (x10)	pNN50 (x10)	SD1 (x10)	SD2 (x10)	LF (ms^2)	HF (ms^2)	LF (nu)	HF (nu)	LF/HF
RAC Pre	-1.3	0	-70.1	-75.1	-48.4	168.5	43.45	-191.7	17.2	-10.79	2.9
RAC Post	-1.5	0.01	-115.7	-44.2	-53.6	47.7	-31.21	-114.1	25.18	-25.38	7.6

*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 DAS_{28}, 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
TJ Tender joint count
SJ Swollen joint count
PaGA Patient's Global Assessment
PhGA Physician's Global Assessment
CRP C-reactive protein
DAS Disease Activity Score
HAQ Health Assessment Questionnaire
VAS Visual Analogue Scale
1 Pre-intervention values
2 Post-intervention values

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, DAS_{28} 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 diffe-rence	↑↓	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. TJdiff = 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

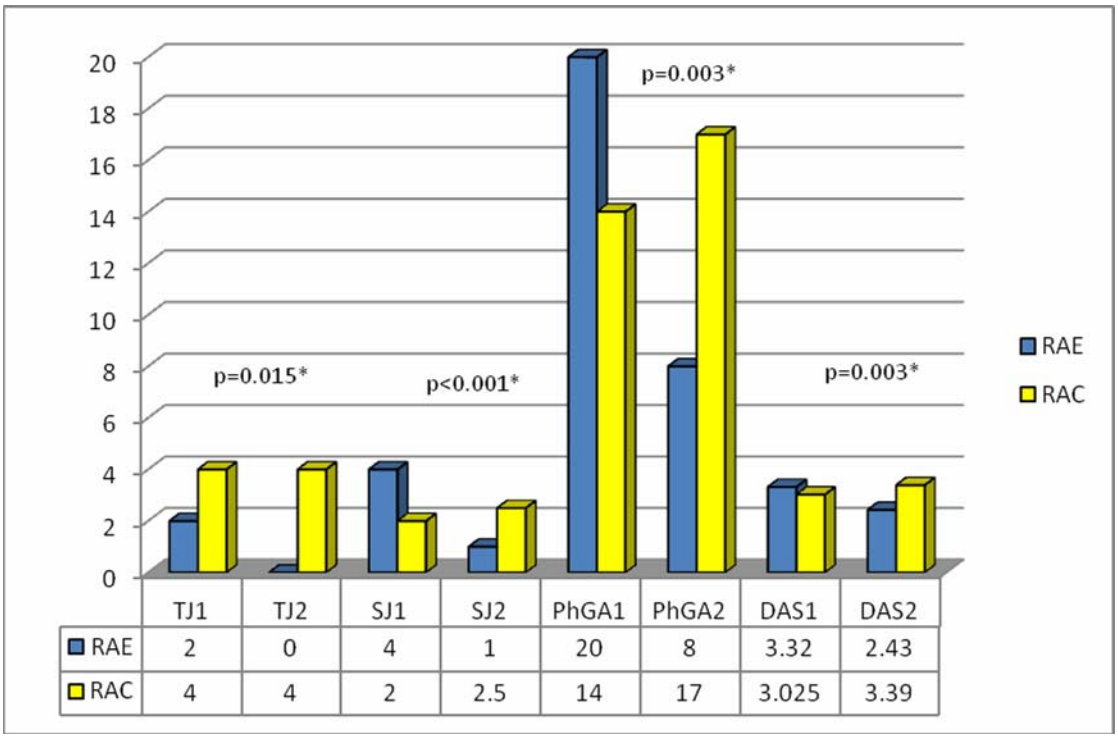
determine if the change in RAE is larger than in RAC, MWU-tests were performed. As can be seen in Table 4.15, significant improvements in favour of RAE were found for tender joint count, swollen joint count, physician's global assessment and disease activity score.

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).



	TJ1	TJ2	SJ1	SJ2	PhGA1	PhGA2	DAS1	DAS2
RAE	2	0	4	1	20	8	3.32	2.43
RAC	4	4	2	2.5	14	17	3.025	3.39

*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.

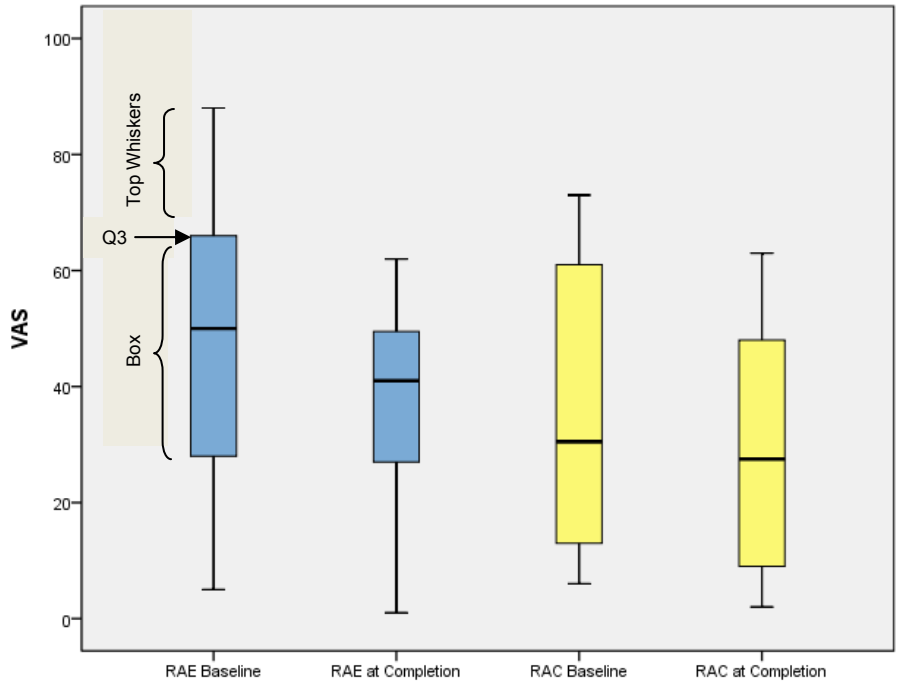


Figure 4.16: Clustered Box Plot on VAS at baseline and at completion of study for both groups

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
IQR Interquartile range
kg kilogram
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
IQR Interquartile range
min minutes
bpm beats per minute
mmHG millimetres of mercury

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; s seconds to complete 20 repetitions
deg degree; * <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_2max	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, VO_2 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 Diffe-rence	↑↓	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
cm centimetres
kg kilogram
s seconds
min minutes

bpm beats per minute
mmHG millimetres of mercury
** p<0.01
* p<0.05

I Improvement on median values
D Deterioration on median values

⅄ 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 Diffe-rence	↑↓	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

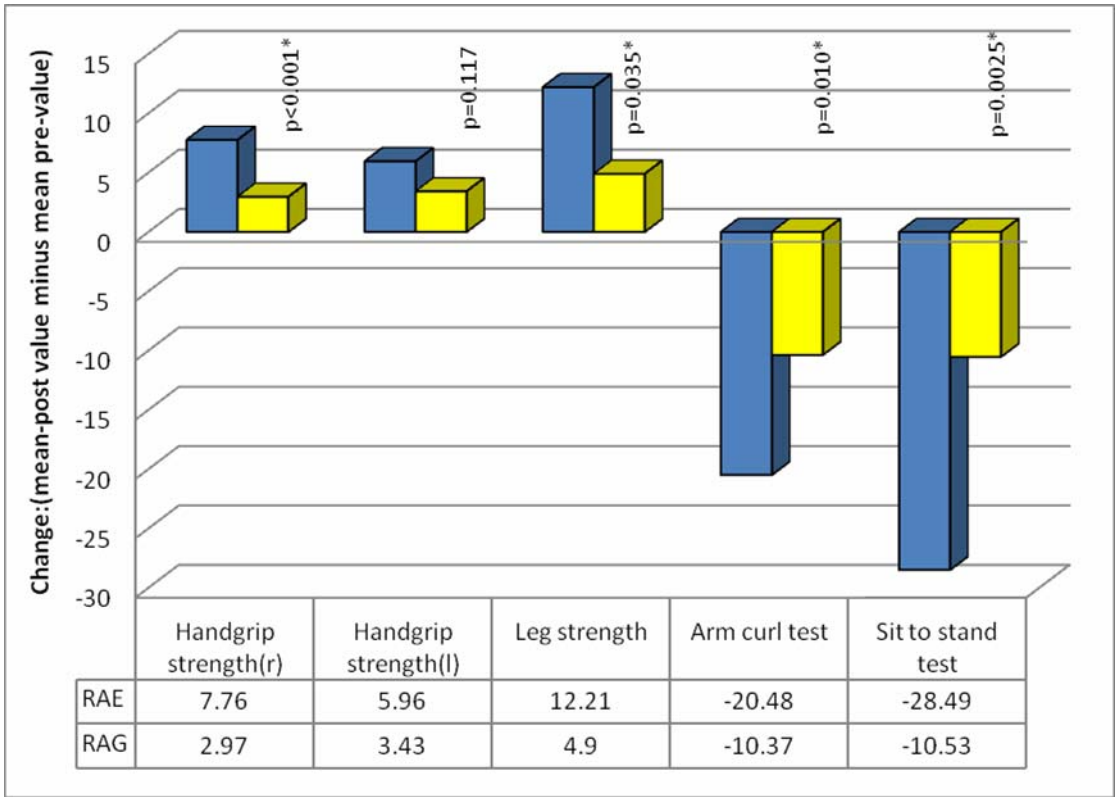
deg degree
cm centimetre
kg kilogram
s seconds

mmHG millimetres of mercury
** p<0.01
* p<0.05

I Improvement on median values
D Deterioration on median values

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.



	Handgrip strength(r)	Handgrip strength(l)	Leg strength	Arm curl test	Sit to stand test
RAE	7.76	5.96	12.21	-20.48	-28.49
RAG	2.97	3.43	4.9	-10.37	-10.53

*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 VO_2 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 VO_2max to improve statistically significantly in comparison to RAC.

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CHAPTER FIVE: DISCUSSION

This chapter will be divided into two parts:

5.1 Comparison of cardiac autonomic nervous system function as measured by short-term HRV, between a healthy control group (females) and a group of RA patients (females).

5.2 Influence of a 12-week training program in females with RA on the:

5.2.1 Autonomic nervous system as measured by short-term HRV in the supine position, standing position and with posture change

5.2.2 Disease outcome as measured by the Disease Activity Score (DAS_{28}), Health Assessment Questionnaire (HAQ) and Visual Analogue Scale (VAS).

5.2.3 Functional parameters including flexibility, strength and aerobic fitness.

5.1 CARDIAC AUTONOMIC FUNCTION BETWEEN HEALTHY PARTICIPANTS AND RA PATIENTS

In the first phase of this study, using standardised methods to measure short-term HRV, the RA group (RAG) showed less variability (i.e. less healthy heart) compared to a healthy age- and sex matched control group (HAG).

All three methods used to measure HRV (time domain, frequency domain and Poincare analysis) yielded similar results. The results in this study are in contrast to

Evrengul's study (one of the first authors applying HRV to assess autonomic function in RA patients), who measured time domain and frequency domain, but had conflicting results[1]. For time domain parameters, Evrengul showed a slightly higher RMSSD and pNN50 (i.e. parasympathetic influence) and a significant lower SDNN (i.e. combined sympathetic and parasympathetic influence) for the patient group. The frequency domain parameters however, showed a significant lower HF(ms^2) (parasympathetic), but higher LF(ms^2) and LF/HF (sympathetic and parasympathetic). Possible explanations for the discrepancies in results might be that Evrengul included both males and females in the groups and recordings were done over an hour. This is contrary to our study where only females were included and recordings were done over 10 minutes.

Similar work done by authors like Fei (1996) and Howorka (1998) stated that frequency domain analysis are better for mortality prediction when using short-term recordings[2,3]. However, the current study showed the same results for time domain and frequency domain analysis, using short-term recordings. Fei evaluated patients after acute myocardial infarction and Howorka evaluated diabetic patients. Our findings perhaps warrant further investigation of accuracy of time domain analysis to predict mortality when using short-term recordings.

In support of our study, other authors also reported an elevated resting heart rate in the RAG compared to the HCG, again indicating a lower vagal and/or an increased sympathetic drive in RA patients[4,5]. According to Jouven et al (2005), patients with a resting heart rate of ≥75 beats per minute and no clinical evidence of cardiac disease have a 4-fold risk for sudden cardiac death[6]. Our patient group had, on average, a resting heart rate of 77 [95% confidence interval (75; 80)]. Only two studies measured HR response (i.e. posture change) by means of HRV in RA patients[5,7]. Aydemir and Vlcek could not show a difference for heart rate response between controls and patients; neither did they offer an explanation. Our RAG had a significant lower HR response compared to the HCG[5,7]. This finding supports the other measurements in the current study, as with less HRV shown in the RAG one would expect a decreased heart rate response in comparison to the controls.

Two studies that evaluated autonomic dysfunction in RA patients of recent disease onset, showed abnormal sympathetic function, but normal parasympathetic

function[8,9]. Our RA study group had relative early disease (4.26 years disease duration), with moderate disease activity (DAS_{28} 3.27, CRP 8.55mg/l) and no clinical determined signs or symptoms of autonomic impairment. Despite this, most HRV indicators showed statistically significant less variability in the RAG compared to the HCG, designating the RAG as having less healthy hearts. In the supine (resting) position variables assessing parasympathetic variability were all lower for the RAG. This is in agreement with other authors' work, where Anichkov using 24-hour Holter recordings in patients with 4-year disease, showed statistical differences for RMSSD and SD1[10] and Milovanovic using 10 minute recording periods showed differences for pNN50, RMSSD and HF(ms^2) indicating less variability for the RA subjects[11]

In the present study indicators for autonomic balance showed higher values for those indicators [LF(nu) and LF/HF] predominantly controlled by sympathetic influence and lower values for HF(nu) (predominantly parasympathetic) for the RAG. In the resting position, normally parasympathetic dominance is to be expected, which was not the case in our patient group. The inflammatory markers (CRP) in our group of relative early RA were within normal limits, indicating the absence of clinical significant inflammation and possibly arguing for an increased dysrhytmogenic potential and not inflammation contributing to increased cardiovascular morbidity.

As previously pointed out, only two other studies used HRV to evaluate posture change in RA patients compared to a control group. They evaluated only frequency domain parameters, but the outcomes were the same as for our study[5,7]. Both LF(ms^2) and HF(ms^2) had significant lower values comparing the RAG to the HCG. One would expect a bigger sympathetic drive changing from supine to standing as is seen in the normal population[12,13]. The RA patients had a poorer response to posture change. Vagal withdrawal, indicated by RMSSD, pNN50, SD1 and HF(ms^2), was significantly increased in the control group. Also, the indicators SD2 and LF(ms^2), representing the combined influence of vagal and sympathetic cardiac control, were significantly higher in the control group, thereby indicating higher autonomic responsiveness to the posture change. Not only does an absent or decreased HRV response to posture change point to early sympathetic damage and autonomic dysfunction[13], but it has been suggested that the parasympathetic nervous system has anti-arrhythmic properties[6,14].

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

5.2 EFFECT OF EXERCISE ON CARDIAC AUTONOMIC FUNCTION, DISEASE ACTIVITY AND FUNCTIONAL PARAMETERS IN RA PATIENTS

In the second phase of the study an RA exercise group (RAE) was compared to an RA control group (RAC). The null hypothesis was rejected, in that the results showed that exercise intervention had a meaningful effect on cardiac autonomic function, disease activity and functional capacity in females diagnosed with RA.

The subjects that completed the study did not suffer any injuries sustained due to the training programme. Although we had patients who withdrew from the exercise study, figures are still comparable to what is reported in other studies[15,16]. Compliance to the exercise program is on average reported to be between 50% and 95%, depending on accessibility, duration, cost and comfort for the patient[15]. Our exercise group had a 79.17% compliance rate and the control group 81.82% (p=0.821).

5.2.1 AUTONOMIC NERVOUS SYSTEM (HRV)

This study demonstrated that exercise intervention had a positive effect on autonomic function of RA patients, as measured by short-term HRV. Comparing the exercise group to the control group at baseline, the control group showed better HRV. However, at study completion this changed in favour of the exercise group who then showed better HRV. Our results are similar to that of Jurca et al (2004) who after eight weeks of moderate exercise training in females, showed improved vagal modulation of heart rate on 10 minute resting ECGs[17].

There are no other data or studies that evaluated the effect of exercise in this manner in RA patients.

Many previous studies done on diseased populations to evaluate the effect of short-term exercise intervention on short-term HRV modification, assessed only supine variables[18-27]. Sandercock observed significant increases in the supine RR-interval, SDRR, LF(ln) and HF(ln) in a group of patients, who had coronary artery bypass grafting and angioplasty following myocardial infarction (MI), after 8 weeks of cardiac

rehabilitation[18]. Malfatto (1996) also showed significant increases for RR-interval, SDRR, RMSSD, pNN50 and HF but a decline in LF in patients who followed a training programme after MI[24]. On the other hand Oya et al (1999) could not show any significant difference in HRV in MI patients after a 3 months training programme[21]. Figueroa (2007) observed a significant increase in LF and HF in a 16 week study in obese women with and without type 2 diabetes mellitus[27]. All the above mentioned studies (except Oya), thus showed increased vagal tone (HF, RMSSD, pNN50) after exercise intervention, but the LF variable seems to be difficult to interpret with changes in different directions in the various studies.

In the present study, only the RR-interval increased significantly in the supine position, while the other variables did not show significant changes in favour of the exercise group. It is not clear why increased vagal tone was not demonstrated in the supine position in our analyses; however Iwasaki (2003) did a study where HF and RR-interval increased early in the training of young previously sedentary subjects, but at study completion after one year HF regressed towards initial values whereas RR-interval uniformly increased. They suggested that initial increases may be due to higher vagal modulation, while other factors such as heart geometry may play a role in further adaptation[28].

It was mainly the standing variables that were affected favourably in our exercise group in comparison to the control group. Zoppini (2007) had similar results in a study on patients with type 2 diabetes mellitus where they showed significant changes in standing, but not supine variables after a six months exercise programme[29].

In the current study the changes reflected a greater effect on increased vagal rather than decreased sympathetic influence. Buch in 2002 pointed out that patients may have a better survival advantage with enhanced vagal tone. Reasons offered were that greater vagal influence will: decrease heart rate and myocardial contractility (i.e. due to less workload and oxygen consumption); hinder sympathetic influence on the sinus node; and reduce the risk of ventricular disrhythmias[30]. Therefore, improving the vagal tone in RA patients may be an instrument to decrease their cardiovascular morbidity and mortality.

With regards to posture change, the current study showed a mixture of outcome, where for some variables indicating vagal influence, there is a definite exercise induced withdrawal as expected (e.g. $HFms^2$ in the exercise group), while for others (e.g. RMSSD, SD1 in the exercise group) the contrary happens. This may be due to the small participant number, moderate intensity of the intervention, and/or relative short duration of the study.

In conclusion De Meersman commented that “Ultimately, all of these cardiovascular diseases are associated with a common denominator, namely a perturbed autonomic balance. It is tempting, therefore, to hypothesize that preservation of cardiac autonomic function by lifestyle or interventions should be associated with a marked reduction in the risk of cardiovascular disease and death”[31]. Exercise intervention appears to have an advantageous effect on cardiac autonomic function in RA patients as measured by short-term HRV. Especially vagal modulation seems to improve and this can lead to improved cardiac health in a patient group already suffering from impaired lifestyle due to joint pain and other complications following a diagnosis of RA.

5.2.2 DISEASE OUTCOME

In this study a supervised training programme was effective in decreasing perception of pain as well as disease activity in female RA patients. Stenstrom stated that there are no specific response criteria to measure outcome of disease activity following exercise intervention in RA patients[32] but Aletaha and Smolen argued that it is reasonable to use the same measurements (including DAS-scores) that have originally been developed for the purpose of facilitating clinical trial reporting. International bodies introduced the term “core set” comprising of tender and swollen joint counts, global assessments by the patient and the assessor (mostly the physician), pain assessment by the patient, acute-phase response and a functional element[33]. For the purpose of this study, it was decided to make use of the VAS[34-36], HAQ[37,38] and DAS_{28} scores[39-41], which have all been validated previously in the literature, in order to address all elements of the core set.

The perception of the presence of pain as measured by the visual analogue scale (VAS) did not differ significantly between the two groups at study completion. Lee reported similar results[42], but Flint-Wagner reported a decrease in pain for their exercise group[43]. Observing within group changes from start to study completion, the exercise group had a significant improvement in the VAS in accordance to other studies[44,45].

The HAQ scores did not show statistical significant differences between the groups, or within the exercise group. In previous studies done, only one study reported improved quality of life[46] while others could not show any change[44,47-50]. Previous authors mentioned the fact that the HAQ might not be sensitive enough to capture changes[16,32,51]. It will be worthwhile to investigate the use of other means of scoring quality of life, perception of health and well-being in future exercise intervention studies.

Improvement in DAS scores following exercise intervention as demonstrated in this study are supported by many previous studies[15,16,44,47,51-56]. At baseline all our participants had moderate disease activity i.e. DAS between 3.2 and 5.1. At study

completion the exercise group had a DAS-score of 2.51 implying disease remission [57]. The EULAR (European League against Rheumatism) response criteria on disease intervention are based on DAS_{28}. These criteria require a patient to achieve a certain amount of improvement and also a particular disease activity state after intervention[33]. According to these criteria, our exercise group achieved a mean DAS_{28} of less than 3.2 (i.e. 2.51) and had a moderate improvement between 0.6 to 1.2 (i.e. 0.78). The control group deteriorated with their mean DAS_{28} being higher at study completion (Baseline DAS_{28} 3.25; End of study DAS_{28} 3.27) Therefore our patients did achieve the EULAR response criteria after exercise as compared to the controls.

Given our findings of improved pain levels and decreased disease activity, it seems warranted to include physical exercise as part of the treatment prescription of patients with Class I and II RA.

5.2.3 FUNCTIONAL PARAMETERS

Research has shown that regular, controlled exercise for those RA patients whose disease is under control, decreases joint stiffness and improves joint mobility, strength and aerobic capacity without exacerbating pain or disease activity[58,59]. The flexibility findings of this study supports findings of previous studies done in RA populations, in that there was significant improvements in joint range of movement of all major joints in the exercise group, whereas flexibility of the control group remained mainly unchanged and even deteriorated[46,47,60]. Efficiency of movement and normal daily activities are dependant on functional range of movement[61].

Interestingly, strength improved for both groups. A study by Bykerk and Keystone had similar results[62]. This occurrence has previously been explained by Hakkinen as a learning effect of repeated physical testing and variation in symptoms[63]. Referring to Figure 4.16 in this study though, one can appreciate that the exercise group had larger improvements from start of study to completion compared to the control group. This is in agreement with other studies like Van den Ende, Hakkinen and Stenstrom[47,53,60]. It is important to maintain muscle strength for normal functioning and joint stabilisation to prevent future deformities[64].

Exercise programmes with the specific purpose of improving aerobic fitness have attracted attention in this population[65]. Previous studies made use of cycling[66,67], aquatics[46,68], dancing[69,70] and walking[46,71]. However, the combined use of aerobic and strength training has been the exercise programme of choice in recent research[32,47,52,72] and the ACR subsequently updated treatment guidelines to include dynamic exercise as part of the management[73]. In keeping with previous studies using combined exercise programmes, our exercise group significantly improved both the time it took to complete the 1 mile walk test, as well as their VO_2 max.

With improvements in flexibility, strength and aerobic fitness it can thus be concluded that the exercise group had improved functional capacity as a result of a relatively short, but well controlled exercise programme of 12 weeks. If one observes the

decline in the control group for many parameters, it is important to note that this happened over a relatively short period of time, and also that even small changes may have a detrimental impact on the RA patient.

5.3 CONCLUSION

5.3.1 ADDED VALUE

- The current report is the only study on the effect of exercise on cardiac autonomic function in RA patients. From our results it appears that cardiac autonomic dysfunction, as measured by standardised short-term HRV, is a definite underlying physiological problem in RA patients, even in the early stages of the disease. Exercise intervention may have an advantageous effect on cardiac autonomic function which may improve long term cardiovascular outcome. Unfortunately at this stage it is still pure conjecture whether exercise should form part of the management of RA patients.

- Our results on the effect of exercise in a South African based RA population also support previous literature on the meaningful positive effect of training on disease activity and functional capacity.

- The results of this study indicate that health care practitioners should include a prescribed exercise program in all RA patients as the benefit of such a prescription has meaningful clinical benefit.

5.3.2 LIMITATIONS OF THE STUDY

- Due to the unavoidable small sample size in PHASE 2, this study suffers from the implication of low statistical power. However, comparing other studies that have been published on the effect of exercise on autonomic function in diseased populations, the number of patients in our study were quite similar to the literature[19,21,23-25,27]. Routledge in 2010 summarised 19 published articles on HRV modification through exercise intervention in the clinical setting. The average sample size was calculated as 21.2 (±10.6)[74]. Our study had 19 participants in the exercise group and 18 in the control group. Furthermore, effect sizes were reported in our study.

- The exercise intervention in our study was only 12 weeks. However, an 8-12 week exercise programme, was the norm in previous published studies on the effect of exercise on HRV in diseased population.

- No long term follow-up on the effect of exercise in the RA exercise group were reported. However, it was logistically impossible to increase the length of the intervention, as participants already struggled to conform to the supervised training programme (i.e. training under supervision 2-3 times per week) for 12 weeks. Future studies should perhaps focus on home-based training which may motivate patients more effectively to continue for a longer period.

- Only HRV was used to indicate the health of the autonomic nervous system in our study. Including tests such as analysis of blood pressure variability may add information and support results obtained by HRV analysis. Blood pressure variability could thus be included in future studies.

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Glossary

A

ACE	Angiotensin converting enzyme
ACPA	Anti-citrullinated peptide antibody
ACR	American College of Rheumatology
ACSM	American College of Sports Medicine
ANS	Autonomic nervous system
Anti-CCP	Anti-cyclic citrullinated peptide antibodies
ARA	American Rheumatism Association

B

BMI	Body mass index
BP	Blood pressure
bpm	Beats per minute

C

CAD	Cardiac autonomic dysfunction
CG	Control Group
CL	Constriction latency
cm	Centimetres
CRP	C-reactive protein
CRT	Cardiovascular reflex tests
CT	Computed tomography
CTD	Cardiac thoracic disease
CV	Cardiovascular
CVD	Cardiovascular disease

D

D	Deterioration
DAS	Disease activity score
deg	Degree
dif	Post-value minus Pre-value
DL	Dilation latency
DM	Diabetes mellitus
DMARDs	Disease modifying drugs

E

ECG	Electrocardiogram
EG	Experimental group
ESR	Erythrocyte sedimentation rate
EULAR	European League against Rheumatism

H

HAQ	Health assessment questionnaire
HCG	Healthy control group
HF	High frequency

HF(nu)	High frequency normalised units
HIV	Human immune-deficiency virus
$HMGB_1$	High mobility group box-1
HR	Heart rate
HRT	Heart rate turbulence
HRV	Heart rate variability
HT	Hypertension

I

I	Improvement
IL	Interleukin
IQR	Interquartile range

K

kg	Kilogram

L

L	Left
LDH	Lactate dehydrogenase
LF	Low frequency
LF/HF	Low frequency/high frequency ratio
LF(nu)	Low frequency normalised units
Ln	Natural logarithm

M

MANOVA	Multivariate analyses of variance
MCP	Metacarpophalangeal
MCV	Maximum constriction velocity
MI	Myocardial infarction
min	Minutes
mmHG	Millimetres of mercury
MS	Multiple sclerosis
MTP	Metatarsophalangeal
MWU	Mann Whitney U test

N

NE	Norepinephrine
NPY	Neuropeptide Y
NSAIDs	Non-steroidal anti-inflammatory drugs

O

OA	Osteo-arthritis

P

P	Parasympathetic
PAD	Pupillary autonomic dysfunction
PADI	Peptidyl arginase deaminase
PaGA	Patient global assessment
PhGA	Physician global assessment
PIP	Proximal interphalangeal
PMR	Polymyalgia rheumatica

pNN50	The percentage of successive RR-interval differences larger than 50ms computed over the entire recording, indicator of vagal influence on HRV
PP	Pancreatic polypeptide
PsA	Psoriatic arthritis

R

r	Right
RA	Rheumatoid arthritis
RAC	Rheumatoid arthritis control group
RAE	Rheumatoid arthritis exercise group
RAG	Rheumatoid arthritis group
RCT	Randomised controlled trial
RF	Rheumatoid factor
RM	Repetition maximum
RMSSD	Root mean square of the standard deviation between RR-intervals, indicator of vagal influence
ROM	Range of motion
RR	The mean of the intervals between successive QRS complexes, result of vagal and sympathetic influence on HRV
RRIV	RR-interval variation
RRSD	Standard deviation of intervals between successive QRS complexes, indicator of vagal and sympathetic influence on HRV (Overall HRV)

S

s	Seconds
S	Sympathetic
SD	Standard deviation
SD1	Indicator of the standard deviation of the immediate, or short-term, RR variability due to parasympathetic efferent (vagal) influence on the sino-atrial node
SD2	Indicator of the standard deviation of the long-term or slow variability of the heart rate. It is accepted that this value is representative of the global variation in HRV
SJ	Swollen joint
Sjö	Sjögrens
SLE	Systemic lupus erythemathosus
sqrt	Square root
SSc	Systemic sclerosis
SSR	Sympathetic skin response

T

TJ	Tender joint
TNF	Tumour necrosis factor
TO	Turbulence onset
TS	Turbulence slope

V

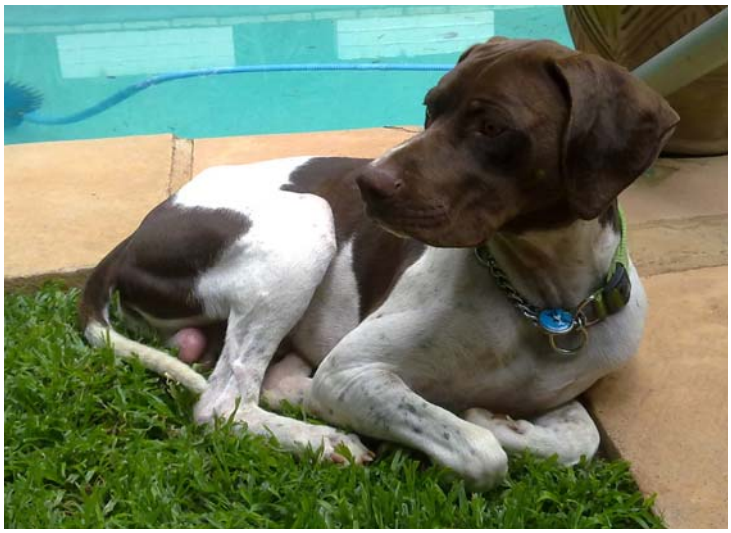
VAS	Visual analogue scale
VLF	Very low frequency

W

WHO	World Health Organisation

My husband, Hans

My dog, Remi



APPENDICES

Appendix 1

WHO definition of Health

Health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity.

The correct bibliographic citation for the definition is:

Preamble to the Constitution of the World Health Organization as adopted by the International Health Conference, New York, 19-22 June, 1946; signed on 22 July 1946 by the representatives of 61 States (Official Records of the World Health Organization, no. 2, p. 100) and entered into force on 7 April 1948.

The Definition has not been amended since 1948

Appendix 2

Medical History Questionnaire

Demographic Information

Last name	First name	Date of Birth
Home phone	Work phone	General
Address		

Section A

1. When was the last time you had a physical examination?
2. If you are allergic to any medications, foods, or other substances, please name them.
3. If you have been told that you have any chronic or serious illnesses, please list them.
4. Give the following information pertaining to the last 3 times you have been hospitalized. *Note:* Women, do not list normal pregnancies.

	Hospitalisation 1	Hospitalisation 2	Hospitalisation 3
Reason for hospitalisation			
Month and year of hospitalisation			
Hospital			

Section B

During the past 12 months

1. Has a physician prescribed any form of medication for you?	Yes	No
2. Has your weight fluctuated more than a few kilograms?	Yes	No
3. Did you attempt to bring about this weight change through diet or exercise?	Yes	No
4. Have you experienced any faintness, light-headedness, or blackouts?	Yes	No
5. Have you occasionally had trouble sleeping?	Yes	No
6. Have you experienced any blurred vision?	Yes	No
7. Have you had any severe headaches?	Yes	No
8. Have you experienced chronic morning cough?	Yes	No
9. Have you experienced any temporary change in your speech pattern, such as slurring or loss of speech?	Yes	No
10. Have you felt unusually nervous or anxious for no apparent reason?	Yes	No
11. Have you experienced unusual heartbeats such as skipped beats or palpitations?	Yes	No
12. Have you experienced periods in which your heart felt as though it were racing for no apparent reason?	Yes	No

At present

1. Do you experience shortness or loss of breath while walking with others your own age?	Yes	No
2. Do you experience sudden tingling, numbness, or loss of feeling in your arms, hands, legs, feet, or face?	Yes	No
3. Have you ever noticed that your hands or feet sometimes feel cooler than other parts of your body?	Yes	No
4. Do you experience swelling of your feet and ankles?	Yes	No
5. Do you get pains or cramps in your legs?	Yes	No
6. Do you experience any pain or discomfort in your chest?	Yes	No
7. Do you experience any pressure or heaviness in your chest?	Yes	No
8. Have you ever been told that your blood pressure was abnormal?	Yes	No
9. Have you ever been told that your serum cholesterol or triglyceride level was high?	Yes	No
10. Do you have diabetes?	Yes	No

If yes, how is it controlled?

☐ Dietary means ☐ Insulin injection
☐ Oral medication ☐ Uncontrolled

11. How often would you characterize your stress level as being high?

☐ Occasionally ☐ Frequently ☐ Constantly

12. Have you ever been told that you have any of the following illnesses?

☐ Myocardial infarction ☐ Arteriosclerosis ☐ Heart disease
☐ Coronary thrombosis disease ☐ Rheumatic heart ☐ Heart attack
☐ Coronary occlusion ☐ Heart failure ☐ Heart valve
☐ Heart block ☐ Aneurysm ☐ Heart murmur
☐ Thyroid disease ☐ Angina

13. Have you ever had any of the following medical procedures?

☐ Heart surgery ☐ Pacemaker implant
☐ Cardiac catheterization ☐ Defibrilator
☐ Coronary angioplasty ☐ Heart transplantation

Section C

Has any member of your immediate family been treated for or suspected to have had any of these conditions? Please identify their relationship to you (father, mother, sister, brother, etc.).

A. Diabetes C. Stroke
B. Heart disease D. High Blood Pressure

Section D

How long have you had arthritis (in years)?_____

Did you do any training/exercising one year ago? If so, what did you do?

_____

Are you currently involved in training/exercising? If so, what do you do?

_____

Appendix 3

The 1987 revised criteria for the classification of rheumatoid arthritis (traditional format)*	
Criterion	Definition
1. Morning stiffness	Morning stiffness in and around the joints, lasting at least 1 hour before maximal improvement.
2. Arthritis of 3 or more joint areas	At least 3 joint areas simultaneously have had soft tissue swelling or fluid (not bony overgrowth alone) observed by a physician. The 14 possible areas are right or left PIP, MCP, wrist, elbow, knee, ankle, and MTP joints.
3. Arthritis of hand joints	At least 1 area swollen (as defined above) in a wrist, MCP, or PIP joint
4. Symmetric arthritis	Simultaneous involvement of the same joint areas (as defined in 2) on both sides of the body (bilateral involvement of PIPs, MCPs, or MTPs is acceptable without absolute symmetry).
5. Rheumatoid nodules	Subcutaneous nodules, over bony prominences, or extensor surfaces, or in juxta articular regions, observed by a physician.
6. Serum rheumatoid factor	Demonstration of abnormal amounts of serum rheumatoid factor by any method for which the result has been positive in <5% of normal control subjects
7. Radiographic changes	Radiographic changes typical of RA on postero-anterior hand and wrist radiographs, which must include erosions or unequivocal bony decalcification localised in or most marked adjacent to the involved joints (osteoarthritis changes alone do not qualify)

*For classification purposes, a patient shall be said to have RA if he/she has satisfied at least 4 of these 7 criteria. Criteria 1 through 4 must have been present for at least 6 weeks. Patients with 2 clinical diagnoses are not excluded. Designation as classic, definite, or probable RA is *not* to be made.

PIP proximal interphalangeal joint
MCP metacarpophalangeal joint
MTP metatarsophalangeal joint

Arnett FC, et al. Arthritis and Rheumatism. The American Rheumatism Association 1987 revised criteria for the classification of Rheumatoid Arthritis. Vol. 31, No 3 (March 1988), 315-324

Appendix 4

Classification of Global Functional Status in Rheumatoid Arthritis

Class I	Completely able to perform usual activities of daily living (self-care, vocational, and avocational)
Class II	Able to perform usual self-care and vocational activities, but limited in avocational activities
Class III	Able to perform usual self-care activities, but limited in vocational and avocational activities
Class IV	Limited in ability to perform usual self-care, vocational, and avocational activities

Usual self-care activities include dressing, feeding, bathing, grooming, and toileting. Acovational (recreational and/or leisure) and vocational (work, school, homemaking) activities are patient-desired and age- and sex-specific.

Appendix 5

UNIVERSITEIT VAN PRETORIA
UNIVERSITY OF PRETORIA
YUNIBESITHI YA PRETORIA

essment Questionnaire

This questionnaire identifies information from you to provide a record of your health status

SCORING
1. Score each item within the 8 categories.
2. Select and add the highest score within each category
3. Divide the sum of the category scores by the number of answered categories.
4. 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.

(Subtotal 1	+	Subtotal 2)	÷	No. of answered categories	=	HAQ

Circle the one best answer for your usual abilities **DURING THE PAST WEEK**

	Without ANY Difficulty	With SOME difficulty	With MUCH difficulty	UNABLE to do	Total
1 DRESSING AND GROOMING					
Were you able to:					
1. Dress yourself, including tying your shoelaces and doing buttons?	0	1	2	3	
2. Shampoo your hair?	0	1	2	3	
2 GETTING UP					
Were you able to:					
1. Stand up from a chair without armrests?	0	1	2	3	
2. Get in and out of bed?	0	1	2	3	
3 EATING					
Were you able to:					
1. Cut up your meat?	0	1	2	3	
2. Lift a full cup or glass to your mouth?	0	1	2	3	
3. Open a new milk carton?	0	1	2	3	
4 WALKING					
Were you able to:					
1. Walk outdoors on flat ground?	0	1	2	3	
2. Climb up five steps?	0	1	2	3	
				Subtotal 1	

Please tick (✓) any of the following AIDS or EQUIPMENT that you usually use for any of these activities mentioned above:

	Walking stick		Wheelchair		Specially adapted chair
	Walking frame		Aids used for dressing (button hook, zip-puller, long-handled shoe horn, etc.)		Other (Please Specify)
	Crutches		Specially adapted utensils (such as for eating and cooking)		

Please tick (✓) any of the following categories for which you usually need HELP FROM ANOTHER PERSON:

	Dressing and Grooming		Walking
	Getting up		Eating

Circle the one best answer for your abilities **OVER THE PAST WEEK**

	Without ANY difficulty	With SOME difficulty	With MUCH difficulty	UNABLE to do	Total
5 HYGIENE					
Were you able to:					
1. Wash and dry your body?	0	1	2	3	
2. Have a bath?	0	1	2	3	
3. Get on and off the toilet?	0	1	2	3	
6 REACHING					
Were you able to:					
1. Reach up for and take down a 2.5 kg object (e.g. a bag of sugar) from just above your head?	0	1	2	3	
2. Bend down to pick up clothing from the floor?	0	1	2	3	
7 GRIPPING					
Were you able to:					
1. Open car doors?	0	1	2	3	
2. Open jars that have been previously opened?	0	1	2	3	
3. Turn taps on and off?	0	1	2	3	
8 ACTIVITIES					
Were you able to:					
1. Go shopping (supermarket, post office, bank etc.)?	0	1	2	3	
2. Get in and out of a car?	0	1	2	3	
3. Do domestic tasks such as vacuuming or gardening?	0	1	2	3	
				Subtotal 2	

Please tick (✓) any of the following AIDS or EQUIPMENT that you usually use for any of the activities mentioned above:

	Raised toilet seat		Bath rail
	Bathtub seat		Long-handled aids for reaching things
	Jar opener (for jars previously opened)		Long-handled aids in bathroom (e.g. a long handled brush for the body)
			Other (Please specify)

Please tick (✓) any of the following categories for which you usually need HELP FROM ANOTHER PERSON:

	Hygiene		Gripping and opening things
	Reaching		Shopping and domestic tasks

Patient Signature: ..... Date: .....

Appendices on CD

Appendix 6 T08165 HRV Normality Tests.docx

Appendix 7 T08165 HRV MANOVA using ln(HRV).docx

Appendix 8 T08165 HRV analysis 24 March.docx p69-71 and p74-76

Appendix 11 T08165 Confidence intervals

Appendix 12 T08165 Phase II HAQ Analysis p1-6

Appendix 9

Participant Informed Consent form: Rheumatoid Arthritis Group

AUTHORISATION TO PARTICIPATE IN A RESEARH PROJECT.

TITLE OF STUDY: Influence of water and land based exercise on the autonomic function, disease activity and functional capacity in females suffering from Rheumatoid Arthritis: Randomised Control Trial.

1. THE NATURE AND PURPOSE OF THIS STUDY

You are invited to take part in a research study. The aim of this study is to determine if endurance exercise will improve heart related problems, disease activity and functional capacity in patients with Rheumatoid Arthritis.

Motivation

Rheumatoid Arthritis is an inflammatory disease affecting the joints and other organs. Patients experience difficulty in performing activities of daily living and have a risk of heart related problems. Exercise is known to increase functional capacity and decrease heart related problems.

Further studies are needed to proof that this is true in Rheumatoid Arthritis patients.

2. EXPLANATION

- A Rheumatologist will confirm the diagnosis of Rheumatoid Arthritis.
- Information regarding the study will be given. Questions will be answered and then you will sign the Informed Consent.
- Certain measurements that will be done, will be explained to you, including:
    - Heart Rate Variability:
        - You will lie down in a supine position in a low noise area, at a comfortable temperature (±22 degrees Celsius) for 5 minutes.
        - A 10-minute ECG will follow. The first 5 minutes in a supine position and the next in an upright position. Evaluation of the autonomic control of your heart will be done on the sampled

RR intervals. The blood pressure will be monitored during both phases.

- CRP (inflammatory marker):
  - Blood test. Blood will be drawn from a vein in the arm.
- Biokinetic measurements:
  - Height/Body mass/Leg strength/Heart rate/Blood pressure/Walking test/Handgrip strength/Flexibility

- You will be asked to complete a questionnaire (Health Assessment Questionnaire). It will take about 10 minutes to complete.
- You will also be asked to complete a questionnaire on your medical history. This will take 20-30 minutes.
- You will be involved in an exercise programme. The exercise programme will consist of
  - Warm up
  - Walking or aerobic water exercise program, depending on the group you are in
  - Stretching
  - Cool down

The exercise will be done at a level at which you will still be comfortably able to talk (60-80% of your maximum heart rate)

- The exercise programme will last for 3 months. Patients who wish to continue with their exercise programme after the 3-month period, will be allowed to do so. All procedures will be explained and a biokineticist will oversee the programme.
- Depending on what group you are in, you will either do water exercises, land exercises or no exercises. This allocation will be random and you will be asked to accept your allocated position.

3. RISK AND DISCOMFORT INVOLVED

The only possible risk and discomfort involved is the taking of blood from a vein and the performance testing. There might be some muscle stiffness at the start of the exercise programme, but this will diminish.

4. POSSIBLE BENEFITS OF THIS STUDY

It is expected that the quality of life will improve, and that the risk for heart related problems would decrease.

In case of any medical emergency arising, medical treatment will be provided on the premises. Should any referrals be required, costs incurred by private patients will be referred to their medical aids. Patients who do not have medical aids will be referred to an approved state hospital.

5. CONFIDENTIALITY

All records obtained whilst in this study will be regarded as confidential. Results will be published or presented in such a fashion that patients remain unidentifiable.

PARTICIPANT

- I understand that I am being asked to take part in a research study. The aim of this study is to determine if endurance exercise will improve heart related problems, disease activity and functional capacity in patients with Rheumatoid Arthritis.
- I understand that if I do not want to participate in this study, I will still receive standard treatment.
- I may at any time withdraw from this study.
- I give my approval that results obtained may be published anonymously.
- **INFORMATION**
  If I have any questions concerning this study, I should contact:

  Dr DC Janse van Rensburg (Section Sports Medicine, University of Pretoria)

  (Tel: 012-420 6057. After hours: 083 305 6036)

- **CONSENT TO PARTICIPATE IN THIS STUDY**

I have read or had read to me in a language that I understand the above information before signing this consent form. The content and meaning of this information have been explained to me. I have been given opportunity to ask questions and am satisfied that they have been answered satisfactorily. I hereby volunteer to take art in this study.

Participant…….. 2008/……Date

Witness……..

Participant Informed Consent form: Healthy Control Group

AUTHORISATION TO PARTICIPATE IN A RESEARH PROJECT.

TITLE OF STUDY: Influence of water and land based exercise on the autonomic function, disease activity and functional capacity in females suffering from Rheumatoid Arthritis: Randomised Control Trial.

6. THE NATURE AND PURPOSE OF THIS STUDY

You are invited to take part in a research study. The aim of this study is to determine if endurance exercise will improve heart related problems, disease activity and functional capacity in patients with Rheumatoid Arthritis. We want to compare normal healthy controls such as yourself to people suffering from Rheumatoid Arthritis.

Motivation

Rheumatoid Arthritis is an inflammatory disease affecting the joints and other organs. Patients experience difficulty in performing activities of daily living and have a risk of heart related problems. Exercise is known to increase functional capacity and decrease heart related problems.

Further studies are needed to proof that this is true in Rheumatoid Arthritis patients.

7. EXPLANATION

- Information regarding the study will be given. Questions will be answered and then you will sign the Informed Consent.
- Certain measurements that will be done, will be explained to you, including:
    - Heart Rate Variability:
        - You will lie down in a supine position in a low noise area, at a comfortable temperature (±22 degrees Celsius) for 5 minutes.
        - A 10-minute ECG will follow. The first 5 minutes in a supine position and the next in an upright position. Evaluation of the autonomic control of your heart will be done on the sampled RR intervals. The blood pressure will be monitored during both phases.
    - Height measurement with a tape measure
    - Weight measurement with a standardised scale.
- You will also be asked to complete a questionnaire on your medical history. This will take 20-30 minutes.

8. RISK AND DISCOMFORT INVOLVED

None.

9. POSSIBLE BENEFITS OF THIS STUDY

Although you will not directly benefit by the study, your willingness to participate by having your Heart Rate Variability measured, might make it possible for us to improve the quality of life and increased health risks of patients with Rheumatoid Arthritis.

In case of any medical emergency arising, medical treatment will be provided on the premises. Should any referrals be required, costs incurred by private patients will be referred to their medical aids. Patients who do not have medical aids will be referred to an approved state hospital.

10. CONFIDENTIALITY

All records obtained whilst in this study will be regarded as confidential. Results will be published or presented in such a fashion that patients remain unidentifiable.

PARTICIPANT

- I understand that I am being asked to take part in a research study. The aim of this study is to determine if exercise will improve heart related problems, disease activity and functional capacity in patients with Rheumatoid Arthritis.
- I understand that if I do not want to participate in this study, I will still receive standard treatment.
- I may at any time withdraw from this study.
- I give my approval that results obtained may be published anonymously.
- **INFORMATION**
  If I have any questions concerning this study, I should contact:

  Dr DC Janse van Rensburg (Section Sports Medicine, University of Pretoria)

  (Tel: 012-420 6057. After hours: 083 305 6036)

- **CONSENT TO PARTICIPATE IN THIS STUDY**

I have read or had read to me in a language that I understand the above information before signing this consent form. The content and meaning of this information have been explained to me. I have been given opportunity to ask questions and am satisfied that they have been answered satisfactorily. I hereby volunteer to take art in this study.

Participant…….. 2010/……Date

Witness……..

Appendix 10

BCOMPLIANT CC

CERTIFICATE OF PARTICIPATION

THIS SERVES TO CERTIFY THAT

Dr. D.C. Janse van Rensburg

HAS ATTENDED AND SUCCESSFULLY COMPLETED A

GCP REFRESHER COURSE

IN PRETORIA

TRAINER SIGNATURE: RETHA BRITZ

06 FEBRUARY 2010
DATE:

CPD Accreditation Number: MDB015/002/01/2010 – 6 Ethics & 6 Clinical CPD Points

Materials Received at Training:

- ICH GCP Booklet
- SA GCP Booklet (2006)
- Presentations printed as hand-outs
- ABPI Guidelines
- World Medical Association: Declaration of Helsinki (Oct 2008)