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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