

## CHAPTER FIVE: DISCUSSION

- 5.1 CARDIAC AUTONOMIC FUNCTION BETWEEN HEALTHY PARTICIPANTS AND RA PATIENTS
- 5.2 EFFECT OF EXERCISE ON CARDIAC AUTONOMIC FUNCTION, DISEASE ACTIVITY AND FUNCTIONAL PARAMETERS IN FEMALES WITH RA
- 5.3 CONCLUSION

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<sub>28</sub>), 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<sup>(1)</sup>. 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<sup>2</sup>) (parasympathetic), but higher LF(ms<sup>2</sup>) 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<sup>(2,3)</sup>. 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<sup>(4,5)</sup>. According to Jouven et al (2005), patients with a resting heart rate of  $\geq 75$  beats per minute and no clinical evidence of cardiac disease have a 4-fold risk for sudden cardiac death<sup>(6)</sup>. 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<sup>(5,7)</sup>. 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<sup>(5,7)</sup>. 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<sup>(8,9)</sup>. Our RA study group had relative early disease (4.26 years disease duration), with moderate disease activity (DAS<sub>28</sub> 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<sup>(10)</sup> and Milovanovic using 10 minute recording periods showed differences for pNN50, RMSSD and HF(ms<sup>2</sup>) indicating less variability for the RA subjects<sup>(11)</sup>

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 dysrhythmogenic 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<sup>(5,7)</sup>. Both LF(ms<sup>2</sup>) and HF(ms<sup>2</sup>) 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<sup>(12,13)</sup>. The RA patients had a poorer response to posture change. Vagal withdrawal, indicated by RMSSD, pNN50, SD1 and HF(ms<sup>2</sup>), was significantly increased in the control group. Also, the indicators SD2 and LF(ms<sup>2</sup>), 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<sup>(13)</sup>, but it has been suggested that the parasympathetic nervous system has anti-arrhythmic properties<sup>(6,14)</sup>.

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 disrhythmogenic 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<sup>(15,16)</sup>. 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<sup>(15)</sup>. 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<sup>(17)</sup>.

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<sup>(18-27)</sup>. 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<sup>(18)</sup>. 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<sup>(24)</sup>. 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<sup>(21)</sup>. 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<sup>(27)</sup>. 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<sup>(28)</sup>.

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<sup>(29)</sup>.

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 dysrhythmias<sup>(30)</sup>. 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<sup>2</sup> 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”<sup>(31)</sup>. 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<sup>(32)</sup> 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<sup>(33)</sup>. For the purpose of this study, it was decided to make use of the VAS<sup>(34-36)</sup>, HAQ<sup>(37,38)</sup> and DAS<sub>28</sub> scores<sup>(39-41)</sup>, 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<sup>(42)</sup>, but Flint-Wagner reported a decrease in pain for their exercise group<sup>(43)</sup>. Observing within group changes from start to study completion, the exercise group had a significant improvement in the VAS in accordance to other studies<sup>(44,45)</sup>.

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<sup>(46)</sup> while others could not show any change<sup>(44,47-50)</sup>. Previous authors mentioned the fact that the HAQ might not be sensitive enough to capture changes<sup>(16,32,51)</sup>. 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<sup>(15,16,44,47,51-56)</sup>. 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<sup>(57)</sup>. The EULAR (European League against Rheumatism) response criteria on disease intervention are based on DAS<sub>28</sub>. These criteria require a patient to achieve a certain amount of improvement and also a particular disease activity state after intervention<sup>(33)</sup>. According to these criteria, our exercise group achieved a mean DAS<sub>28</sub> 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<sub>28</sub> being higher at study completion (Baseline DAS<sub>28</sub> 3.25; End of study DAS<sub>28</sub> 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<sup>(58,59)</sup>. 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<sup>(46,47,60)</sup>. Efficiency of movement and normal daily activities are dependant on functional range of movement<sup>(61)</sup>.

Interestingly, strength improved for both groups. A study by Bykerk and Keystone had similar results<sup>(62)</sup>. This occurrence has previously been explained by Hakkinen as a learning effect of repeated physical testing and variation in symptoms<sup>(63)</sup>. 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<sup>(47,53,60)</sup>. It is important to maintain muscle strength for normal functioning and joint stabilisation to prevent future deformities<sup>(64)</sup>.

Exercise programmes with the specific purpose of improving aerobic fitness have attracted attention in this population<sup>(65)</sup>. Previous studies made use of cycling<sup>(66,67)</sup>, aquatics<sup>(46,68)</sup>, dancing<sup>(69,70)</sup> and walking<sup>(46,71)</sup>. However, the combined use of aerobic and strength training has been the exercise programme of choice in recent research<sup>(32,47,52,72)</sup> and the ACR subsequently updated treatment guidelines to include dynamic exercise as part of the management<sup>(73)</sup>. 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<sub>2</sub> 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<sup>(19,21,23-25,27)</sup>. 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 ( $\pm 10.6$ )<sup>(74)</sup>. 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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