The effect of intensive physical training on cardiac autonomic variability

Factors that may influence the results

by

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Dedication

To my family; Japie, Thelani, Walter and Tiaan

Julle het dit moontlik gemaak

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Summary

Candidate: CC Grant

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The study dealt with the influence of exercise on the autonomic nervous system (ANS) and with factors that may influence the results. ANS function was measured in 183 young, healthy participants, before and after a twelve week standardised, medium-to-high volume physical training programme, in a controlled environment. The effects of the training programme were assessed on resting ANS functioning, during standing and on the response to an orthostatic challenge. ANS function was assessed by means of heart rate variability (HRV) determination. HRV was quantified by three different analytical techniques, i.e., time domain analysis (RR, STDRR, RMSSD and pNN50), frequency domain analysis (LF,LFnu, HF, HFnu and LF/HF) and Poincaré plot analysis (SD1 and SD2). The influence of technical variations, such as variations in tachogram length and period of recording, as well as the influence of pre-intervention values of physiological variables, such as blood pressure, BMI, VO_2max and ANS functioning, on the response to the exercise intervention, were assessed.

Results on the exercise intervention showed:

- Increased supine, as well as standing, parasympathetic cardiac control as indicated by time domain, frequency domain and Poincaré analyses.
- Decreased sympathetic control in the supine position and increased sympathetic control during rising and standing.
- Increased vagal withdrawal, as well as increased sympathetic control during the first phase of the orthostatic response to rising from the supine position.
- Only an exercise-induced increase in sympathetic control when the orthostatic response was measured as the difference between standing and supine.

Results on exercise-induced changes in sympathetic and parasympathetic ANS control differ, depending on posture. It is suggested that the effects of an exercise intervention on sympathetic and parasympathetic ANS control of the heart should be assessed from measurements in the supine, in the standing, and in response to an orthostatic stressor. It is further suggested that information obtained during rising will give additional information on the response of the ANS.

This study showed that technical as well as physiological variations may lead to differences in the outcome of HRV studies. Results from the technique evaluation showed that the length and period of tachogram recordings should be standardised, especially during an orthostatic challenge. Starting the recording too late will miss out on the initial response to a change in body position. Longer recording times will represent the mean of HRV values obtained during the orthostatic response and that obtained after stabilisation in the standing position. Investigations into the influence of pre-intervention physiological status on exercise-induced changes showed:

- Baseline ANS functioning is a significant contributor to variations in the ANS response to an exercise intervention.
- Pre-intervention values for physiological variables, such as blood pressure, BMI and VO_2 max do not have a significant influence on the HRV response to exercise in young, healthy individuals of average fitness
- Regression analyses confirm the correlation results, *i.e.* that baseline ANS function is a significant predictor of the ANS response to exercise.
- However, regression results indicated that the combination of pre-intervention values for $LFms^2$, $HFms^2$, BMI, VO_2 max, gender and blood pressure, contributes only between 12.83% and 29.82%, depending on the HRV variable, to the exercise induced changes in the autonomic nervous system.

Key words:
Exercise effects, autonomic nervous system, cardiac control, heart rate variability, standardization.

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CHAPTER 1 INTRODUCTION

Exercise is accepted to be of physical and psychological benefit for normal healthy individuals. However, it is also known to be of benefit in many types of physical and psychological disorders where it is associated with beneficial metabolic, psychological and neuro-vegetative effects.1

Research has shown the benefits of exercise and training in controlling risk factors for coronary artery disease and in decreasing its incidence. Exercise studies in cardiac and hypertension patients showed that exercise may result in positive changes in the cardiovascular functioning.2,3,4 Population-based studies have shown regular physical activity to be inversely proportional to long-term cardiovascular mortality when controlled for the presence of other risk factors in both men and women.5,6 The risk of coronary artery disease in physically inactive individuals are said to be twice that of their active counterparts. Importantly, the relative risk for cardiovascular mortality in the least fit or least active compared to the most fit or active, approaches a factor of six.5

Even though exercise is often beneficial in individuals with cardiovascular problems, it is also in this group where it can have the more serious negative consequences. It is, for instance, reported that acute myocardial infarction may be precipitated by exercise. Studies have shown the relative risk of myocardial infarction within 1 hour after strenuous physical exertion, in those at risk, to be two to six times greater than that of comparable individuals who are sedentary or less active during the same time.7,8,9 It is also known that endurance training and the

presence of arrhythmias are linked by the fact that the 'Athlete's heart' (a physiological adaptation to extreme training), is a risk factor for the development of atrial fibrillation. Athlete's heart is a well known consequence of endurance sport practice with symptoms such as dilatation, hypertrophy and above average enhanced vagal tone, indicating autonomic nervous system dysregulation.[10] Heidbüchel hypothesized that long-lasting, competitive endurance activities may induce right ventricle structural changes, leading to 'acquired right ventricular dysplasia'- thus increasing the risk of ventricular arrhythmias and sudden death.[11] There are also reports of endurance athletes showing enhanced parasympathetic activity that may co-exists with cardiac sympathetic excitation, also implicating autonomic nervous system (ANS) dysregulation.[12]

As indicated by the above, high intensity exercise programs might require changes in the cardiovascular and autonomic nervous system that are not beneficial to the person. This poses the problem of the identification and measuring of what is and what is not healthy behaviour. In 2003 Heidbüchel and co-workers asked the fundamental question: what is the reasonable limit for the practice of sport and exercise?[11] Mont and Brugada indicated the same year that endurance training may have harmful consequences for the heart, but that this needs to be confirmed by case-control studies of non-selected populations.[13]

Heart rate variability (HRV) assessment is a popular tool for the assessment of autonomic cardiac control. Many publications exist on the effect of exercise on HRV and by implication on cardiac functioning. As will be seen below, results on the effects of exercise on the autonomic control of the heart are often

contradictory and incomplete in the normal population and in disease. In order to understand and employ the effects of exercise in patients with cardio vascular disorders it is of primary importance that agreement should be reached on the effects of exercise in the normal healthy population.

Autonomic control of the heart by sympathetic and parasympathetic modulation, is amongst others, assessed by the variability of heart rate[14-20] and blood pressure.[21,22] Different frequency peaks reflect specific physiological stimuli and it is possible to estimate the involvement of the autonomic nervous system (ANS) influence and balance on heart rate (HR) regulation.[14,23,24] With power spectral analysis of HR, two characteristic peaks between 0.04 Hz and 0.15 Hz (A) and between 0.15 Hz and 0.5 Hz (B) are used to quantify the autonomic balance in terms of the low-frequency (LF)/high-frequency (HF) ratio.[14,24,19] Peak A is found in the region of Mayer waves (0.1 Hz) and is situated in the so-called LF area. It appears to be linked to the combined activities of the sympathetic and parasympathetic branches of the ANS. Peak B is synchronous with respiration, reflects vagal activity, is situated in the so-called HF area and also gives an indication of respiratory sinus arrhythmia (RSA).[14,19] During measurement of systolic blood pressure variability (BPV) the LF peak corresponds to sympathetic activity, while the HF peak is determined by mechanical effects of respiration on intra-thoracic pressure and cardiac filling.[21,22] The variability in blood pressure and the corresponding physiological stimuli are difficult to identify. Indications are that the very low frequencies (≤0.04 Hz) are influenced by vascular tone, endothelium factors and thermoregulation, while the LF peak (0.07 - 0.15 Hz) relates to sympathetic activity and represents vasomotor tone.[22,23] Baro-receptor sensitivity

(BRS) reflects mainly vagal modulation of the HR by the arterial baroreceptors and the magnitude of response in heart beat interval to a change in blood pressure (ms/mmHg).[24]

In addition to frequency domain analysis, the HRV can be quantified with normal descriptive statistics called time domain analysis and by the Poincaré Plot analysis, also called return maps. The latter being a diagram (scatter gram) in which the RR intervals of the tachograms are plotted as a function of the preceding intervals.[16]

1.1 INCONSISTENCIES IN REPORTS ON EXERCISE INDUCED CHANGES IN THE AUTONOMIC CONTROL OF THE HEART

The effect of exercise on the ANS as measured by cardiovascular variability quantification (HRV and BPV) can be summarised in three categories: the response of the ANS measured during a bout of exercise, [25-34] directly after a bout of exercise,[31,32,35-42] and the long-term effect of regular exercise on the ANS (Table 1-1).[34,42-77]

The publications listed below and in Table 1-1 are included to indicate the differences in results published with the aid of signs (↑,↓,↔) for the same variability indicators and is not a comprehensive meta-analysis of published material on the topic.

1.1.1 THE RESPONSE OF THE ANS MEASURED DURING A BOUT OF EXERCISE

A review by Sandercock et al. on HRV measured during exercise showed that the interpretation of variability measurements is difficult because indicators reflecting

sympathovagal interactions at rest do not behave as expected during exercise and that the increased respiratory effort has a confounding effect on HF bands.[25] They concluded that standard HRV analysis during exercise is not recommended but that non-linear analyses methods and the use of coarse grain spectral analysis has potential and should be investigated.

Banach *et al.* also expressed doubt on the applicability of the HRV power-spectrum analysis, with its present interpretation, to assess the sympathovagal interaction during exercise.[26] However, other authors encouraged the use of HRV components at rest and during exercise as prognostic indicators, but called for the refinement of exercise measurements.[27] Eryonucu *et al.* used HRV as an indicator of ANS activity before, during and after exercise in a comparative study.[28] Two other studies reported increased sympathetic influence (measured by LF and LF/HF) on autonomic cardiac control during graded exercise,[29,30] including increased, peripheral, vascular sympathetic activation at 30% of maximum exercise in the study by Saito and Nakamura.[30] These results were in direct conflict with studies indicating significant suppression of both SNS and PNS autonomic cardiac control during graded exercise measured by the LF and HF of the power spectrum of HRV.[32,31] In 1991 Yamamoto *et al.*[33] reported decreased PNS activity (HF) and unchanged SNS activity (LF/HF) up to 100% of the predetermined ventilatory threshold (T_{vent}), with an abrupt increase in SNS activity (LF/HF) only at 100% T_{vent}. Perini and Veicsteinas[34] concluded that changes in HF and LF power and in LF/HF observed during exercise do not reflect the decrease in vagal activity and the activation of the sympathetic nervous system (SNS) at increasing loads; neither do fitness level, age and hypoxia have any influence.

However, exercising at medium-high intensities in the supine position did produce measurable increased power in LF (combination of vagal and sympathetic influence).

1.1.2 THE RESPONSE OF THE ANS MEASURED AFTER A BOUT OF EXERCISE

There is still no general agreement on the activity of the ANS as measured during recovery. Heffernan *et al.* reported that cardiovascular variability measured during recovery from a single bout of endurance exercise indicated that the total power of HRV did not alter compared with significantly reduced total power found after resistance exercise. [35] However, the LF/HF ratio was significantly increased after both resistance and endurance exercise, indicating increased SNS (LF) and/or decreased PNS (HF) influence.[35] This corresponds with results published by Terziotti *et al*. who found a reduced HF (vagal) component of HR and decreased BRS during 15 minutes of recovery.[36] Another study[37] also found suppressed vagal (HF) activities during 10 minutes of recovery after 100% of the individual ventilatory threshold compared with baseline values. Raczak *et al.* found no differences in HF and LF activities between pre- and post-exercise measurements, but increased BRS and overall HRV as measured by SDNN (standard deviation of all intervals) after exercise.[38] However, Kamath *et al.*[31] and Figueroa *et al.*[42] reported significant increased LF power during post-exercise recovery. This contrasts with findings by Arai *et al.* who reported significantly decreased HR power at all frequencies compared with baseline values in normal subjects.[32] Decreased BRS and HRV after exercise were also reported in other studies.[39,40] Lucini *et al.* reported that ageing progressively reduces the cardiac autonomic excitatory response to light exercise.[41]

1.1.3 LONG-TERM EFFECT OF REGULAR EXERCISE ON THE ANS

Table 1-1 shows findings on the long-term effect of regular exercise on the ANS. [34,42-77] Techniques used to estimate cardiovascular variability were mostly time domain and spectral analysis of HRV. BRS was quantified by means of sequence technique and the alpha index, spectral analysis of BRS and also BRS by means of the slope of the baroreflex sequences and transfer function gain.

Table 1-1 Examples of the regular / long term exercise induced ANS responses reported for the same HRV indicators

Ref	First author	Participants	Review, intervention or cross sectional study	Main Results
42	Figueroa	8 female obese patients with T2D 12 female obese patients without T2D	16 weeks training	Spectral analysis of HRV BRS via sequence technique ↔HRV and BRS: no baseline changes
43	Spierer	48 healthy subjects & HIV patients (38 males)	Cross-sectional design	Spectral analysis of HRV BRS via alpha index; ↑BRS increased, ↑HF ↓LF/HF
44	Verheyden	14 sedentary men 15 controls	Intervention 1 year training	Spectral analysis of HRV ↔LF, HF, LF/HF
45	Martinelli	11 sedentary men 10 cyclists	Cross-sectional design	Spectral analysis of HRV ↑SDNN ↔LF, HF: SNS/PNS↔
46	Sharma	25 healthy males	15 days exercise training	Time domain and spectral analysis of HRV ↔HRV indicators
47	Buchheit	55 healthy subjects	Cross-sectional design	Time domain and spectral analysis of HRV ↑HF, RMSSD, pNN50
48	Raczak	24 healthy subjects (22 males)	Longitudinal design Long term training	Time domain and spectral analysis of HRV, spectral analysis of BRS ↑SDNN, pNN50, RMSSD, ↑Total power and LF ↑BRS
49	Okazaki	10 healthy sedentary seniors, 10 masters athletes, 11sedentary young men	Longitudinal (12 months) & Cross-sectional design	Spectral analysis of HRV BRS via transfer function gain ↑SDRR, LF, HF ↑BRS

Ref	First author	Participants	Review, intervention or cross sectional study	Main Results
50	Melo	41 healthy males	Cross-sectional design	Time domain and spectral analysis of HRV ↑RMSSD ↓HR
51	Goldsmith	NA	Literature review	Review ↓SNS activity ↑PNS activity
52	Goldsmith	37 healthy subjects	Cross-sectional design	Spectral analysis of HRV ↑HF
53	Kiviniemi	17 healthy males	8 weeks training	Spectral analysis of HRV ↑HF
54	Cooke	11 healthy males	4 weeks training	Time domain analysis of HRV, BRS; ↑SDRR ↑BRS
55	Costes	21 COPD patients, 18 healthy subjects	8 weeks rehabilitation programme	BRS via the slope of the baroreflex sequences between systolic blood pressure changes ↑BRS
56	Monahan	133 healthy males	Cross sectional and 3 months intervention	BRS via linear regression between BP en RR intervals during a Valsalva maneuver ↑BRS
57	Carter	Healthy participants, effects of age, gender	Review	↓SNS activity ↑PNS activity
58	Iellamo.	7 healthy subjects	Longitudinal design, seasonal training	Spectral analysis of HRV BRS via the sequences method 100% training load reverse effects: ↑LF,↓HF, BRS↓
59	Bowman	26 healthy subjects (16 males)	6 weeks aerobic training	BRS via the alpha index ↔BRS
60	Nagai	305 healthy subjects (167 males)	12 months exercise	Spectral analysis of HRV ↑LF, ↓HF
61	Pigozzi	26 female athletes	5 weeks training	Time domain and spectral analysis of HRV; ↔Time domain ↔ LF, HF (daytime)
62	Gulli	11 healthy females	6 months training	Spectral analysis of HRV and BPV ↑BRS ↑LF (RR), LF (SAP)
63	Goldsmith	16 healthy males	Cross-sectional design	Report conflicting results Spectral analysis of HRV ↑HF
64	Hautala	51 healthy men	8 weeks training	Baseline vagal (HF) influence determines effect of exercise training
65	Laoutaris	23 chronic heart failure patients	10 weeks training	↔HRV markers
66	Billman,	NA	Literature review	↑parasympathetic regulation, ↓sympathetic activity
67	Borghi-Silva	40 COPD patients	6 week training	↑ sympathetic ↑ parasympathetic

Ref	First author	Participants	Review, intervention or cross sectional study	Main Results
68	Soares-Miranda	84 adults	Cross sectional	↑ vagal HRV
69	Sridhar	52 normotensive & 53 hypertensive diabetic patients	12 months training	↑ HRV
70	Cornelissen ,	36 healthy subjects (17males)	3x10 week crossover design	↓ HR ↓ ↔sympathovagal balance
71	Kouidi	44 hemodialysis patients (20 controls)	1 year training	↑ SD of RR intervals ↑MSSD ↑pNN50
72	Knoepfli-Lenzin	57 healthy males	Longitudinal design	↑ supine heart rate variability
73	Routledge	NA	Literature review	↑vagal tone ↓ sympathetic activity
74	Albinet	24 healthy subjects (11 males)	12 weeks training	↑ vagal-mediated HRV ↑SDRR, ↑RMSSD, ↑HF power
75	Riesenberg	45 lung cancer patients	28 days rehabilitation	↑HRV, ↑ RMSSD ↓ HR
76	Sato	20 coronary heart disease patients (13 males)	1 year Tai Chi conditioning	↑BRS ↔HRV
77	Kingsley	9 Fibromyalgia subjects, 15 health subjects (24 females)	12 weeks resistance exercise training	No significant effects of RET on HRV at rest or post exercise
78	Sandercock	Healthy subjects	Review	HF power↑ RR interval↑
79	Hautala	Clinical and sport	Review	↑vagal tone ↓ Sympathetic inconsistent
80	Sandercock	28 patients (21 males)	8 weeks of cardiac rehabilitation	LFpower↑, HF↑, SDNN↑ RMSSD↑, LF:HF ratio↔
81	Laing	Patient coronary artery disease n=17	Intervention: Phase2 cardiac rehab	Recovery vagal influence↑ Resting RMSSD↔
82	Montano	Clinical and experimental populations	Review	↑Parasymp ↓ Sympathetic
83	Billman	Clinical and experimental populations	Review	↑parasymp=enhance electrical stability
84	De Meerman	Aging population	Review	↑vagal tone in old age
85	Gademan	Clinical populations	Review	↓ Sympathetic sympathoinhibitory effects in CHF
86	Montano	Clinical populations	Review	↑Parasymp ↓ Sympathetic

Ref: Reference number, LF: Low frequency, HF: High frequency, SDNN: Standard deviation of all intervals, Ptot: Total frequency power, pNN50: Percentage of successive interval differences greater than 50ms, SNS: Sympathetic nervous system, PNS: Parasympathetic nervous system, SAP: Systolic arterial pressure, ↑:increase, ↓:decrease, ↔:no changes in variability indicators

Articles on the effect of a training program over a period of time also showed a wide range of results. One study reported no change in baseline baro-receptor sensitivity (BRS) and HRV values after a 16-week fitness programme, [42] while another found increased BRS when comparing fitness levels.[43] Aubert *et al.* also found no evidence of significant changes in resting autonomic modulation of the sinus node after a low-volume, moderate-intensity 1-year exercise programme.[44] Comparing 11 young sedentary participants and 10 endurance-trained cyclists Martinelli *et al.* found no difference in power-spectral components of HRV at rest.[45] However, a lower HR and higher values for time domain HRV indicators were reported during rest and head-up tilt, concluding that resting bradycardia seems to be more related to changes in intrinsic mechanisms than to ANS control modifications. Sharma *et al.* found no statistically significant changes in autonomic cardiovascular control of adult men measured by HRV after a physical training programme of 15 days.[46] Perini and Veicsteinas[34] reported no influence of factors such as age and fitness level, while Bucheit and Gindre[47] showed that modifications in autonomic activities induced by training are visible in HRV power spectra at rest. Rackzak *et al.*[48] reported parasympathetic nervous system (PNS) dominance by measuring HRV and increased BRS after long-term exercise training. Another study reported increased HRV and BRS in Masters Athletes compared with decreased values for sedentary seniors. [49] Several other studies also concluded that regular physical activity increases vagal influence on the HR and BRS, while the sympathetic tone may be decreased.[50-59] However, Iellamo *et al.*[58] found a reversal of these effects after a period of training at 100% training load. Very intensive training shifted the CV autonomic modulation from PNS toward SNS predominance. Increases were reported in all components of HRV

after a 1-year exercise training programme in children who initially had low HRV.[60] In 2001 Pigozzi *et al.*[61] found that a 5-week exercise training period in female athletes increased the sympathetic nervous system (SNS) cardiac modulation, which may coexist with relatively reduced or unaffected vagal modulation. Gulli *et al.*[62] reported increased LF reactivity (SNS) and BRS after a moderate aerobic training programme in older women, while Goldsmith *et al.*[63] noted that, although exercise training may increase PNS activity, studies report conflicting results.

1.1.4 EXAMPLES OF REPORTS ON EXERCISE AND HRV LITERATURE AFTER 2005

A trend indicating increased resting vagal cardiac control is visible in reports on exercise induced changes measured by HRV,[73,74,78,79,80,81] with overall increased HRV,[69,71,72,75] accompanied by a possible decrease in ↓sympathetic activity.[66,67,73] Studies reporting no effect on HRV markers,[65,76,77] are few and seems to be linked to the exercise intervention intensity and also the specific type of exercise intervention. For example Tai Chi conditioning and resistance training did not show significant changes in HRV indicator values.[76]

In 2005 Sandercock *et al.* reviewed existing literature and came to the conclusion that significant exercise induced increases in RR interval and HF power are influenced by age and suggest that training bradycardia is caused by factors other than just increased vagal modulation.[78] Intervention results published in 2007 Sandercock *et al.* showed increases in sympathetic and parasympathetic HRV indicators after an eight week rehabilitation program.[80] A review by De Meerman and Stein (2006) reported the potential benefit of increasing or maintaining fitness in order to slow the decline of parasympathetic control of HR with normal aging.[84] Gademan *et al.* concluded that exercise has beneficial direct and reflex sympatho-

inhibitory effects in chronic heart failure (2007).[85] Montano *et al.* (2009) commented on moderate exercise training that may result in overall improvement in cardiac vagal control and reduced sympathetic activation in hypertensive patients who feature clear signs of elevated sympathetic activity.[86] According to Billman *et al.* endurance training alter autonomic nervous system activity by an apparent increase in cardiac parasympathetic tone coupled with decreases in sympathetic activity.[83] They suggested that the training bradycardia in both healthy subjects and patients with cardiovascular disease merits further investigation. A review by Routledge *et al.* (2010) on the use of exercise therapy as a method of HRV modification in clinical populations, reported that a shift toward greater vagal modulation may positively affect the prognosis of these individuals.[73]

Many of the above mentioned reports (Table 1-1) and citations were based on supine HRV indicator values using only time domain and frequency domain analysis techniques.

Many factors in HRV analysis have the potential to lead to inconsistencies in results. Some studies used non-homogeneous participant groups with regard to age, gender and BMI, while, in a number of manuscripts, such information is not even mentioned. Factors generally not taken into consideration include baseline blood pressure, blood cholesterol, diet, fitness and other physiological characteristics. Other factors that could have an influence include the duration and intensity[37] of the training programs, as well as the type of exercise (endurance or resistance).[35] When developing standardised procedures, inter-

individual differences, duration and intensity of the exercise program, and the choice and implementation of a specific variability analysis technique should be carefully planned. Note should be taken of the specific techniques used when trying to compare values obtained by different laboratories. It may be incorrect to compare ANS results from publications where different techniques were employed. In addition to the type of analytical techniques used, elements in the practical implementation could very well also have an influence. Differences in tachogram length and period of recording used for analysis may contribute to controversies. The Task Force recommended that sampling time (tachogram) for short term HRV analysis should be 5 minutes,[19] but different time windows are often selected by different authors, for example: 2 minutes, 5 minutes, 10 minutes, 15 minutes. HRV is known to be often non-normally (positively skewed) distributed. However non-parametric analytical techniques are sometimes used to analyse the data.[66] This may contribute to erroneous assumptions of statistical significance. Another possible explanation for conflicting results is that the individual's response may be greatly influenced by the baseline cardiovascular autonomic function, thus producing large inter-subject variation in the conventional non-spectral and spectral measures of cardiovascular variability.

Most studies incorporated in Table 1-1, used traditional measures of variability, such as time and frequency domain analysis. However, it is known that non-linear phenomena are also involved in cardiovascular control.[65] Therefore, it is of paramount importance that studies, using HRV as indicator of exercise induced changes in the ANS, should include analysis techniques that acknowledge this fact and non-linear measurements should be reported together with traditional

measures. Examples of techniques that measure these aspects include the measurement of fractal scaling components (describes the fractal-like correlation properties of R-R interval data) and ApEn (quantifies the amount of complexity in the time series data). [65] Another technique is the Poincaré plot where The RR intervals of the tachograms are plotted as a function of the preceding intervals. Examples of non-linear methods are discussed in Chapter 2.

The above overview demonstrates the wide variety of results published on the effect of training on the ANS as measured by cardiovascular variability indicators. It is clear from the results that standardization and refinement of these measuring tools are essential to produce repeatable results that can be used as references in other studies. This is necessary as these measurements are increasingly employed in studies ranging from investigations of central autonomic regulation; to studies exploring the link between psychological processes and physiological functioning; to the indication of ANS activity in response to exercise, training and overtraining. Much more research needs to be done to fully describe and accurately quantify the effect of exercise on the ANS.

In summary it can be said that the majority of recent review articles and individual research reports indicate increases in resting vagal cardiac control after exercise interventions as measured by HRV. [73,78,79,80,81] However, little is known about the influence of exercise on standing HRV or sympathetic cardiac control.[79] Claims of lower exercise induced sympathetic outflow as measured by HRV remains controversial as there is no single HRV indicator that represents pure sympathetic outflow.[83]

The fact that the complex nature of the interaction between ANS function and exercise may not be fully explained by only one or two HRV indicator or in one position (such as the supine position), is not realized by many HRV users and may contribute to these inconsistent results. In the supine position cardiac control is mainly controlled by vagal outflow, while during an orthostatic stressor the ANS balance is tipped towards sympathetic control.[82] As most reported exercise induced changes in RR intervals are measured only in the supine position, these changes may not depict the complete picture of exercise induced changes in the ANS. Measurements taken in the standing position may reveal important information on the sympathetic branch of the ANS that is not evident in the supine position.

1.2 AIMS AND HYPOTHESES

The first aim of this study was to assess the influence of a standardised, intensive, physical training programme, in a controlled environment, on resting autonomic nervous system (ANS) function and on the response to an orthostatic challenge, in a young healthy population. Analytical techniques used were time domain, frequency domain and non-linear (Poincaré) analysis of heart rate variability (HRV). It was hypothesized that results of exercise induced changes on ANS are dependent on the body position and should be assessed not only in the resting position but also during standing and during an orthostatic stressor. It was also hypothesized that it is possible to better distinguish between exercise induced changes in vagal and sympathetic influence by taking measurements in different body positions. Results are reported and discussed in Chapter 5.

The second aim was to investigate factors that may influence the results of HRV studies. This included technical aspects such as the assessment of the importance of tachogram length, and period of recording, as well as the influence of baseline physiological characteristics, on the response to an exercise intervention. The results from the first part of the second aim, i.e., the assessment of the influence of tachogram length and period of recording, were necessary for the investigation of the influence of the exercise intervention. It was therefore completed before the latter and appears in the thesis in Chapter 4, preceding that on the exercise intervention (Chapter 5).

Blood pressure, fitness, body mass index (BMI) and baseline autonomic function were included for the investigation of physiological factors that may influence the results of HRV studies. It was hypothesized that baseline/pre-intervention systolic blood pressure (), diastolic blood pressure (), fitness (VO_2max), BMI, as well as the pre-intervention status of the autonomic nervous system, as reflected by HRV indicators, correlate significantly with the exercise induced response of HRV indicator values (ΔHRV = Post HRV indicator - Pre HRV indicator value). Results are reported and discussed in Chapter 6.

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CHAPTER 2 THEORETICAL BACKGROUND ON HEART RATE VARIABILITY QUANTIFICATION

2.1 THEORETICAL BACKGROUND

As this study deals primarily with HRV, a short overview on the theoretical background of HRV quantification is presented in this chapter.

2.1.1 HEART RATE VARIABILITY

An oscillation around a mean value is found in the interval, measured in milliseconds (ms), between consecutive heartbeats (measured as RR intervals), as well as between consecutive instantaneous heart beats. This oscillation, in both instantaneous heart rate and RR intervals (time between QRS complexes), is known as heart rate variability (HRV). The principle behind the variable regulation of the heart rate is to maintain homeostasis. The autonomic nervous system reacts, via activity of the sympathetic and parasympathetic branches, to external and internal influences to regulate the heart rate.[1,2]

It follows that the activity and integrity of the autonomic nervous system can be assessed by the quantification of various aspects of heart rate dynamics, associated with beat-to-beat fluctuations. Interpretation of this data is used as a non-invasive window on the dynamic interplay between sympathetic and vagal control of the heart. [3] It is a tool for assessing the interaction between psychological states, autonomic control, and the patho-physiology of diseases affecting autonomic function. HRV is also used to quantify individual differences in

adrenergic reactivity during exposure to stressors and as an independent predictor of all-cause mortality.[4]

2.1.2 MEASUREMENT OF HRV

2.1.2.1 Duration of recording

The starting point for any HRV analysis is to obtain a set of measurements of the interval between consecutive heartbeats (ms), or a set of instantaneous heart rates (beats/min). According to the recommendations of the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, the duration of the recording can extend from as short as 3 minutes to 24-hour recordings.[1,2,3]

Good frequency resolution can only be obtained by a sufficiently long and stationary recording period. Based on signal processing theory, a recording duration of at least ten times the wavelength of the lowest frequency component is recommended. [1,9] In order to capture the biological rhythms that in general vary from cycle to cycle, recordings should be long enough to sample across these variations. Recordings of not less than 1 minute are usually recommended to assess high frequency (HF) components and of at least 2 minutes are needed to investigate the low frequency (LF) component. Five minutes recording time is often used as a standard in clinical studies. [1]

From this it may be deducted that longer term recordings may have the advantage to observe the whole spectrum of HRV, from high frequency (0.15-0.4Hz) to the very low frequency (0.0033-0.04Hz).[1] However, this may lead to a violation of the

requirement for stationary signals. Stationarity is important because irregular or slow trends in a data series can lead to misinterpretation of the data. Biological rhythms, for example respiratory sinus arrhythmia (RSA), often vary over time thereby violating the assumption of stationarity.[1,3] Non-stationarity can be reduced by maintaining the test and subject conditions as stable as possible for the whole recording period. Recording periods (tachograms) must be just long enough to extract periodicities of interest, as the probability of non-stationarities increases with sample time length.[1,3].

2.1.2.2 Signal Processing

The discrete, unevenly spaced time event series produced from the series of RR intervals is called a tachogram. The information contained in the tachogram forms the main data pool for all the HRV analysis techniques used during this study.

Artifacts, that is, missed R-waves or spurious detections, from a variety of sources are able to contaminate the tachogram.[5,6] Resolution of these artifacts is necessary to prevent seriously biased results. Artifact-laden epochs in a RR series may not be simply deleted because this would disturb the continuity of the series that is necessary for analysis of rhythmical variations. The large deviations in the RR intervals caused by artifacts, can be visually detected in the tachogram, or an artifact-detection algorithm can be used to perform swift, unbiased processing of data. A combination of visual and algorithm techniques is seen as optimal.[7,8]

In this study, R-R interval data was automatically filtered by the HRV analysis software to eliminate spurious peaks, and interpolation algorithms was used for replacing beats to be corrected by the mean of a combination of preceding and following beats.

2.1.3 HRV ANALYSIS

A vast array of measures has been introduced into the field of HRV analysis. Some are purely statistical and other describes directly particular quantities of clinical interest. HRV quantification can be approached using normal descriptive statistics called time domain analysis. These relative straightforward calculations are able to show the data distribution, but do not support quantitative assessment of the autonomic nervous system activity as compared to, for example, frequency domain analysis and non-linear analysis (Poincaré plot analysis).

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The methods used in the evaluation of HRV can be broadly grouped into three categories, namely time domain, frequency domain and non-linear analysis. In each group, a number of different HRV indicators can be calculated:

1. Time Domain Analysis[1,3,9]
   - Statistical Methods
   - Geometric Methods

2. Frequency Domain Analysis [9,10,11]
   - Auto regression
   - Fast Fourier transforms

3. Non-linear Analysis[12-16]

- Spectral slope in the log-log scale
- Correlation dimension
- Kolmogorof entropy
- Approximate entropy
- Lyapunov exponents
- Spectral Coarse Graining
- Poincare plots[3]
- Complex demodulation / Homomorphic filtering[12]
- QIS-A (Quartile deviation of integrated and subtracted fluctuation)[13]
- Detrended fluctuation analysis[14]
- Higher order spectral methods[15].
- Alpha-stable distributions[16]

The following methods of analysis, used in this study, are described below:

- Time domain analysis (Statistical method)
- Frequency domain analysis
- Non-linear Analysis (Poincare plot analysis)

2.1.3.1 Time Domain Analysis

Analysis of data available in the tachogram by using time domain parameters, is done easily on long and short time epochs.[1-3] A limitation is the lack of discrimination between the activity of the sympathetic and parasympathetic (vagal) branches of the autonomic nervous system. However some of the indicators (RMSSD, NN50, pNN50) determined with time domain are highly

correlated to high frequency (HF) power in the frequency domain analysis which is believed to represent pure vagal modulation.[1] Time domain parameters include:

a) Average heart rate (HR) in beats per minute.
b) The average RR interval, (mRR also depicted as mNN) in ms.
c) Standard deviation (SD) of all the NN intervals (SDRR or SDNN) in ms over the recorded time interval (tachogram data). Mathematically, heart rate variance calculated as $(SDNN)^2$ and the total power of spectral analysis are identical. In practice however, correspondence between SDNN and the total power depends on data processing, e.g. treatment of ectopic beats, and interpolation. SDNN is normally calculated over a 24-hour period and represent short as well as log term influences.[1]
d) The standard deviation of the mean NN intervals (SDANN), averaged over 5-minute periods within a longer recording (24 hours) in msec. As SDANN values are obtained from successive short 5-minute periods, it can only estimate changes in heart rate caused by cycles shorter than 5 minutes
e) The square root of the mean of the sum of the squares of differences between adjacent NN intervals (RMSSD), in msec.
f) The number of successive NN intervals, which differ by more than 50 msec (NN50).
g) The proportion of NN50 (pNN50) in the entire recording in %.

According to the report from the Task Force of the European Society of cardiology, the selection of variables used should be determined by the aim of the study.[1] Time domain measures recommended for short term recordings (shorter

than 20 minutes) are NN50, pNN50 and RMSSD. From these pNN50 and RMSSD were calculated for the current study. Although not HRV indicators for short period tachograms, heart rate (HR), standard deviation of the heart rate (STDHR), RR interval (RR) and the SDRR are included in all tables of the study.

The examples in Table 2-1 contain typical time domain variable values, found in the literature.[9] Mean NN, SDNN, RMSSD, and pNN50 values are given. These values were obtained from a control group of 10 sedentary individuals and 10 aerobically trained athletes. The values are the mean and the standard deviation. In the athletes a higher NN (lower HR), RMSSD, and pNN50 was found in supine as well as standing position.

Table 2-1 HRV parameters in the time domain obtained from 10 control (sedentary) individuals and ten aerobically trained athletes. Values are mean ± standard deviation.

	Mean NN (ms)	SDNN (ms)	RMSSD (ms)	pNN50 (%)
Supine				
Control	880,7 SD=263,8	69,7 SD=37	45,5 SD=26,8	21,8 SD=19,7
Athletes	1100,3 SD=158,5*	97 SD=15,7*	73,5 SD=23,7*	40,1 SD= 6,6*
Standing				
Control	749,7 SD=165,6	65,4 SD=38,9	30,6 +- 16,9	10,5 SD=12,4
Athletes	947,7 SD=108,8	92,9 SD=30,9	47,2 SD=11,1	22,4 SD=8,9*

NN= normal-to-normal interval; pNN50= percentage of successive interval difference larger than 50ms; RMSSD=square root of the mean squared successive differences between adjacent intervals; SDNN= standard deviation of the NN interval; *p<0.05 [reproduced from Aubert et al.[9])

2.1.3.2 Frequency Domain Analysis

Any steady, stationary time-dependent signal that do fluctuate can be decomposed by spectral analysis into its sinusoidal components.[1] In other words; spectral methods produce a decomposition of total variation of a 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 technique is widely used in the analysis of repetitive phenomena. It allows for:

a) The plotting of each of the components as a function of its frequency and

b) the computation of the power in each defined frequency region.

Power spectral analysis can be performed by fast Fourier transform (FFT),[17] by autoregressive (AR) modelling[18] and by wavelet decomposition.[19] Power spectral density (PSD) analysis indicates how power (variance) distributes as a function of frequency. It must be noted that, independent of the method used, only an estimate of the true power spectrum density of the signal can be obtained by mathematical algorithms.[1,17] During this study autoregressive (AR) modeling were used to quantify the spectral power for a given frequency band, by deriving the area under the spectral density function within the specified frequency range. Both FFT and AR models provide very comparable results, with AR models providing a smoother spectral shape.[1,3,9]

The Fast Fourier Transform (FFT Non-Parametric Method)

The tachogram can be shown in the frequency domain after FFT and can also be transformed back to the original tachogram: thus it is called an objective method

(no information is lost). The units of the spectral components are; ms^2/Hz.[20]. The spectrum computed with the FFT is derived from all the data, regardless of how well they fit a model based on peaks in the spectral distribution. This method is relatively easy to apply with high processing speed; it can be represented graphically and the software is readily available (8). A disadvantage is the limited frequency resolution, which is directly related to the duration of the recording period. The recording period also determines the limit of phenomena that can be detected. Phenomena with a frequency lower than the inverse of the recording period will not be visible in the FFT data.

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The Autoregressive Modelling (Parametric method)[1,7]

With the Autoregressive Modelling (AR) techniques, the time-domain data are used to identify a best-fit model from which a number of peaks and the final

spectrum are derived. The time series is seen as a difference equation, such that the signal at every time step is expressed as a function of its values. Thus the basic disadvantage of the parametric method is the need of verification of the correctness of the chosen model and of its complexity (the order of the model)

The advantages of the parametric method are:[1]

- smooth spectral components that can be distinguished independent of pre selected frequency bands,
- the easy post processing of the spectrum with an automatic calculation of low- and high-frequency power components with an easy identification of the central frequency of each component,
- and an accurate estimation of power spectrum density (PSD) even on small sample numbers.

In Figure 2-1 the two frequency analysis methods described were compared Graphs were again obtained from a study in the literature: a control group of 10 individuals and 10 aerobically trained athletes.[9]

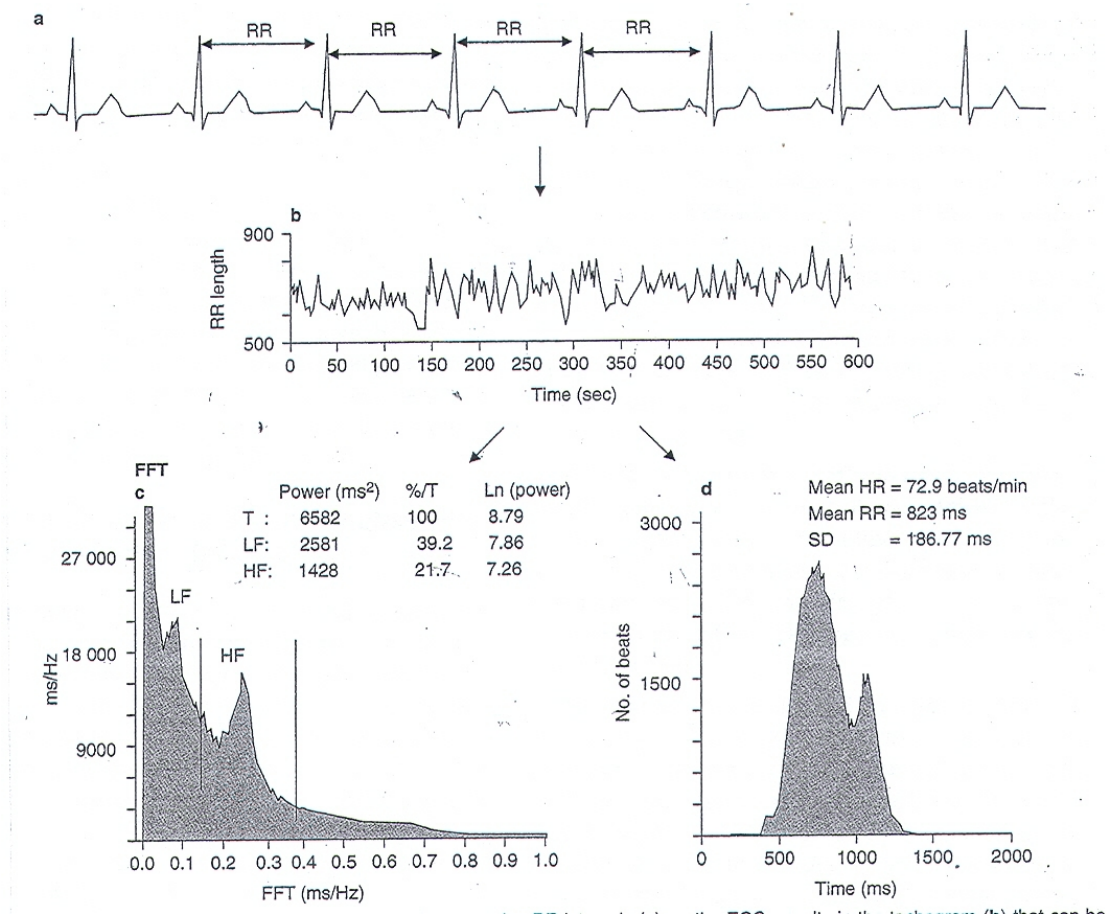

Figure 2-1 Comparison of spectral analysis methods. Upper panel shows AR. Peaks are at the same frequency, but the AR signal is smoother than the FFT signal. Recordings were obtained in the supine position.[9]

Power spectrum analysis of a tachogram distinguishes between the intrinsic sources of HRV, as these rhythms occur at different frequencies. These variations allow for the mapping of the ECG power spectra into indices that reflect autonomic mediation of the heart rate. Short-term intrinsic fluctuations in HR are coupled with internal regulatory mechanisms such as respiration and blood pressure (BP) regulation.[1,9,11]

The high frequency (HF) respiratory components, are found in the power spectrum at ~0.25 Hz. High frequency power, has been shown to reflect mostly the quantity of parasympathetic efferent (vagal) modulation of the heart. Thus,

except at very slow breathing frequencies, the respiratory component is solely mediated by vagal (cholinergic) activity. For this reason HF spectral power is often used as an index of cardiac vagal tone. This frequency peak shifts with changes in the respiratory rate. Previous studies have shown that the maximal gain response of the HRV signal to each breathing rate input was at respiratory frequencies of 0.1 (6 breaths per min) and 0.25 Hz (15 breaths per min). The 0.25 Hz frequency is close to the usual breathing frequency, and the frequency of 0.1 is the frequency of the Traube-Hering-Mayer wave. [1,9,11]

A slower, low frequency (LF) component, are found at ~0.10Hz. The autonomic underpinnings of the LF component are more controversial and are still investigated. Both parasympathetic and sympathetic outflows are considered to determine LF, together with other regulatory mechanisms such as the renin-angiotensin system and baroreflex.[21]

The LF/HF ratio is used to assess the fractional distribution of power. This value is an indicator of the cardiac autonomic balance. The very low frequency (VLF) component is believed to be due to temperature, hormonal influences and circadian patterns, as well as non-harmonic direct current noise and the windowing process (8). These very slow frequency oscillations cannot be quantified by the traditional spectral analysis methods that are performed on short recordings (minutes). For this reason frequency domain calculations during this study, primarily used the HF, LF and LF/HF values.[9]

The limits of the three frequency bands of heart rate oscillations used in the power spectral analysis was the following: high-frequency band (HF, 0.15-0.40 Hz), low-frequency band (LF, 0.04-0.15 Hz) and very low-frequency band (VLF, less than 0.04 Hz). Different frequency limits and names to these areas have been used in different studies. Power in the LF and HF bands was also expressed in normalised units: the values of LF and HF divided by the total power minus the VLF and multiplied by 100 (expressed as percentage). The distribution of the power and the central frequency of these components are not fixed and vary in relation to changes in autonomic modulation of heart rate and blood pressure.[1,9,11]

2.1.3.3 Non-linear Analysis

Non-linear analysis techniques have been developed over the past two decades to take into account the non-linear nature and dynamics of the cardiac control system. HRV spectra show a broad band of noise-like variability over a large frequency span.[1,23] Both short-term periodic modulations (e.g. respiratory) and non-periodic fluctuations are present in long-term heart rate regulation. It is suggested that a decrease in parasympathetic activity simplifies (reduction in complexity) cardiac HRV, indicating that this branch of the ANS provides a large amount of non-linear behaviour.[23]

Methods related to the chaos theory are used to describe the above-mentioned non-linear properties of heart rate fluctuations. Examples are: attractors, 1/f behaviour of the power spectrum, fractal dimension and correlation dimension.[24] Also Poincare- and higher order moment plots, approximate entropy,[25] point wise

correlation dimension, detrended fluctuation analysis,[14] and Lyapunov exponents.[26]

These non-linear dynamic methods provide tools for HRV assessment. It may produce a more sensitive way to characterise cardiac control function or dysfunction. However; the development of these measures had outpaced their clinical validation. Standard or normal values has not been determined and validated. The absence of standards makes it difficult to interpret data obtained with these techniques and there is a lack of understanding of the limits of use of the methods. For this reason, the perhaps best validated technique, Poincaré plot indexes, were included in this study.

Poincaré Plot or Return maps [24-29]

The Poincaré Plot or Return maps illustrate the relationship between successive time-series samples. The Poincaré plot is a diagram (scatter gram in Figure 2-2 in which each R-R interval of a tachogram is plotted as a function of the previous one. Poincaré plots have been evaluated in a qualitative way using their visual pattern,[24] in a quantitative form through the computation of the autocorrelation of the plot[25] and by geometric procedures.[26,27] The individually developed geometric techniques by Copie et al,[26] Tulppo et al,[28] and Toichi et al,[27] are very similar. The vagal induced RR interval changes develop faster than the sympathetically induced changes. Given this fact, the transversal axis is seen by these authors, as an indicator of vagal-mediated short-term variability, while the longitudinal axis, global variability reflects as an inverse function of sympathetic modulation.[29]

During this study a quantitative analysis of the Poincaré plots was performed. This was done by using the POLAR software. The following parameters were calculated for each individual scatter gram:

SD1: The standard deviation of the instantaneous beat-to-beat variability data. SD1 reflects parasympathetic efferent (vagal) activity on the sinus node

SD2: The standard deviation of the continuous long-term variability. SD2 is less well defined and is believed to reflect both the vagal and sympathetic modulations to the sinus node

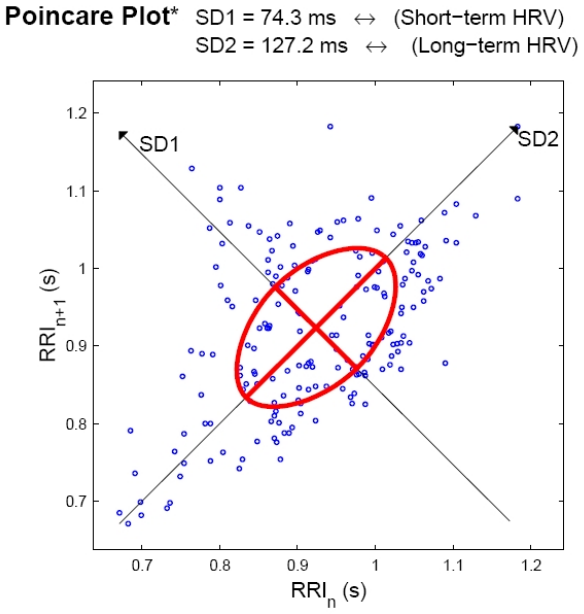

Figure 2-2 Example of the Poincaré plot determined from RR intervals obtained from a healthy person (supine position)

2.2 REFERENCES

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CHAPTER 3 MATERIALS AND METHODS

The study design was an experimental, prospective, longitudinal study on a group of the South African population between the ages of 18 and 22, where the participants acted as their own controls.

3.1 PARTICIPANTS

Participants were volunteers from the South African National Defense Force intake reporting for basic training. They were informed about the aim and nature of the study. All questions that arose were answered. The participants were given the opportunity to volunteer. After eliminations due to exclusion criteria, 185 volunteers completed and signed an informed consent form. The final group consisted of 185 volunteers, i.e. 100 male and 85 female recruits between the ages of 18 and 22 years. However, during the 12 weeks of basic training, two female volunteers resigned from the South African National Defense Force, while 100 male and 83 female volunteers completed the study.

3.1.1 INCLUSION CRITERIA

- South African National Defence Force (SANDF) male and female recruits between the ages of 18 and 22.

3.1.2 EXCLUSION CRITERIA

- Refusal to freely give written informed consent
- A history of cardiovascular, hepatic, respiratory, renal, pulmonary, metabolic, and/or orthopedic disease requiring medical attention
- Any injury or illness

- Psychological disorders
- Medication that could influence cardiovascular control

3.2 PROCEDURE

3.2.1 ETHICAL APPROVAL

Ethical approval was obtained from the South African Defence Force Ethics Committee (Ethical clearance number SG/R&D/2-Jun-06/ 083) to conduct the study. The research protocol was also submitted and approved by the Research Proposal and Ethics Committee of the Faculty of Health at the University of Pretoria.

3.2.2 SETTING

All tests were done during the first week after enlisting at the head quarters of the South African Health and Medical Service, Voortrekkerhoogte, Pretoria. The 12-week exercise intervention took place in Lohathla, Northern Cape, followed by the post-intervention testing which took place again at Voortrekkerhoogte, Pretoria. The exact similar testing protocols were adopted for pre- and post-testing procedures.

Prior to participation a pre-study orientation and screening session was held, where volunteers were screened to ensure compliance with criteria for participation in the study. Thereafter, the pre-intervention / baseline tests were performed:

- Tachogram recordings
- Physical fitness assessment

- Anthropometric evaluations

3.2.3 MEASUREMENT OF HRV

The Polar 810i heart rate monitor system was used to record RR intervals. Recordings were made over a period of ~22-25 minutes, according to all recommendations by the Task Force of the European Society of Cardiology.1 RR intervals were thus sampled in the morning in a quiet environment at a room temperature of 20-22 ˚C. The participants were instructed not to drink any alcohol or caffeine during the preceding 24 hours, or to smoke during the morning of testing. They were allowed to eat a low protein breakfast (cereal with milk, no coffee) on the morning of testing. The Polar 810i strap and transmitter were applied followed by a 12 minute supine resting period. RR intervals (accuracy of 1 ms) were recorded for ~twelve minutes in the supine position and 10 minutes standing; thus leaving 2 minutes for hemodynamic stabilizing, 10 minutes for a supine RR recording and 10 minutes for a standing RR recording. This standing orthostatic stressor consisted of standing upright, leaning with their backs against the wall and feet apart. Different tachogram (RR recording) periods, as discussed in Chapter 4, were selected for analysis from the supine and standing recordings. These data sets (tachograms) were used to determine the autonomic nervous system functioning and balance by quantification of the variability of the inter-beat intervals.

The tachograms were analyzed using HRV Analysis Software obtained from the University of Kuopio, Finland.[2] Smooth n priors for trend and Model Eye programme settings were used for detrending with an Alpha value of 500. The

auto regressive model order value 16 and the interpolation rate of 4 Hz were selected.

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 (Poincaré analysis).1 The HRV indicators calculated in the study are the following:

- Time domain measures recommended for short term recordings (shorter than 20 minutes) are pNN50 and RMSSD. Although not HRV indicators for short period tachograms, 1 heart rate (HR), standard deviation of the heart rate (STDHR), RR interval (RR) and the SDRR are included in all tables.
- Frequency domain analysis included low frequency (LF) power (0,04-0,15 Hz), high frequency (HF) power (0,15-0,4 Hz), LF in normalised units (LFnu), HF in normalised units (HFnu) and the ratio between low and high frequency (LF/HF).
- Non-linear analysis (Poincaré analysis) included the standard deviation of the immediate or short-term variation (SD1) and standard deviation of the long-term or slow variability (SD2).

Further discussion of the background and standardisation of these techniques follow in Chapter 4.

3.2.4 BLOOD PRESSURE MEASUREMENT

A mercury sphygmomanometer, cuff and stethoscope were used to determine the blood pressure of each participant. The sphygmomanometer was placed on a bench where the participant could not see the mercury column. Blood pressure

was recorded after the participant had rested quietly for 5 minutes, and this measure preceded all the other measures in the biokinetic and fitness test battery. The participant was seated with the arm resting on the bench, the elbow approximately at the level of the heart. The cuff was attached over the upper arm and then the pressure increased to approximately 180 mmHg. The stethoscope was placed over the brachial artery in the cubital fossa. The pressure was released at a rate of approximately 2 mm per second. The pressure at which the first sounds were heard (systolic pressure) and the pressure when all sounds disappeared (diastolic pressure) was recorded.[3]

3.2.5 MEASUREMENT OF PHYSICAL FITNESS

Maximal oxygen uptake (VO_{2max}) is used as an indicator of exercise capacity and predictor of survival and performance in a variety of clinical and athletic populations. [4,5] VO_{2max} is normally assessed in a laboratory setting by means of respiratory gas analysis equipment. This method is expensive, time consuming and requires the expertise of qualified laboratory personnel. This direct determination of VO_{2max} is the preferred method to assess aerobic capacity. However, due to the large number of participants in the current study aerobic capacity was indirectly calculated by using the statistically significant negative correlation between the 2.4 km run time of the recruits and their VO_{2max}. Burger *et al.* reported that that the 2.4 km timed out and back run test, reliable predicts the directly measured VO_{2max}. [6] For study purpose the running time to complete a distance of 2.4 km on a flat surface was recorded and used to calculate the. VO_{2max}. of participants.

3.2.6 ANTHROPOMETRIC EVALUATION

A complete anthropometric evaluation was done by a registered biokineticist from the South African National Defence Force. Only the height, body mass and BMI data were included in this study.

3.2.6.1 Height

Height was determined with the aid of a stadiometer. It was calculated to the nearest 0, 1 centimetre (cm). Height, defined as the distance between the soles of the feet and the vertex (highest point), was taken whilst the participant stood up straight, barefoot, with heels, gluteus maximus, upper-back and back of head against the anthropometer. Measurement was taken at the end of a deep inhalation.[10]

3.2.6.2 Body mass

Participants were weighed, in kilograms (kg), on a calibrated Detecto standing scale wearing only underwear, running shorts and a t-shirt. Each participant's mass was calculated to the nearest 0, 1 kg.[10]

3.2.6.3 Body Mass Index

The Body Mass Index (BMI) is a known measure of body fat based on height and weight that applies to both adult men and women. It is used in epidemiologic research and has a moderately high correlation (r_{xy}= 0.69) with body density. It was calculated using the following formula: BMI = Mass ÷ Height^2; Mass (kilograms), Height (m).[11]

The following ratings[3] can be applied to the BMI:

Underweight: <18.5 kg.m^{-2}

Normal: 18.5-24.9 $kg.m^{-2}$

Overweight: 25.5-29.9 $kg.m^{-2}$

3.3 THREE MONTHS BASIC TRAINING (BT) AND INTENSIVE PHYSICAL (PT) PROGRAMME

All participants followed a standardised Basic Training Programme. Activities included drill, regimental aspects, compliments and saluting, general military aspects, musketry, shooting, signal training, mine awareness, map reading, buddy aid, field craft, water orientation, parade rehearsal and physical training.

The physical training programme was developed by Major P Wood, a registered biokineticist from the SANDF. According to Major Wood the main aim of the physical training programme was to develop the physical fitness of the participants in order to assist in making them combat ready. Physical fitness can be defined as the healthy and efficient functioning of the various body systems that allows one to engage in activities of daily living, recreation and leisure (DOD policy on Physical Training, DOD Instruction: SG no 00006/2000). Physical fitness can be classified into seven fitness components, namely: cardio respiratory endurance, muscular strength, muscular endurance, flexibility, speed, power and agility.[3] The aim of the physical training program was to develop the basic fitness components, namely cardio respiratory endurance, muscular strength and also muscular endurance Additionally, flexibility training was included due to its possible role in injury prevention.

Quantification of the basic training and physical training programmes was necessary to be able to compare HRV results with similar interventions published. Thus, the energy expenditure for the BT and PT programmes followed in this study was derived by calculating the Basal Metabolic Rate (BMR), minus the energy that is necessary to maintain life or organ function in the body.[12] This was determined by taking weight, age and gender into consideration. The daily kilojoules used for men and women were calculated as well as the average BMR (Chapter 5

3.3.1 DATA ANALYSIS

The data was captured on computer and the statistical analysis was done with the support of the University of Pretoria, Department of Statistics. The specific statistical test used for pre-and post-intervention comparisons and correlations are discussed in Chapter 5 and Chapter 6.

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CHAPTER 4 INFLUENCE OF TACHOGRAM LENGTH ON QUANTIFICATION OF HEART RATE VARIABILITY

4.1 INTRODUCTION

It is believed that the tachogram length (period over which RR intervals are recorded) and the environment during sampling of RR intervals, are important for producing repeatable and between-project comparable results. Many published articles on HRV claim adherence to the general guidelines and recommendations by the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology.[1] This article recommend a sampling time (tachogram length) for short term HRV analysis 5 minutes. However, numerous studies employ different time windows. For example 2 minutes, 3 minutes, 5 minutes, 10 minutes, and 15 minutes, with or without an initial standard resting period for reaching homeostatic equilibrium.[2] Information on the influence of these variations on study results is not readily available.

Information on the influence of tachogram length is not only required for the recording of supine RR intervals, but also during orthostatic testing. The latter is important as it is accepted that reduced responsiveness to a postural change (supine to sit or standing, and head up tilt), is a HRV trademark of certain patho-physiological conditions.[3] Albert Malliani, for instance, reported a reduction in the responsiveness of sympatho-vagal balance in several conditions marked by abnormal autonomic regulation.[4] However, despite the diagnostic importance of

the orthostatic response, the same technical variations found in the assessment of supine HRV are also seen in the assessment of orthostatic responses. No standardised methodology indicating the best timing or duration of the tachogram sample is available. Some studies include 2 or even 3 minutes for blood pressure equilibration upon standing before recording of the RR intervals,[5,6,7] while other just state that 256 continuous RR intervals were selected from standing tachograms.[8]

In the present technique evaluation the aim was a) to assess whether mean HRV indicator values obtained by different tachogram lengths (in the supine position and during an orthostatic stressor) are comparable, and b) to determine the stability of HRV indicator values over a 10 minute period by analysing successive 3 minute periods or snapshots (supine and standing).

4.2 METHODOLOGY

Participants consisted of 150 healthy and active individuals between 18-22 years of age (Mass= 61.11kg, SD= 8.32 kg; Height= 165.88 cm, SD=12.75 cm). All were volunteers and gave written informed consent.

4.2.1 PROCEDURES

The heart rate variability was determined by analysis of the RR interval data sets (tachograms), which were obtained by POLAR RS800 heart rate monitors. The data, RR-intervals, were sampled while the participants were lying supine in a quiet environment at a room temperature of 22 ˚C, between 07H00 and 11H00 in the morning. The participants were instructed not to drink any alcohol or caffeine

the previous 24 hours and they were allowed to eat a low protein breakfast (cereal with milk) on the morning of testing.

4.2.2 MATERIALS AND METHODS

For determination of the influence of the tachogram length on the mean HRV indicator values in the supine position (after a two minute resting period), comparisons were made between results obtained over 180, 300, 420 and 600 second tachogram periods, respectively. Registration of the standing measurements started from the moment participants changed from supine to the upright position, standing with their backs against a wall and feet apart. Again 180, 300, 420 and 600 second tachogram periods were compared for the standing period.

To examine the possible changes in mean HRV indicator values over a 10 minute period, 3 minute supine periods (snapshots) were recorded, analysed and compared commencing a) directly after, b) 180 sec after and c) 360 sec after the initial 2 min resting period and again a) directly after, b) 180 sec after and c) 360 sec after standing up. This resulted in three datasets containing RR intervals of 3 min tachograms from the supine period and three datasets from the standing period.

4.2.3 HEART RATE VARIABILITY QUANTIFICATION

The RR interval sets were analysed using HRV Analysis Software 1.1 for windows developed by The Biomedical Signal Analysis Group, Department of Applied Physics, University of Kuopio, Finland. Smoothness priors for trend and Model Eye programme settings were used for de-trending with an Alpha value of 500.

The auto regressive model order value was 16 and the interpolation rate was 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 variability. HRV indicators determined are listed in Table 4-1 with an explanation of the efferent source of stimulation (sympathetic or parasympathetic branch of ANS).[1,9]

Table 4-1 Summary of HRV indicators used and origins of variability

Indicator and unit	Variability origin
Mean RR (s)	The mean of the intervals between successive QRS complexes, result of vagal (short term) and sympathetic (long term) influence on HRV.
STDRR (s)	Standard deviation of intervals between successive QRS complexes, indicator of vagal (short term) and sympathetic (long term) influence on HRV (Overall HRV).
RMSSD (ms)	Root mean square of the standard deviation between RR intervals, indicator of vagal influence (short term).
pNN50 (%)	The percentage of successive RR interval differences larger than 50ms computed over the entire recording, indicator of vagal influence (short term) on HRV.
SD1 (ms)	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 (ms)	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.
LF Power (ms^2)	Indicator of sympathetic influence including a parasympathetic component.
HF Power (ms^2)	Indicator of only parasympathetic influence.
LF/HF	Indicator of autonomic balance

4.2.4 Statistical Analysis

The SAS procedure MIXED was used to determine the effect of the different time intervals on each of the HRV measurements. A linear model with HRV measurement as dependent and time as explanatory variable was fitted to the

data allowing for correlation between consecutive time intervals [AR (1) covariance structure]. An F-test was performed in each case to test whether there is an overall time effect and for each time interval the least squares means were estimated.

4.3 RESULTS

When the influence of different tachogram lengths (180, 300, 420 and 600 seconds) on mean HRV indicator values were examined (Table 4-2), results from recordings in the supine position showed that the mean values of the parasympathetic nervous system-dependent indicators (RMSSD, pNN50, SD1, $HFms^2$) and the indicator of autonomic balance (LF/HF), did not differ significantly ($p>0.05$). However, as seen in Table 4-2, HRV indicators influenced simultaneously by both the sympathetic and parasympathetic branches of the ANS (STDRR, SD2 and $LFms^2$), showed significant ($p<0.05$) tachogram length-dependency in the supine position. During application of an orthostatic stressor, the indicator of autonomic balance (LF/HF) remained stable ($p>0.05$), while all HRV indicators showed significant differences ($p<0.05$) between recording times of 180, 300, 420 and 600 minutes (Table 4-2).

Table 4-2 A comparison between HRV indicator values obtained with four different tachogram lengths in the supine and standing position: 0 to 180 seconds, 0 to 300 seconds, 0 to 420 seconds and 0 to 600 seconds.

	Supine					Standing				
HRV Indicator	**180s**	**300s**	**420s**	**600s**	**P-value**	**180s**	**300s**	**420s**	**600s**	**P-value**
Mean HR	73.75	73.57	73.47	73.49	**0.019**	89.02	90.39	91.13	91.85	**0.0001**
Mean RR	0.84	0.84	0.84	0.84	**0.22**	0.69	0.69	0.68	0.67	**0.0001**
STDRR	0.05	0.052	0.052	0.051	**0.016**	0.047	0.044	0.040	0.042	**0.0001**

	Supine					Standing				
HRV Indicator	**180s**	**300s**	**420s**	**600s**	**P-value**	**180s**	**300s**	**420s**	**600s**	**P-value**
RMSSD	60.90	61.14	61.26	61.69	**0.69**	38.81	35.00	32.39	30.31	**0.0001**
pNN50	33.46	33.22	33.03	32.86	**0.44**	14.32	11.71	10.37	9.39	**0.0001**
SD1	43.21	43.45	43.55	43.51	**0.60**	27.89	25.09	23.19	21.70	**0.0001**
SD2	73.26	75.51	78.31	81.97	**0.0001**	118.7	104.3	95.14	101.4	**0.0001**
LFms^2	320.8	349.54	351.5	366.2	**0.014**	451.5	367.4	328.8	301.8	**0.0001**
HFms^2	403.6	387.11	384.4	389.2	**0.17**	156.0	137.7	113.6	98.31	**0.011**
LF/HF	1.12	0.96	1.04	1.09	**0.74**	5.45	6.48	7.09	6.56	**0.67**

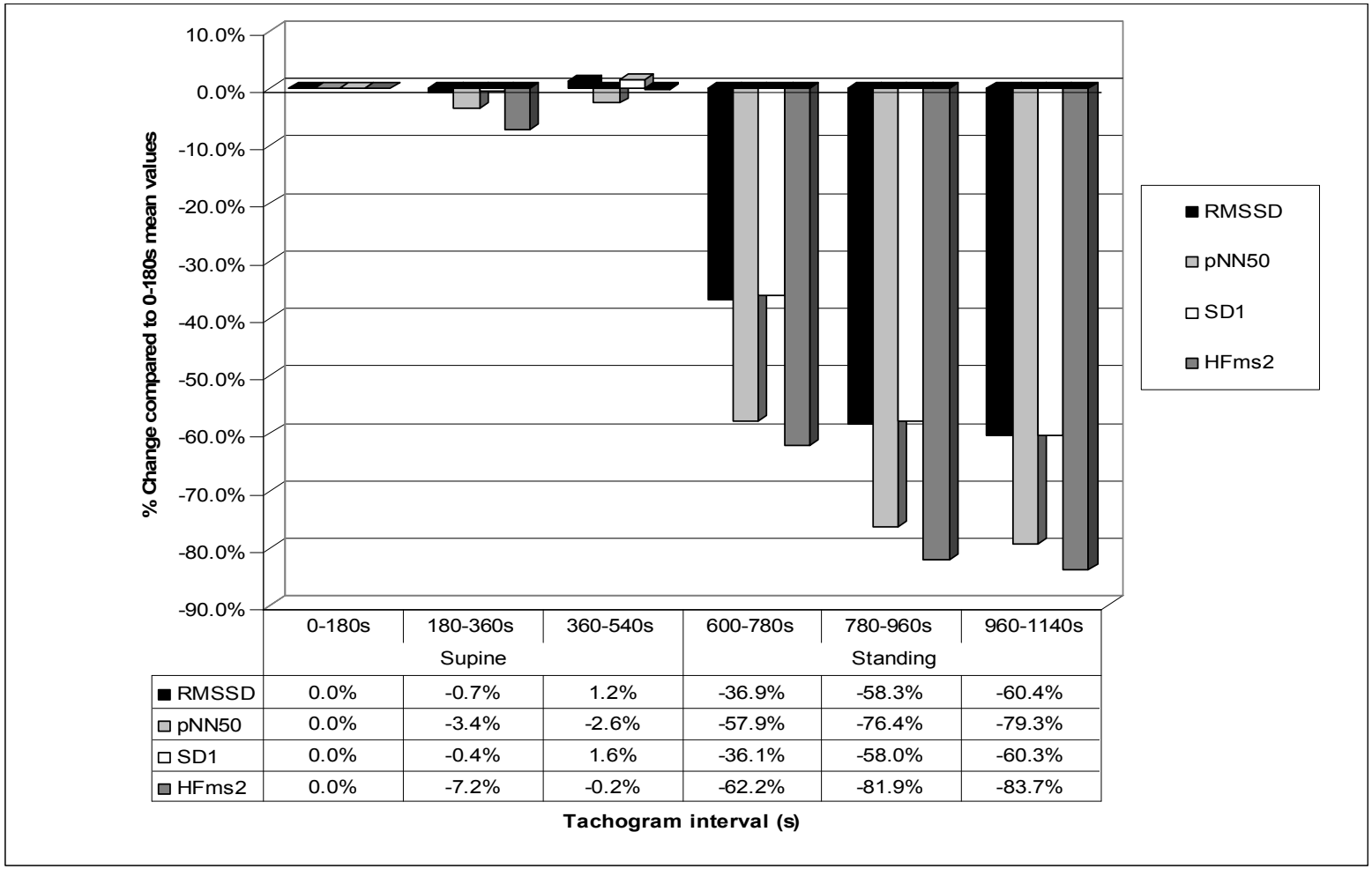
During investigation of the stability of supine HRV indicator values over different 3 minute periods (Table 4-3), there were no significant differences except for SD2 (p=0.03). However, in the standing position all HRV indicator values measured during the 2nd (780-960 seconds) period and the 3rd (960- 1140 seconds) period were highly significant different (p<0.0001) from the 1st standing period (600-780seconds) indicating time-period dependency.

Table 4-3 Changes in mean HRV indicator values from six different 180 second tachograms (snapshots) starting at 0 seconds (supine), 180 seconds (supine), 360 seconds (supine), 600 seconds (standing), 780s seconds (standing) and 960s seconds (standing).

	Supine				Standing			
HRV Indicator	**0-180s**	**180-360s**	**360-540s**	**P-value**	**600-780s**	**780-960s**	**960-1140s**	**P-value**
Mean HR	73.74	73.20	73.02	**0.06**	89.04	92.11	93.44	**<0.0001**
Mean RR	0.84	0.85	0.85	**0.29**	0.69	0.67	0.66	**<0.0001**
STDRR	0.051	0.052	0.053	**0.34**	0.047	0.033	0.033	**<0.0001**
RMSSD	61.36	60.93	62.11	**0.58**	38.72	25.56	24.27	**<0.0001**
pNN50	33.79	32.64	32.92	**0.25**	14.22	7.97	7.00	**<0.0001**

	Supine				Standing			
HRV Indicator	**0-180s**	**180-360s**	**360-540s**	**P-value**	**600-780s**	**780-960s**	**960-1140s**	**P-value**
SD1	43.55	43.37	44.23	**0.59**	27.83	18.29	17.27	**<0.0001**
SD2	73.49	74.22	78.90	**0.03**	119.19	57.41	55.42	**<0.0001**
LFms^2	321.79	354.48	360.4	**0.48**	453.68	246.75	218.94	**<0.0001**
HFms^2	410.63	380.99	410.0	**0.39**	155.20	74.24	67.01	**<0.0001**
LF/HF	1.93	2.13	2.15	**0.78**	5.83	12.82	11.22	**0.0026**

For the purpose of the discussion below, the HRV indicators are grouped according to the origin of variability. Figure 4-1 represent the HRV indicators influenced by only the parasympathetic branch of the ANS (RMSSD, pNN50, SD1, HFms^2), and Figure 4-2 the HRV indicators influenced by both the sympathetic and parasympathetic branch (STDRR, SD2 and LFms^2). These figures represent an overview of the reaction of the ANS branches to standing (10 min) after 10 min in the supine position. The HRV indicator values were expressed as % change (Δ) of the first 3 minutes mean supine values. Example: % change (Δ) RMSSD during the 180-360s supine period: (60.93-61.36)/61.36x100= -0.7%



	0-180s	180-360s	360-540s	600-780s	780-960s	960-1140s
	Supine			Standing		
RMSSD	0.0%	-0.7%	1.2%	-36.9%	-58.3%	-60.4%
pNN50	0.0%	-3.4%	-2.6%	-57.9%	-76.4%	-79.3%
SD1	0.0%	-0.4%	1.6%	-36.1%	-58.0%	-60.3%
HFms2	0.0%	-7.2%	-0.2%	-62.2%	-81.9%	-83.7%

Figure 4-1 Parasympathetic mediated (vagal) ANS activity during 600 seconds in the supine position followed by 600 seconds standing.

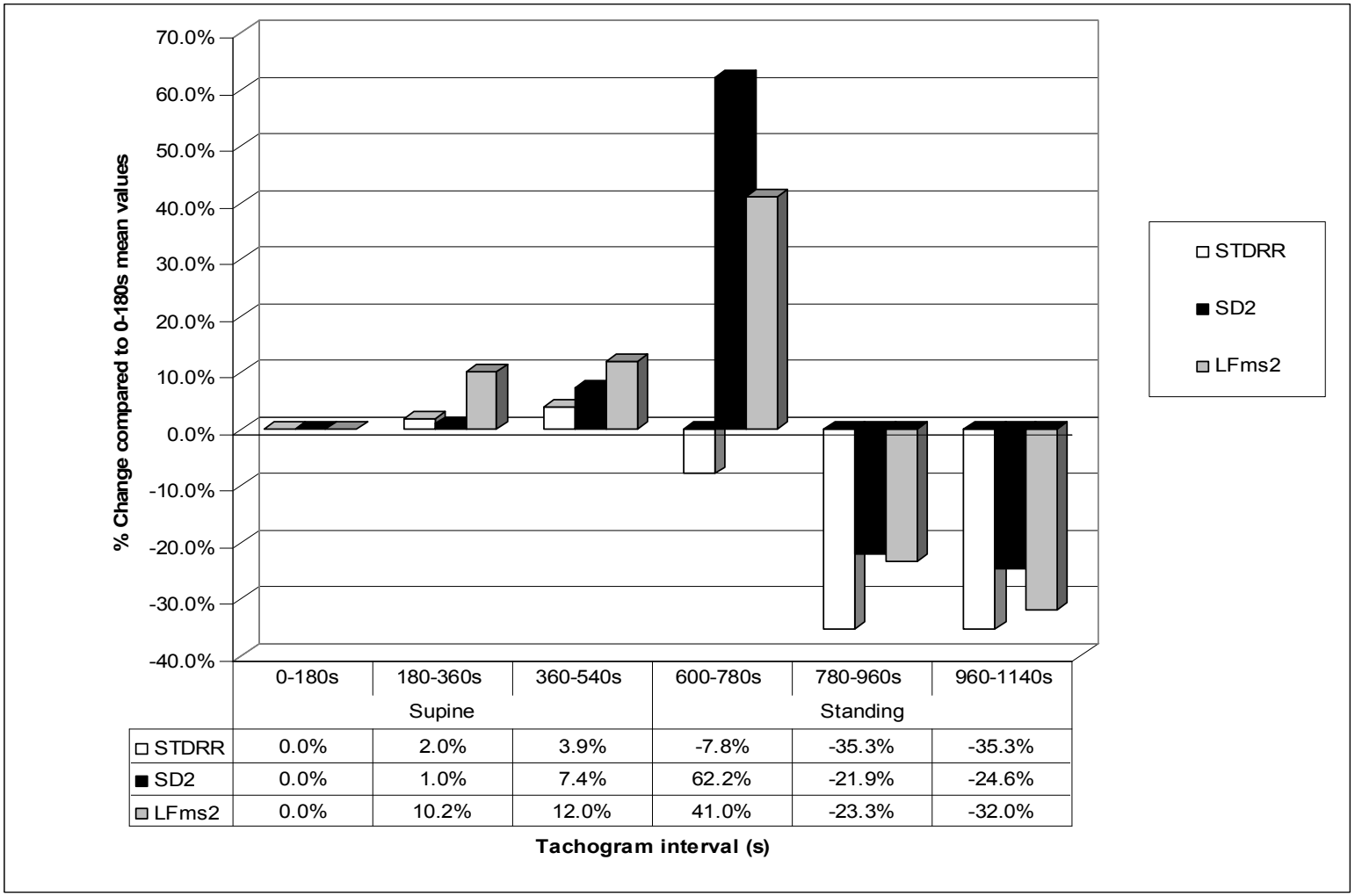


Figure 4-2 HRV indicators influenced by sympathetic and parasympathetic (vagal) ANS activity during 600 seconds in the supine position followed by 600 seconds standing.

4.4 DISCUSSION

When comparing the findings of different studies it is important to know the validity of comparing results from studies that used different recording times. It is fairly obvious that recording times, or tachogram lengths, would be a factor when long tachograms are involved, but the situation is not clear for periods between 3 and 10 minutes. As recording times of between 180 and 600 seconds are generally used, it is important to see whether comparable results are obtained with different tachogram lengths of 600 seconds and less. The aim of this investigation was therefore to assess whether mean HRV indicator values are, within this period, influenced by the length and period during which the tachogram is recorded. To test for a possible influence of the length of the recording time, HRV indicator values calculated from 180, 300, 420 and 600 seconds recording periods, respectively, were compared. This was done for the supine position, as well as during the application of an orthostatic stressor. As a number of HRV indicator values differed between the different recording times (tachogram lengths), different 3 minutes periods (snapshots) from a 10 minute supine recorded tachogram were subsequently compared, as well as different 3 minute snapshots from a 10 minute tachogram recorded during application of an orthostatic stressor.

When the influence of different tachogram lengths on mean HRV indicator values were examined, results from recordings in the supine position showed that the mean values of the parasympathetic nervous system-dependent indicators (RMSSD, pNN50, SD1, $HFms^2$) did not differ significantly ($p>0.05$) when measured by different tachogram lengths (180, 300, 420 and 600 seconds). These results are seen in Table 4-2. HRV indicators influenced simultaneously by

the sympathetic and parasympathetic branches of the ANS (STDRR, SD2 and $LFms^2$), showed significant ($p<0.05$) tachogram length-dependency in the supine position.

As the mean values of parasympathetic (vagal) HRV indicators did not differ between tachograms of different lengths it is feasible to accept that recordings varying between 3 and 10 minutes give similar results. Studies focusing only on quantification of the supine parasympathetic (vagal) induced variability of heart rate where tachograms vary between 180 and 600 seconds, can thus be compared. As HRV indicators influenced simultaneously by the sympathetic and parasympathetic branches ($LFms^2$, SD2, STDRR), showed significant tachogram length-dependency, the same couldn't be said for comparisons between studies employing different tachogram lengths for these HRV indicators.

During application of an orthostatic stressor, and as would be expected from a physiological point of view, most HRV indicators showed significant differences ($p<0.05$) between recording times of 180, 300, 420 and 600 minutes (Table 4-2). This tachogram length-depended effect from the moment of rising until the end of the 10 minute period is due to the homeostatic processes involved in the regulation of blood pressure upon postural change. The question is therefore not whether different tachogram lengths will give different results during the application of an orthostatic stressor, but rather the length of the period over which changes in autonomic function will occur before stabilisation in the standing position.

In an attempt to gain a better understanding about differences found with variations in tachogram lengths, different 180 second periods (snapshots) from a 600 second supine recorded tachogram were compared, as well as different 180 second snapshots from a 600 second tachogram recorded during application of orthostatic stress.

With comparison of the supine tachograms recorded over different 3 minute periods (Table 4-3) there were no significant differences in the vagal-determined indicators (RMSSD, pNN50, SD1, $HFms^2$) between the first 180 seconds and the second 180 seconds, the second 180 seconds and the third 180 seconds, or between the first and third 180 seconds tachograms. This confirms the possibility of comparing vagal-dependent variables from recording times between 3 and 10 minute. For HRV indicators influenced simultaneously by the sympathetic and parasympathetic branches of the ANS, the third period SD2 value differed significantly from that obtained in the first and second 180 second periods. STDRR and $LFms^2$ did not differ significantly ($p>0.05$) between the different 180 second periods.

Upon standing most HRV indicators (RMSSD, pNN50, SD1, $LFms^2$, SD2, $HFms^2$) obtained during the second standing period (780-960s) and third standing period (960-1140s) differed significantly from that of the first 180 seconds standing (600-780s). The initial response (600-780s) to standing can be explained by the fact that the maintenance of blood pressure in rising from the supine position is in the first few minutes dependent on increased sympathetic activity and vagal withdrawal.[10] This was illustrated in the decreased values of vagal-dependent

indicators RMSSD (62.11-38.72), pNN50 (32.92-14.22) and SD1 (44.23-27.83). At the same time, increased values of SD2 (78.90-119.19), $LFms^2$ (360.35-453.68), were observed. As these values are indicators of the combined power/strength of the vagal and sympathetic branches, the higher values thus reflect increasing sympathetic activity, as vagal activity decreased.

The overt changes in response to standing up (600-780s) did not continue. Except for SD2, no significant differences were found between the second and third periods of standing - pointing towards stabilisation of autonomic nervous system activity in the standing position. It is thus obvious that variation in the recoding time (tachogram length) will give different values for the orthostatic response, as longer periods will include values obtained after stabilisation in the standing position.

In an effort to demonstrate the changes occurring throughout the total period of recording, i.e. from after the two minute stabilisation period in the supine position up to the last 180 seconds of standing, mean HRV indicator values of the different periods (supine 180-360, supine 360-540, standing 600-780, standing 780-960, and standing 960-1140 seconds), were expressed as a percentage change of the values obtained in the first 3 minutes supine position (0-180 s). This can be seen in Figure 4-1 (vagal activity indicators) and Figure 4-2 (combined vagal and sympathetic activity indicators).

Figure 4-1 shows a dramatic vagal withdrawal during the first 180 second period of application of the orthostatic stressor (600-780s), with stabilisation from the

second 180 second period onwards (780-960s and 960s-1140s). The indicators SD2 and LFms2, influenced by sympathetic as well as parasympathetic activity (Figure 4-2), show increased activity over the first 180 second period (600-780s). During the second and third periods (780-960s and 960s-1140s) a decline was noted in these indicators (SD2 and LFms2), but, in view of the overt decrease in parasympathetic activity, this decline can most probably be ascribed to the overt decline in parasympathetic activity. Although STDRR is considered, by some, as comparable to SD2 and LFms2 (indicators of combined ANS influences), parasympathetic activity would appear to have a stronger influence on STDRR than sympathetic activity.

These results show that for the supine position, even with recording times of 10 minutes and less, standardisation is preferable - especially with indicators that are influenced by both vagal and sympathetic. However, due to the activation and normalisation of normal homeostatic mechanisms standardisation becomes imperative during estimation of the orthostatic response. It is therefore necessary to come to an agreement on a standardized time of tachogram length. Alternatively, variations in normal as well as pathophysiology could perhaps be better expressed as the slope of the line from the beginning of the response until stabilisation, than by absolute values.

In summary, it was found that the mean HRV indicator values, representing only vagal/parasympathetic efferent activity, was not influenced by tachogram length in the supine position, but definitely upon standing up. HRV indicators influenced by the sympathetic branch of the ANS or a combination of sympathetic/

parasympathetic influences were tachogram length-dependent in the supine, as well as standing positions. When, during the supine position, individual three minute snapshots within a 10 minute recording were compared, significant differences between the different periods were found only for SD2 ($p=0.038$). During application of the orthostatic stressor, all HRV indicators measured during the first 3 minute period differed significantly from that measured during the second and that measured during the third three minute periods.

In conclusion it can be said that recording times in the supine position should preferably be standardised. However, standardisation is absolutely necessary during assessment of the orthostatic stress response. Upon standing-up (orthostatic stressor), the exact starting point, as well as the length of recording, is critical due to the activation and normalisation of homeostatic mechanisms. Starting the recording too late will miss out on the initial response to a change in body position. Longer recording times during application of the orthostatic stressor will give values, not representative only of the individual's orthostatic response, but will represent the mean of HRV values obtained during the orthostatic response and that obtained after stabilisation in the standing position.

4.5 REFERENCES

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CHAPTER 5 HEART RATE VARIABILITY ASSESSMENT OF PHYSICAL TRAINING EFFECTS ON AUTONOMIC CARDIAC CONTROL

Regular physical activity has many health benefits such as the prevention of, or decreasing in, the incidence of coronary heart disease, positive changes in cardiovascular functioning and beneficial metabolic, psychological and neurovegetative effects.[1-3] Exercise based clinical interventions are widely recommended to reduce morbidity and all-cause mortality.[4,5] The protective influence of exercise on the heart to counter damaging cardiac events is believed to be the result of adjusted influences by the autonomic nervous system (ANS) on, for example, heart rate (HR) and heart rate variability (HRV). However, certain questions remain as to the effects of exercise on ANS control of the heart.[6-8]

It is generally known that the initial aerobic training-induced effects on indices of HRV were heterogenic and controversial,[9-11] According to Hautala et al.[1] reasons for this heterogeneity in reports may lay in age, small sample size, the duration and also the intensity of the intervention. However, as discussed in Chapter 1, there is a consistent body of evidence that exercise increases resting vagal cardiac control, in healthy as well as patient groups.[1,12-15] Although it is theorized that posture change and an orthostatic challenge may highlight ANS changes better than the resting supine position,[16,17] and that reduced ANS responsiveness to an excitatory stimulus is seen as the most common feature of patho-physiological states,[18] exercise induced changes in HRV during standing and in response to an orthostatic stressor is less known.

In this Chapter the influence of a standardised, intensive physical training programme, in a controlled environment, on ANS cardiac control by means of HRV quantification, is reported. The exercise induced changes in overall HRV were measured in the supine, rising and standing positions as well as the adjustments in orthostatic response. Analytical techniques used were time domain, frequency domain and non-linear (Poincaré) analysis.

It was hypothesized that results of exercise induced changes on ANS are dependent on the body position and should be assessed not only in the resting position but also during standing and during an orthostatic stressor. It was also hypothesized that it is possible to better distinguish between exercise induced changes in vagal and sympathetic influence by taking measurements in different body positions.

Hypothesis 1:

There is no difference in the exercise induced changes on the ANS, quantified by HRV in the supine position, during rising and standing position.

Hypothesis 2:

There are no associations between baseline physiological characteristics, such as BMI, VO2 max, blood pressure and baseline autonomic nervous system functioning ($LFms^2$, $HFms^2$), and the autonomic nervous system's response to exercise.

5.1 METHODS

5.1.1 STUDY TYPE AND STUDY POPULATION

This was a prospective twelve week exercise intervention study with a self-control design. The volunteers were between 18 and 22 years of age, consisted of 100 males and 83 females, and were of predominantly African ethnicity (African = 171; Mixed = 5; Caucasian = 5; Indian = 2). Mass and body mass index remained relatively constant over the study period as can be seen in Table 5-1. None of the participants were professional athletes or high level sport participants. Exclusion criteria included refusal to freely give written informed consent; history of cardiovascular, hepatic, respiratory or renal impairment, as well as pulmonary, metabolic, and orthopaedic disease requiring medical attention; lung/ respiratory tract infection in the previous two weeks; medication that could influence cardiovascular control and psychological disorders.

All participants were subjected to the same standardised 24 hour routine (exercise, diet and sleep) for the duration of the twelve week exercise intervention. The calculated average basal metabolic rate (BMR) for participants, taking weight, age and sex into account, was 6371 kJ/day. This, in addition to the energy expenditure of the training and exercise activities, resulted in a calculated average energy consumption of 8485 kJ/day, which can be classified as a medium to high intensity exercise program.[19] The study protocol was submitted and approved by the Ethics Committee of the University. All participants gave written informed consent before commencement of the intervention.

5.1.2 DATA SAMPLING AND HRV QUANTIFICATION

Participants were instructed not to exercise or drink any alcohol or caffeine the 24 hours before measurements. They were allowed to eat a low protein breakfast (cereal with milk) on the morning of testing. POLAR RS800 heart rate monitors were used to obtain RR interval data sets (tachograms) from participants at the start (pre-intervention) and at the end (post-intervention) of the twelve week exercise period. After a 2 min stabilisation period in the supine position, ten minute tachograms were obtained for supine and 10 minute tachograms during standing upright, leaning with their backs against a wall, feet 30cm apart and 30cm from the wall.

Data sets were exported and artefacts in RR interval data were removed with standard Polar software programmes with a low filter power and a minimum beat protection zone of six beats per minute. The RR interval sets were analysed using HRV Analysis Software 1.1 for windows developed by the Biomedical Signal Analysis Group, Department of Applied Physics, University of Kuopio, Finland. Smoothness priors for trend and Model Eye programme settings were used for detrending with an Alpha value of 500. The autoregressive model order value was 16 and the interpolation rate was 4 Hz. Standard time domain, frequency domain and non-linear (Poincaré analysis) techniques were implemented.[20,21]

The Poincarè analysis method was included due to its applicability to data that include non-linear phenomena[20] and also non-stationary data sets.[22] With this method SD1 and SD2, were determined. SD1 is an 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 is an indicator of the standard deviation of the long-term or slow variability of the heart rate representing global variation.[21] Recommended time domain HRV indicators such as STDRR, RMSSD and pNN50 were determined and reported with RR interval and heart rate. Spectral components analysed with frequency domain analysis included high frequency (HF), 0.15 – 0.40 Hz, low frequency (LF), 0.04 – 0.15 Hz, and the LF/HF ratio. The indicators LF/HF, LFnu and HFnu were used as indicators of autonomic balance or relative power distribution between the sympathetic and parasympathetic branches of the ANS.[20] LFnu (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). The HFnu (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), while LF/HF is used to assess the fractional distribution of power. [20]

A minimum tachogram length of 1 minute is essential to assess the high frequency (HF) components, and at least 2 minutes for the low frequency LF components during HRV analysis.[20] In the current study the non-stationary period during rising were analysed separately. One tachogram in supine position (directly before rising), one tachogram during rising (0 to 180s), one tachogram during standing (180 sec to 360s standing) and one tachogram during continued standing (360s to 540s standing) were used for HRV quantification.

The orthostatic response was quantified by the percentage difference (%Δ) between the HRV indicator values obtained during the first stabilised standing

period (180-360s) and that obtained during the supine position (%Δ HRV indicator value = [standing – supine]/ supine x100). In addition, the percentage change was also calculated between the non- stationary rising-to-standing period HRV values (0-180s) and supine, as well as between the second stationary standing period (360-540s) and supine.

5.1.3 STATISTICAL ANALYSIS

The T-test is based on the assumption of normality, hence it is necessary to confirm that this assumption is met. In this study the chi-square goodness-of-fit test was used due to the relatively large sample size (rather than a test such as Kolmogorov-Smirnov which is usually used for smaller samples). The Chi-Square test was applied to all data sets (HR, RR, RRSTD, RMSSD, pNN50, SD1, SD2, LF Power (ms^2), HF Power (ms^2), HF Power (nu.), LF Power (nu.) and LF/HF to determine which indicator values were non-normally distributed. From these, RMSSD, pNN50, SD2, LF Power (ms^2), HF Power (ms^2) showed P-values < 0.05 providing statistical evidence of significant differences from the normal distribution. This violates the assumption of normality of the T-Test. In such cases, two options are available; transformation of the data (using ln or square root) to obtain a more symmetrical distribution; or the use of non-parametric tests. As interpretation of transformed variables may be complicated, it was decided to use the Wilcoxon signed rank test (95% confidence level) to assess exercise intervention induced changes in the non-normal distributed data sets and the Matched T-Test for the rest. These tests was also used to determine if there was a difference in the % change (%Δ) in HRV indicator values in response to an orthostatic stressor as measured before and after the training period.

5.2 RESULTS

The anthropometric characteristics of the group are shown in Table 5-1. As can be seen the mass, and therefore the BMI, remained relatively constant over the period.

Table 5-1 Anthropometric characteristics of the study group: Mean and standard deviation

Characteristic	Males Pre-Intervention	Males Post-intervention	Females Pre-Intervention	Females Post-intervention
Height (cm)	171.36 (SD=5.86)	171.36 (SD=5.86)	159.26 (SD=5.49)	159.26 (SD=5.49)
Mass (kg)	61.78 (SD=6.89)	63.18 (SD=6.61)	60.22 (SD=8.99)	60.04 (SD=7.48)
Body Mass Index (kg.m^2)	21.43 (SD=2.16)	22.42 (SD=2.47)	23.40 (SD=3.04)	22.52 (SD=2.34)

SD= Standard Deviation

In Table 5-2 the HRV indicator values and standard deviations for the supine, rising and standing periods are depicted including the level of significance in differences found between pre-and post-intervention values (Appendix 1). All HRV indicators, except the standing ANS balance indicators, showed significant exercise induced changes. All vagal and mixed origin HRV indicators (sympathetic and vagal) showed significant increased variability, while the supine ANS balance indicators, LF/HF and LFnu, showed significant decreases.

Table 5-2 Comparison of average HRV indicator values as determined before and after the exercise intervention for the Supine, Rising and Standing periods. The significance of difference (Pre Δ vs. Post Δ) was determined by the Matched t-test and Wilcoxon signed-rank test depending on distribution of data.

Indicator	Pre (SD)	Post (SD)	P-value	Pre (SD)	Post (SD)	P-value
	Supine			Rising (0-180s)		
HR(bpm)	72.58 (10.94)	61.38 (9.96)	<0.0001	89.28 (12.49)	80.12 (12.14)	<0.0001
RR(ms)	0.85 (0.13)	1.01 (0.16)	<0.0001	0.70 (0.11)	0.78 (0.13)	<0.0001
STDRR(ms)	0.05 (0.02)	0.07 (0.03)	<0.0001	0.05 (0.02)	0.06 (0.02)	<0.0001
RMSSD(ms)	57.35 (33.36)	83.95 (44.72)	<0.0001	33.2 (20.73)	47.1 (26.26)	<0.0001
pNN50(%)	34.55 (21.83)	58.45 (22.03)	<0.0001	9.4 (13.96)	14.9 (17.10)	0.0003
SD1(ms)	44.72 (23.74)	64.61 (31.58)	<0.0001	24 (14.79)	34.2 (18.70)	<0.0001
SD2(ms)	72.8 (36.95)	86.1 (47.15)	0.0020	108 (49.0)	130.6 (54.31)	<0.0001
LF(ms^2)	243 (396.9)	329.5 (873.2)	0.017	356 (373.8)	472.5 (501.4)	0.0001
HF(ms^2)	288.5 (391.3)	525.5 (729.8)	<0.0001	89 (172.9)	161 (225.3)	<0.0001
LF/HF	0.96 (3.13)	0.64 (10.13)	0.044	3.82 (17.50)	3.46 (12.34)	0.93
LFnu	46.45 (19.99)	38.2 (19.16)	0.0022	76.2 (19.03)	73.55 (20.86)	0.47
HFnu	50.1 (19.28)	58.95 (20.38)	0.0071	19.6 (18.60)	22.15 (17.23)	0.96
	Standing (180-360s)			Standing (360-540s)		
HR(bpm)	91.83 (11.69)	81.95 (12.40)	<0.0001	93.10 (12.31)	82.46 (13.62)	<0.0001
RR(ms)	0.67 (0.10)	0.75 (0.12)	<0.0001	0.66 (0.10)	0.75 (0.12)	<0.0001
STDRR(ms)	0.03 (0.01)	0.041 (0.02)	<0.0001	0.03 (0.02)	0.05 (0.02)	<0.0001
RMSSD(ms)	22.2 (15.49)	32 (29.23)	<0.0001	19.65 (16.53)	31.15 (23.44)	<0.0001
pNN50(%)	2.6 (12.57)	8.95 (17.16)	<0.0001	1.95 (12.27)	9.85 (17.30)	<0.0001
SD1(ms)	18.46 (11.03)	27.28 (18.45)	<0.0001	17.43 (11.43)	26.95 (16.71)	<0.0001
SD2(ms)	52.9 (25.55)	76.55 (34.98)	<0.0001	49.85 (25.61)	75.65 (34.48)	<0.0001
LF(ms^2)	155 (254.8)	285.5 (401.1)	<0.0001	143.5 (227.0)	344.5 (510.3)	<0.0001

Indicator	Pre (SD)	Post (SD)	P-value	Pre (SD)	Post (SD)	P-value
HF(ms^2)	35 (105.9)	77.5 (210.6)	<0.0001	32.5 (91.5)	70.0 (187.0)	0.0002
LF/HF	4.91 (24.07)	4.86 (29.70)	0.94	4.47 (20.67)	4.44 (29.49)	0.92
LFnu	80.3 (19.50)	79.75 (18.73)	0.67	80.50 (18.38)	80.00 (17.05)	0.34
HFnu	16.4 (18.15)	16.7 (17.06)	0.52	17.75 (16.66)	17.55 (16.73)	0.48

HR=heart rate; bpm=beats per minute; RR= RR interval; HF=high-frequency components; LF=low-frequency components; pNN50= percentage of intervals differing by >50 ms from preceding interval; RMSSD=root mean square of successive differences in RR intervals; STDRR=standard deviation of RR interval; SD1=standard deviation of short term variability; SD2=standard deviation of the long-term variability s: seconds; SD=Standard Deviation

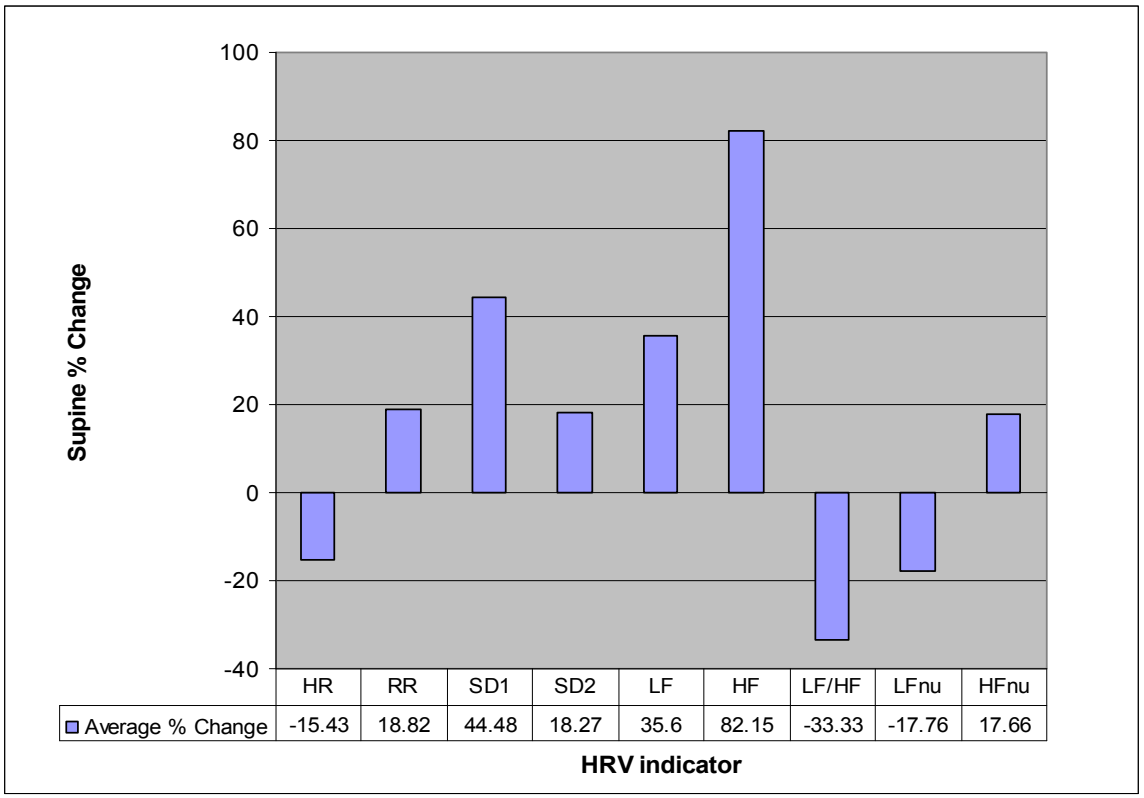

Figure 5-1 Percentage exercise induced changes on supine HRV indicators: [(Post exercise – pre-exercise)/pre-exercise] x 100

The percentage exercise induced changes (pre-intervention vs. post-intervention) in the supine position are shown in Figure 5-1. All indicators were significantly different (P<0.05) after the exercise intervention. It illustrates how variability in

vagal and mixed origin indicators increased, while the ANS balance indicators LF/HF and LFnu decreased.

Table 5-3 shows the exercise induced changes (Δ) in orthostatic response when the orthostatic response was calculated as a) the difference between indicator values obtained during rising (0-180s) and supine, b) the difference between values of the first period of stabilisation in the standing position (180-360s) and supine and c) the difference between values obtain during the second period of standing (360-540s) and supine.

Indicators of vagal influence (RMSSD, pNN50, SD1, $HFms^2$), showed a significant exercise induced decrease when the orthostatic response was calculated from the values during rising, i.e., [(0-180s) – supine]/supine x100. However, when the response was calculated from either the first standing period i.e., [(180-360s) – supine]/supine x100 or, the second standing period, i.e., [(360-540s) – supine]/supine x100, no significant exercise induced changes was visible. In contrast, indicators of mixed origin (SD2, $LFms^2$) did not show significant exercise induced effects when the 0-180s period was used in the calculation, but showed significant increases when the 180-360s and 360-540s periods were used.

Table 5-3 The exercise induced changes (Δ) in orthostatic response determined during a) rising: (0-180s) rising HRV-supine HRV), b) (180-360s standing HRV-supine HRV) and c) (360-540s standing-supine). The significance of difference (Pre Δ vs. Post Δ) was determined by the Matched t-test and Wilcoxon signed-rank test depending on distribution of data.

	Δ orthostatic response: % Change during rising = (0-180s rising-supine)			**Δ orthostatic response: % Change during standing = (180-360s standing-supine)**			**Δ orthostatic response: % Change during continued standing = (360-540s standing-supine)**		
Indicator	**Pre**	**Post**	**P-value**	**Pre**	**Post**	**P-value**	**Pre**	**Post**	**P-value**
ΔHR(bpm)	21.77	33.12	0.0001	26.32	36.75	0.0000	27.94	37.66	0.0001
ΔRR(ms)	-16.18	-22.86	0.0001	-20.07	-25.49	0.0000	-21.09	-25.72	0.0001
ΔSTDRR(ms)	2.53	-8.06	0.035	-26.46	-26.80	0.8582	-29.36	-25.93	0.5780
ΔRMSSD(ms)	-36.32	-46.79	0.0004	-57.05	-60.04	0.2334	-60.72	-60.79	0.5749
ΔpNN50(%)	-58.73	-70.41	0.0068	-88.18	-85.00	0.5311	-92.36	-80.82	0.0595
ΔSD1(ms)	-26.92	-39.82	0.0001	-49.86	-53.73	0.3194	-53.37	-54.00	0.4751
ΔSD2(ms)	55.15	46.53	0.8758	-28.02	10.76	0.0297	-30.77	-13.27	0.0234
ΔLF(ms^2)	67.12	54.52	0.8513	-23.66	-3.26	0.1178	-36.69	0.00	0.0395
ΔHF(ms^2)	-63.10	-72.79	0.0398	-84.08	-87.41	0.2686	-85.95	-85.98	0.4053
ΔLF/HF	269.49	480.00	0.0032	340	567.56	0.1304	331.73	535.09	0.0591
ΔLFnu	48.93	85.96	0.0232	157	131.57	0.0003	46.55	101.27	0.0004
ΔHFnu	-53.15	-63.88	0.0091	-53.4	-51.53	0.1085	-62.28	-70.24	0.1144

HR=heart rate; bpm=beats per minute; RR= RR interval; HF=high-frequency components; LF=low-frequency components; pNN50=percentage of intervals differing by >50 ms from preceding interval; RMSSD=root mean square of successive differences in RR intervals; STDRR=standard deviation of RR interval; SD1=standard deviation of short term variability; SD2=standard deviation of the long-term variability s: seconds; SD=Standard Deviation

5.3 DISCUSSION

Initially there were conflicting reports on the effects of exercise on the autonomic nervous system, but it is now generally accepted, at least for the supine position, that exercise can increase the vagal influence on the heart and thus the RR

interval. However, from the positive, but relatively weak, association between the increase in RR interval and the increase in vagal activity,[12] it is clear that the increase in the vagal regulatory input to the heart cannot be seen as the only contributor to the exercise-induced lowering of heart rate. In contrast to the now accepted fact that physical training can lead to an increase in the parasympathetic control of the heart, the effect on the sympathetic nervous system has not unequivocally been proved by HRV analysis.

As autonomic regulation of the heart is of paramount importance, not only in the supine position, but perhaps even more so during standing and in response to standing up from the supine position, it speaks for itself that the influence of exercise programs would perhaps be better assessed by measuring it in more than one position and in response to an orthostatic challenge. Although it is assumed that RR intervals sampled in the supine position is more reliable than during tilt or standing,[12] Dietricha et al.[22] reported satisfactory reproducibility of these short–term, non-invasive measurements in the supine, as well as in the standing position.

The present study investigated the effect of a 12 week standardised exercise intervention in a controlled environment on a healthy young-adult, predominantly African, population. It investigated the influence of the intervention on the supine, the rising, standing HRV, as well as the orthostatic response. Recordings were analysed by time domain, frequency domain and Poincarè analyses. It was hypothesized that the influence of exercise on the vagal and sympathetic cardiac

control, respectively, can be better assessed and understood by measurements in different positions.

5.3.1 THE INFLUENCE OF AN EXERCISE INTERVENTION ON HEART RATE AND RR INTERVAL IN THE SUPINE AND STANDING POSITIONS AS WELL AS DURING AN ORTHOSTATIC STRESSOR

In the present study the exercise intervention lead to a decreased HR and an increased RR interval in the supine, rising and standing positions (Table 5-2). HR was decreased by on average 15% in the supine position and 11% in the standing position, while the length of the RR intervals increased by 18% and 12%, respectively. HR was significantly lower ($p<0.0001$) with RR and STDRR (standard deviation of RR interval) significantly higher ($p<0.0001$) during all four post-intervention tachogram periods (Table 5-2). The decrease in supine HR and increase in RR intervals are in line with previous publications, as reported in a 2005 meta-analysis of the effect of exercise on HRV in healthy participants[12] as well as that of a more recent review[14] on improvements in HRV with exercise therapy. Several authors referred to the lowering of heart rate by exercise intervention as exercise-induced bradycardia. [10,12,23,24] Textbook bradycardia is characterized by a heart rate below 60 beats per minute while normal resting rate is considered to be between 60 to 100 beats per minute.[25] Thus, although significant decreases in HR occurred in the present study, the twelve week, medium to high intensity intervention, did not result in bradycardia as the average supine heart rate of the participants were still above 60 beats per minute.

In addition to the lowering effect of the exercise intervention on the supine and on the standing heart rate, an effect was also seen on the heart rate during the orthostatic response. During rising from the supine position to the standing position the healthy heart will show an increase in rate. In the present study heart rate increased by 21.77% upon rising before the intervention, and by 33.12% post-intervention.

Before the exercise intervention a 16.18% decrease was found in the length of the RR-intervals upon rising (0-180s), with a post-intervention reduction of 22.86% (Table 5-3). Thus a 7% lower increase in the length of the RR-interval upon rising after the 12 week exercise intervention than before the intervention. This is in agreement with Gilder et al.[6] who, in a cross-sectional study, showed a 6% higher decrease in RR-interval length in a low volume exercise group then in a high volume exercise group. It is said that these exercise induced changes measured in HR and RR interval during rising and standing, indicates increased responsiveness in the vagal reaction and sympathetic vasoconstrictor outflow upon stimulation of the baroreceptors.[27]

STDRR is generally seen as an indicator of global variability. It is of interest, that both in this study and that of Gilder et al.[26] STDRR over the period of rising, was 11% higher after the exercise intervention than before. In view of the relationship between HRV and health, this exercise induced increase in HRV, during the period generally marked by vagal withdrawal, once again illustrates the beneficial effect of exercise interventions on health.

5.3.2 EXERCISE INDUCED CHANGES IN THE PARASYMPATHETIC AUTONOMIC (VAGAL) CARDIAC CONTROL IN THE SUPINE AND STANDING POSITION ANALYSED BY TIME DOMAIN, FREQUENCY DOMAIN AND POINCARÈ ANALYSES

Results of this study (Table 5-2) indicated that the average of all post-intervention indicators of pure parasympathetic (vagal) induced heart rate variation, as measured by RMSSD, pNN50, $HFms^2$ and SD1, were significantly higher ($p<0.0001$ to $p=0.0030$) than pre-intervention. This exercise-induced effect, as in the case for heart rate, was found for all 4 periods measured, i.e., in the supine position, during rising, as well as two standing periods.

A number of past studies reported conflicting results on the effect of exercise on the resting heart rate variability.[28,29] Factors such as differences in study populations, exercise regimes and different analytical techniques (time domain, frequency domain and non-linear analysis), could have contributed to the differences.[1,30] Nevertheless, at present the majority of cross sectional, [1,31,32,33,34,35] as well as longitudinal studies, [1,10,36,37] are in agreement that exercise can increase the vagal cardiac control. Unfortunately, the influence of exercise induced changes measured with short term HRV, are with some exeptions,[38] mostly reported only for the supine position.[12,14]

Our results are thus in agreement with the current view on the effect of exercise on supine vagal control. In addition, it showed that exercise will also increase the average vagal influence during rising and standing. The results of the three HRV

techniques were, although not in the magnitude of change, similar in the direction of change.

5.3.3 THE INFLUENCE OF AN EXERCISE INTERVENTION ON THE SYMPATHETIC AUTONOMIC HR CONTROL IN THE SUPINE, RISING AND STANDING POSITION ANALYSED BY TIME DOMAIN, FREQUENCY DOMAIN AND POINCARÈ ANALYSES

Although it is often assumed that exercise can lower the sympathetic outflow to the heart, the HRV assessment of the sympathetic nervous system's response to exercise remains problematic. This is due to the fact that both sympathetic and parasympathetic influences are present in the LF heart rate oscillations.[39]

The effect of exercise on sympathetic activity has also been assessed by measurement of muscle sympathetic nervous system activity (MSNA). However, these results also vary from increased, to decreased, to unchanged sympathetic activity.[40,41]

Results from the current study (Table 5-2) showed, not only significant increased variation in parasympathetic HRV indicators, but also in indicators of mixed origin (sympathetic activity + vagal activity), such as: STDRR, SD2 and LF(ms^2), over all four time periods. However, as shown in Figure 5-1, the exercise-induced increases in the average values of the mixed indicators (SD2:18.27%; LFms^2:35%) were, for the supine position, consistently lower than the exercise induced vagal increases (SD1:44%; HFms^2:82%). This did not apply to the rising and standing positions. The observation that the pure vagal influence increased

more than the increase in the combination of the two branches is significant as it points towards an exercise-induced decrease in the supine sympathetic influence. It is, however, not possible to state this empirically without examining the effects on the autonomic balance.

Results from the supine recordings on autonomic balance (Table 5-2) showed that the exercise intervention induced a significant shift towards increased parasympathetic influence, as seen in the pre- to post-intervention increase in HFnu (P=0.0071) and decreases in LF/HF (P=0.044) and LFnu (P=0.0022). The autonomic balance indicators for rising and standing did not show any exercise-induced changes. The statistical significant supine values, especially LFnu, supported the notion of an exercise-induced decrease in the sympathetic influence in the supine position.

These findings of an exercise-induced increase in vagal and decrease in sympathetic activity during rest are, although in contrast to a number of other studies,[23,26,42] in line with the conclusions in a review by Carter et al.[10] who reported endurance training to increase resting/supine HRV and parasympathetic activity while decreasing sympathetic activity.

When autonomic balance was taken into consideration, conclusions different from that of the supine was reached for the effects of the exercise intervention on the rising and standing position. In this study, in agreement with Gilder et al. (2008),[26] no significant changes were found in the autonomic balance indicators during either the rising or the standing periods. The non-significance of the rising and

standing exercise-induced changes in the LF/HF, LFnu en HFnu were thus probably due to an equivalent exercise-induced increase in average sympathetic outflow during rising and standing.

The findings of the present study of an increased parasympathetic and decreased sympathetic control in the supine position, are in line with the beneficial effects of a physical training program on the heart and with the lowering of resting heart rate. As the weak association between the effect of exercise on the heart rate and that on the vagal influence suggests that other factors may play a role in the lowering of supine heart rate through exercise interventions, this exercise-induced reduction in the sympathetic outflow could very well make a considerable contribution.[12] In addition, an exercise-induced increase in sympathetic control during rising and standing would be in agreement with the normal homeostatic mechanisms involved in blood pressure regulation upon rising from the supine position, and with the beneficial effects of exercise to individuals prone to syncopy.[43]

5.3.4 Influence of the exercise intervention on the orthostatic response measured during 3 different tachogram periods

HRV quantification of the response to rising from the supine to the standing position can give valuable insight into exercise induced ANS changes. Reduced ANS responsiveness to this type of excitatory stimulus is seen as the most common feature of patho physiological states.[18] It is said that postural changes, such as standing up, elicit sympathetic stimulation which, if attenuated, may be a marker of early sympathetic impairment.[44] However, it may also be an indication of exercise induced changes in the ANS. It is important to take cognisance of the

fact that the orthostatic response can detect effects not visible in the supine position and that it can be a useful clinical tool to measure autonomic responsiveness, both in clinical medicine[45] and in exercise physiology.[26]

Uniformity in the assessment of the ANS to an orthostatic response is problematic and periods and lengths of recording differ. The orthostatic response is generally seen as the difference between values obtained during the supine period and that obtained in response to the orthostatic stressor .[18,26,43] Complicating factors include uncertainties about the exact tachogram starting point during or after standing-up, the length of recording, which is critical due to the activation and normalisation of homeostatic mechanisms,[46] and the importance of stationarity during HRV measurements.[20] The interpretation of when to record the values in response to the stressor differ. While the initial non-stationary period upon rising from the supine to the standing position is discarded by some authors,[47,48] others include this period.[43,46] Even the length of this initial period, whether included or discarded, vary from 30 seconds,[48] to two minutes,[47] to 5 minutes,[46] to 6 minutes.[23]

In the present study, the vagal orthostatic response by the ANS was quantified by determining the % difference between supine vagal indicator values and that of rising/standing values at 0-180s, 180-360s and 360-540s, respectively. The difference between the pre-intervention and the post-intervention responses from supine to rising and standing are seen in Table 5-3. When the period during rising (standing 0-180s) was used for the calculation of the orthostatic response, highly significant exercise induced increases ($P<0.0001$ to $P=0.0398$) in vagal

withdrawal (RMSSD, pNN50, SD1, $HFms^2$) were found from pre- to post-exercise intervention. The exercise intervention did not change the orthostatic response as reflected by the indicators of mixed origin (SD2: P=0.8758; $LFms^2$: P=0.8513). It can thus be inferred that, for the indicators of mixed origin to stay the same, in the presence of a significantly larger vagal withdrawal, the sympathetic response must have increased during post-exercise rising. This was confirmed by the significant changes (P<0.05) in the values of the indicators of autonomic balance (LF/HF. LFnu and HFnu) in favour of increased sympathetic outflow, and the overall decrease in STDRR. These results are in agreement with the study by La Rovere et al.[50] who reported, after 4 weeks exercise intervention, a significant higher resting-to-tilt increase in the LF component of HRV with a significant resting-to-tilt decrease in the HF component. The initial ANS orthostatic response to rising (0-180s), was thus significantly enhanced by the 12 week exercise intervention, both in terms of the vagal and sympathetic response.

The influence of the exercise intervention on the orthostatic response as calculated form the HRV values of the 180 to 360s period of standing minus the supine values was subsequently investigated. We have in a previous publication showed that HRV indicators already stabilized for the standing position during this period (180 to 360s after rising).[46] No significant exercise- induced changes in pure vagal HR control (RMSSD, pNN50, SD1 and $HFms^2$ were found). However, in the face of no exercise-induced change in vagal indicators, the increase in the SD2 indicator of non-linear rhythms and LFnu, showed a pre-post exercise induced increase in the sympathetic response.

In summary it can be said that the results discussed in this chapter are in agreement with the concept of a lowering of heart rate, an increase in resting vagal control of the heart and a general increase in HRV by exercise. The results further confirmed the assumption that a decrease in sympathetic control contributes to exercise-induced lowering of the resting heart rate. In addition, it was shown that both vagal and sympathetic control increased during rising without redistribution of spectral frequency components. In contrast to the post-exercise increase in supine, rising and standing vagal activity, sympathetic activity, while lower at rest, was increased, not only during the period of rising, but also during the standing period. This, in the face of the post-exercise increase in vagal activity during standing, could be an expression of blood pressure maintenance in the standing position. When the effect of the exercise intervention on the orthostatic response was judged by using the values obtained over the non-stationary period (from supine-through-rising- to-standing) a significant stronger response was seen, both in terms of vagal withdrawal and sympathetic activity. However, when the influence of the exercise intervention on the orthostatic response was assessed as the difference between the stationary standing period and supine, the exercise-improved orthostatic response was indicated as a predominantly sympathetic increase. It is thus clear that different results will be obtained on the influence of exercise, depending on the time of measurement relative to body position.

5.4 CONCLUSIONS

Results on the measurement of the influence of exercise on ANS functioning are dependent on the body position and assessments should be done, not only in the resting position, but also during standing and during an orthostatic stressor. It is

possible to better distinguish between exercise-induced changes in vagal and sympathetic influence by taking measurements in different body positions and during orthostatic stress. The same should be done when testing patients with cardiac pathology.

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CHAPTER 6 FACTORS THAT MAY INFLUENCE THE RESULTS

HRV quantification as indicator of exercise induced changes in autonomic cardiac regulation show wide inter-person standard deviations, as well as inconsistencies in study results. This was discussed in Chapter 1. Various factors can, in theory, contribute to the variations, including technical aspects such as length and period of sampling times, choice of analytical techniques, and non-standardisation in the populations investigated.[1,2] The influence of variations in sampling times and periods, as well as body positions, on HRV results, were investigated as part of the work for this thesis (Chapter 4), and has recently appeared in publication.[2] Results on the influence of time and period of recording, as found in Chapter 4, were taken into consideration for the research reported in Chapter 5. Research results on the effects of exercise on autonomic function, was submitted for publication.

In the present chapter the possibility that exercise induced responses may be influenced by pre-intervention physiological status is investigated. Aspects of physiological status included were: blood pressure, fitness, BMI and baseline autonomic function. The independent variables were: baseline/pre-intervention systolic blood pressure (), diastolic blood pressure (DBP), fitness (VO_2max), body mass index (BMI) and HRV indicator values. The dependent variables were ΔRR, ΔSTDRR, ΔHR, ΔRMSSD, ΔpNN50, ΔSD1, ΔSD2, ΔLF, ΔHF, ΔLF/HF, ΔLFnu and ΔHFnu, where the Δ HRV indicator values were calculated as Post-intervention HRV indicator value – Pre-intervention HRV indicator values. The

independent variable is the variable representing the value being manipulated or changed and the dependent variable is the observed result of the independent variable being manipulated.[3]

Hypothesis 1:

Baseline/pre-intervention systolic blood pressure (), diastolic blood pressure (DBP), fitness (VO_2max), BMI, as well as the pre-intervention status of the ANS, reflected by HRV indicators, correlate significantly with the exercise induced response of HRV indicators.

Hypothesis 2:

Pre-intervention values for blood pressure, VO2 max, BMI and pre-intervention status of the ANS reflected by HRV (represented by LFms^2, HFms^2) contribute significantly to the exercise induced changes in the ANS indicated by supine ΔRR, ΔSTDRR, ΔHR, ΔRMSSD, ΔpNN50, ΔSD1, ΔSD2, ΔLF, ΔHF, ΔLF/HF, ΔLFnu and ΔHFnu.

6.1 METHODS

The study type, study population and data sampling methods were described in Chapter 5.

A minimum tachogram length of 1 minute is essential to assess the high frequency (HF) components, and at least 2 minutes for the low frequency LF components during HRV analysis.[4] For the correlation analysis the non-stationary period during rising were analysed separately. One tachogram (180s) in supine position (directly before rising), one tachogram during rising (0 to 180s) and one

tachogram during standing (180 sec to 360s standing) were used for HRV quantification. Only the supine period was used for the regression analysis.

6.2 STATISTICAL ANALYSIS

6.2.1 CORRELATIONAL ANALYSIS

Correlational analysis was employed to test Hypothesis1. Correlation refers to a quantitative relationship between two variables that can be measured either on ordinal or continuous scales.[3] Correlation does not imply causation, rather it implies an association between two variables. The correlation coefficient is a statistic that is calculated from sample data and is used to estimate the corresponding population correlation coefficient. Correlation coefficients generally take values between −1 and +1. A positive value implies a positive association between variables (i.e., high values of one variable are associated with high values of the other), while a negative value implies a negative association between variables (i.e., high values of one variable are associated with low values of the other). Thus, a coefficient of −1 means the variables are perfectly negatively related; while +1 means a perfect positive relation.

Spearman's (rank) correlation coefficient indicates concordance or discordance, i.e. a monotone relationship, while Pearson's product moment correlation is a measure of the strength of the linear association between two variables. Pearson's correlation, "r", is usually squared and interpreted as the % variation in the 1 variant that can be explained by knowledge of the other variable. A coefficient of 0 means the variables are not linearly related.[3]

The Chi-square goodness-of-fit test was used to determine which HRV indicators [HR, RR, RRSTD, RMSSD, pNN50, SD1, SD2, LF Power (ms^2), HF Power (ms^2), HF Power (nu.), LF Power (nu.) and LF/HF] were non-normally distributed. From these, RMSSD, pNN50, SD2, LF Power (ms^2), HF Power (ms^2) had P-values < 0.05, providing statistical evidence of significant differences from the normal distribution. The Chi-square goodness-of-fit test was appropriate because of the relatively large sample size.

The Spearman (non-parametric) correlation coefficient was calculated for those indicators with a non-normal distribution and the Pearson (parametric) statistical correlation coefficient for the rest. The correlation coefficient indicates the strength of the relationship between the physiological measurements (pre-intervention blood pressure, ANS function, BMI, VO_2max) and the exercise induced response of the HRV indicator values (ΔHRV = Post HRV - Pre HRV value) to the exercise intervention.

6.2.2 Regression analysis

Regression analysis was used to test Hypothesis 2. This type of statistical analysis is used when investigating the relationships between variables to determine causal effect of the one on the other.[3] In the current study, linear regression was used to determine the influences of pre-intervention LFms^2, HFms^2, BMI, VO2 max, gender, blood pressure on the exercise induced response of HRV indicator values (Post HRV-Pre HRV value).

6.2.3 KEYS FOR THE HRV INDICATORS AND THEIR UNITS

The keys for the HRV indicators and their units used in the text and tables are: RR (ms): RR interval; SDRR (ms): Standard deviation (SD) of the RR interval; HR (beats per minute): Heart rate; SDHR (beats per minute): Standard deviation (SD) of the heart rate; RMSSD (ms): Root Mean Square Successive Differences; pNN50 (%): Percentage of adjacent cycles that are > 50 ms apart; SD1 (ms): Standard deviation of the immediate, or short-term variation; SD2 (ms): Standard deviation of the long-term or slow variability; LF (ms^2): Low Frequency power (0,04-0,15 Hz); HF (ms^2): High Frequency power (0,15-0,4 Hz); LF/HF (%): Ratio between low and high frequency; LF nu (nu): LF in normalised units (LF/LF+HF); HF nu (nu): HF in normalised units (HF/LF+HF)

6.3 RESULTS

Results of this study are reported in the following order:

1. Correlation between pre-intervention systolic (SBP) and diastolic blood pressure (DBP) and the exercise induced response of HRV indicator values.
2. Correlation between pre-intervention BMI and the exercise induced response of HRV indicator values.
3. Correlation between pre-intervention fitness as estimated by indirect measurement of VO_2max and the exercise induced response of HRV indicator values.
4. Correlation between pre-intervention ANS function as measured by HRV and the exercise induced response of HRV indicator values.

5. Regression analysis to determine the influence of influences of pre-intervention measurements for $LFms^2$, $HFms^2$, BMI, VO2 max, blood pressure, and also gender, on the exercise induced response of HRV indicator values.

6.3.1 CORRELATION BETWEEN PRE-INTERVENTION BLOOD PRESSURE AND THE EXERCISE INDUCED RESPONSE OF THE HRV INDICATOR VALUES

The mean pre-intervention resting systolic (Sy) and diastolic (Dia) blood pressure were 119.03 mmHg (SD=8.52, min=100, max=140) and 75.10 mmHg (SD=9.56, min=60, max=110), respectively. The correlations were calculated from a 180 second tachograms for every participant in the supine, rising and standing position. The results are shown in Table 6-1. The average differences are also reported. No significant associations were found between either Sy or Dia and any of the HRV parameter responses.

Table 6-1 Correlation and significance level between pre-intervention systolic (Sy) and diastolic blood pressure (Dia) and the exercise induced response of HRV indicator values (Δ HRV = Post HRV - Pre HRV)

BP *vs.* ΔHRV Indicator	Supine		Rising		Standing	
	Pre Systolic BP Correlation (P-value)	**Pre Diastolic BP** Correlation (P-value)	**Pre Systolic BP** Correlation (P-value)	**Pre Diastolic BP** Correlation (P-value)	**Pre Systolic BP** Correlation (P-value)	**Pre Diastolic BP** Correlation (P-value)
ΔRR	0.16658 (0.0667)	0.17099 (0.0597)	0.04347 (0.6374)	-0.00502 (0.9566)	0.09086 (0.332)	0.05066 (0.5891)
ΔSTDRR	0.05654 (0.5362)	0.04835 (0.5969)	0.04287 (0.642)	-0.00331 (0.9714)	0.02902 (0.7571)	-0.05335 (0.5335)
ΔHR	-0.15722 (0.0837)	-0.14828 (0.1031)	-0.05952 (0.5184)	0.0157 (0.8648)	-0.11629 (0.2138)	-0.03523 (0.7073)

BP *vs.* ΔHRV Indicator	Supine		Rising		Standing	
	Pre Systolic BP Correlation (P-value)	**Pre Diastolic BP** Correlation (P-value)	**Pre Systolic BP** Correlation (P-value)	**Pre Diastolic BP** Correlation (P-value)	**Pre Systolic BP** Correlation (P-value)	**Pre Diastolic BP** Correlation (P-value)
ΔSTDHR	-0.04983 (0.5857)	-0.01681 (0.8542)	0.00732 (0.9367)	-0.00579 (0.9499)	-0.04166 (0.657)	-0.12313 (0.1879)
ΔRMSSD	0.15666 (0.0848)	0.11159 (0.2211)	0.0944 (0.3051)	-0.01337 (0.8847)	0.04183 (0.6557)	-0.07901 (0.3992)
ΔpNN50	0.13225 (0.1465)	0.13647 (0.1339)	-0.01712 (0.8527)	-0.05545 (0.5475)	0.08032 (0.3914)	-0.02502 (0.7897)
ΔSD1	0.14009 (0.1238)	0.10053 (0.2706)	0.09095 (0.3232)	-0.01231 (0.8938)	0.03913 (0.6766)	-0.07218 (0.4413)
ΔSD2	0.01545 (0.8659)	0.07462 (0.414)	0.03605 (0.6958)	0.03218 (0.7271)	-0.03072 (0.7434)	-0.08736 (0.3511)
ΔLFms^2	-0.06785 (0.4577)	0.05139 (0.574)	0.06985 (0.4503)	0.05089 (0.5826)	-0.00024 (0.9979)	-0.03057 (0.7446)
ΔHFms^2	0.13968 (0.1249)	0.06323 (0.489)	-0.00091 (0.9921)	-0.12191 (0.1866)	-0.0004 (0.9966)	-0.12899 (0.1676)
ΔLF/HF	-0.14353 (0.1147)	-0.03692 (0.6864)	-0.16039 (0.0814)	-0.02746 (0.7669)	-0.08744 (0.3528)	-0.04389 (0.6414)
ΔLFnu	-0.13258 (0.1455)	-0.00879 (0.9234)	-0.01335 (0.8854)	0.04541 (0.6239)	-0.11204 (0.2312)	-0.03758 (0.6888)
ΔHFnu	0.13141 (0.1491)	0.01979 (0.8287)	0.06022 (0.5153)	-0.00522 (0.9551)	0.06324 (0.5001)	-0.03994 (0.6704)

6.3.2 CORRELATIONS BETWEEN PRE-INTERVENTION BMI AND THE EXERCISE INDUCED RESPONSE OF HRV INDICATOR VALUES

The correlation coefficients were calculated to test for an association between pre-intervention BMI and the exercise induced response of HRV indicator values.

The correlations were calculated from a 180 second tachograms for every participant in the supine, rising and standing position. Pre-intervention BMI is summarised in Table 6-2 and the correlation results in Table 6-3.

Table 6-2 BMI determined pre-intervention

Variable	Mean	Std Dev	Median	Minimum	Maximum
BMI	22.33	3.01	21.73	17.03	32.66

Table 6-3 Correlations between pre-intervention BMI value and the exercise induced response of HRV indicator values (Δ HRV indicator values = Post HRV indicator value - Pre HRV indicator value).

BMI *vs.* ΔHRV Indicator	**Supine** Correlation (P-value)	**Rising** Correlation (P-value)	**Standing** Correlation (P-value)
ΔRR	-0.0015 (0.98)	0.1415 (0.12)	-0.0017 (0.98)
ΔSTDRR	-0.0543 (0.55)	-0.1002 (0.27)	-0.1267 (0.17)
ΔHR	-0.0117 (0.89)	-0.125 (0.17)	0.0050 (0.95)
ΔSTDHR	-0.1500 (0.09)	-0.1254 (0.17)	-0.1373 (0.14)
ΔRMSSD	0.0229 (0.80)	-0.0148 (0.87)	-0.0496 (0.59)
ΔpNN50	0.0471 (0.60)	0.0863 (0.34)	-0.0285 (0.76)
ΔSD1	0.0091 (0.92)	-0.014 (0.87)	-0.05637 (0.547)
ΔSD2	-0.1500 (0.09)	-0.0527 (0.56)	-0.1210 (0.195)
ΔLFms^2	-0.1551 (0.08)	-0.0817 (0.37)	-0.1965 (**0.034***)
ΔHFms^2	0.0284 (0.75)	0.0663 (0.47)	-0.0180 (0.847)
ΔLF/HF	-0.1577 (0.08)	-0.1252 (0.17)	0.0165 (0.860)
ΔLFnu	-0.1894 (**0.03***)	-0.0966 (0.29)	-0.0897 (0.338)
ΔHFnu	0.1698 (0.06)	0.1728 (0.06)	0.1242 (0.18)

*P<0.05

Only two correlation coefficients differed significantly from zero, i.e. between the pre-intervention BMI values and the exercise-induced responses LFnu (ΔLFnu) for recordings in the supine position (P=0.03), and $LFms^2$ in the standing position (P=0.034); however, in both cases the correlations were weak.

6.3.3 Correlation between pre-intervention fitness as estimated by indirect measurement of VO2max and the response of HRV indicator values to the exercise intervention

The correlation coefficients were calculated to test for an association between pre-intervention VO_2max and the response of the HRV indicator values to the exercise intervention. The correlations were calculated from a 180 second tachograms for every participant in the supine, rising and standing position. The results are shown in Table 6-4. Only one significant association was found, i.e., between mean HR and VO_2max during rising (r=0.0437).

Table 6-4 Correlations between pre-intervention VO2max and the exercise induced response of HRV indicator values (ΔHRV indicator values = Post HRV indicator value - Pre HRV indicator value).

VO_2max *vs.* ΔHRV Indicator	**Supine** Correlation (P-value)	**Rising** Correlation (P-value)	**Standing** Correlation (P-value)
ΔRR	0.01615 (0.8604)	-0.14961 (0.1044)	-0.03973 (0.6734)
ΔSTDRR	0.03969 (0.6656)	0.02179 (0.814)	0.01942 (0.8368)
ΔHR	0.06836 (0.4562)	0.18521 (**0.0437***)	0.07579 (0.4208)
ΔSTDHR	0.11028 (0.2285)	0.05401 (0.5596)	0.11905 (0.2051)
ΔRMSSD	0.03295 (0.7198)	0.02284 (0.8052)	0.01787 (0.8497)

VO_2max *vs.* ΔHRV Indicator	**Supine** Correlation (P-value)	**Rising** Correlation (P-value)	**Standing** Correlation (P-value)
ΔpNN50	0.03852 (0.6748)	-0.06826 (0.4608)	0.07737 (0.4111)
ΔSD1	0.0284 (0.7572)	0.02297 (0.8042)	0.01817 (0.8472)
ΔSD2	0.06682 (0.4665)	0.13625 (0.1395)	0.05585 (0.5533)
ΔLFms^2	0.06383 (0.4867)	0.05749 (0.5363)	0.0834 (0.3756)
ΔHFms^2	-0.00194 (0.9831)	-0.08192 (0.3779)	-0.04953 (0.5991)
ΔLF/HF	0.1244 (0.174)	-0.01212 (0.8963)	0.05757 (0.5429)
ΔLFnu	0.06 (0.5133)	-0.01159 (0.9009)	0.03566 (0.7052)
ΔHFnu	-0.10582 (0.248)	-0.02596 (0.7802)	-0.10447 (0.2665)
*P<0.05			

6.3.4 Correlation between pre-intervention ANS function as measured by HRV and the response of HRV indicator values

The correlation coefficients were subsequently calculated to test for an association between pre-intervention HRV indicator values and the response of HRV indicator values to the exercise intervention. The correlations were calculated from a 180 second tachograms for every participant in the supine, rising and standing position. Results are shown in Table 6-5. In this table the average pre–intervention HRV indicator is also included, followed by Δ HRV indicator, correlation and P-value.

All the pre–intervention HRV indicator values correlated significantly (P≤0.05) with the differences measured in the supine, rising and standing HRV indicator values, except for ΔpNN50 *vs.* pre–intervention pNN50 (180-360) and ΔHF *vs.* pre–intervention HF.

Table 6-5 Average pre–intervention HRV indicator value, the exercise induced response of HRV indicator values (Δ HRV = Post HRV - Pre HRV), the correlation between pre-intervention HRV indicator value (from 3 different tachograms) and P-value

Pre HRV indicator *vs.* ΔHRV Indicator	**Supine** Correlation (P-value)	**Rising** Correlation (P-value)	**Standing** Correlation (P-value)
PreRR **ΔRR** **Correlation**	0.83 +0.17 **-0.34** (<.0001)	0.67 +0.08 **-0.48** (<.0001)	0.66 +0.09 **-0.34** (<.0001)
PreSTDRR **ΔSTDRR** **Correlation**	0.051 +0.011 **-0.42** (<.0001)	0.045 +0.007 **-0.43** (<.0001)	0.031 +0.009 **-0.39** (<.0001)
PreHR **ΔHR** **Correlation**	72.58 -12.42 **-0.57**) (<.0001	90.74 -8.97 **-0.62** (<.0001)	92.08 -11.07 **-0.55** (<.0001)
PreRMSSD **ΔRMSSD** **Correlation**	57.35 +26.10 **-0.28** (<.0015)	33.2 +11.2 **-0.36** (<.0001)	22.2 +9.3 **-0.29** (0.002)
PrepNN50 **ΔpNN50** **Correlation**	34.55 +20.8 **-0.52** (<.0001)	9.4 +3.9 **-0.37** (<.0001)	2.6 +4.9 ***-0.14*** (0.13)
PreSD1 **ΔSD1** **Correlation**	40.85 +18.6 **-0.27** (0.0023)	24 +8 **-0.39** (<.0001)	15.9 +6.7 **-0.28** (0.0023)
PreSD2 **ΔSD2** **Correlation**	72.8 +11.0 **-0.54** (<.0001)	108 +23.8 **-0.47** (<.0001)	52.9 +16.2 **-0.43** (<.0001)
PreLFms^2 **ΔLFms^2** **Correlation**	243.00 +30 **-0.47** (<.0001)	356 +132.5 **-0.41** (<.0001)	155 +96 **-0.35** (0.0001)

Pre HRV indicator *vs.* ΔHRV Indicator	**Supine** Correlation (P-value)	**Rising** Correlation (P-value)	**Standing** Correlation (P-value)
PreHFms^2 **ΔHFms^2** **Correlation**	288.5 +216 ***-0.15*** (0.097)	89 +41 **-0.37** (<.0001)	35 +22 **-0.27** (0.0028)
PreLF/HF **ΔLF/HF** **Correlation**	0.96 -0.24 **-0.53** (<.0001)	3.82 +0.20 **-0.59** (<.0001)	4.91 +0.049 **-0.49** (<.0001)
PreLFnu **ΔLFnu** **Correlation**	46.45 -6.2 **-0.49** (<.0001)	76.2 -1.35 **-0.58** (<.0001)	80.3 -0.1 **-0.52** (<.0001)
PreHFnu **ΔHFnu** **Correlation**	50.1 +9.0 **-0.48** (<.0001)	19.6 -0.85 **-0.59** (<.0001)	16.4 -0.2 **-0.49** (<.0001)
***P<0.05**			

All the HRV indicators related to heart rate results from all three tachograms periods, *i.e.,* supine, rising and standing, had significant negative correlations between the pre-intervention value and the response to exercise (ΔRR *vs.* PreRR; ΔSTDRR *vs.* PreSTDRR; ΔHR *vs.* PreHR), *i.e.,* the lower the baseline RR the larger the exercise induced increase in RR; the lower the baseline STDRR, the larger the exercise induced increase in STDRR and the lower the baseline HR the smaller the exercise induced decrease in HR.

For all HRV indicators of vagal control, except one (ΔpNN50 *vs.* Pre pNN50), results from all three tachograms periods, *i.e.*, supine, rising and standing, showed significant negative correlations exist between the pre-intervention value and the response to exercise (ΔHFms^2 *vs.* PreHFms^2; ΔRMSSD *vs.* PreRMSSD; ΔpNN50 *vs.* PrepNN50; ΔSD1 *vs.* PreSD1), *i.e.*, the lower the PreHFms^2 , the larger the exercise induced increase in HFms^2; the lower the PreRMSSD, the

larger the exercise induced increase in RMSSD; the lower the baseline pNN50, the larger the exercise induced increase in pNN50, the lower the baseline SD1 the larger the exercise induced change increase in SD1.

For both indicators of mixed origin (vagal and sympathetic influence) all three tachograms periods, *i.e.,* supine, rising and standing, significant negative correlations were seen between the pre-intervention value and the response to exercise (ΔSD2 *vs.* PreSD2; $\Delta LFms^2$ *vs.* $PreLFms^2$), *i.e*., the lower the baseline SD2, the larger the exercise induced increase in SD2, and the lower the baseline $LFms^2$ the larger the exercise induced increase in $LFms^2$.

For the indicator of ANS balance (ΔLF/HF *vs.* PreLF/HF) significant negative correlation was seen between pre-intervention value and the exercise response for all three periods of recording, *i.e.* supine: the lower the baseline LF/HF, the smaller the exercise induced lowering of LF/HF. Rising and standing: the lower the baseline LF/HF the larger the exercise induced increase of LF/HF

For the indicator of ANS balance (ΔLFnu *vs.* PreLFnu) significant negative correlation was seen between pre-intervention value and the exercise response for all three periods of recording, *i.e*: the lower the baseline LFnu, the smaller the exercise induced lowering of LFnu.

For the indicator of ANS balance (ΔHFnu *vs.* PreHFnu) significant negative correlation was seen between pre-intervention value and the exercise response for all three periods of recording, *i.e* .supine: the lower the baseline HFnu, the

larger the exercise induced increase of HFnu. Rising and standing: the lower the baseline HFnu the smaller the exercise induced decrease of LF/HF

6.3.5 REGRESSION ANALYSIS FOR THE SUPINE PERIOD

Regression analysis was performed for the supine period to determine the influences the predictors on the exercise induced response of the dependant variables. The predictors (independent variables) were the baseline values for $LFms^2$, $HFms^2$, BMI, VO2 max, gender, blood pressure and the dependent variables the exercise induced changes in the specific HRV indicator values of: RR, STDRR, HR, RMSSD, pNN50, SD1, SD2, LF, HF, LF/HF, LFnu, HFnu. The results are shown in Table 6-6. The F-statistic is an indication of how the model fits and the P-value for this is also reported in Table 6-6.

Table 6-6 Summary of regression analysis for the supine period

Regres-sion model	Dependent Variable	Does the regression model fit significantly? (F-statistic)	R^2 %	Significant predictors	Significance of predictor
1	**RR**	P=0.0265	12.83	$LFms^2$	0.0279*
2	**STDRR**	P=<.0001	24.94	$LFms^2$	<0.0001*
3	**HR**	P=0.0007	19.52	$LFms^2$ $HFms^2$	0.0092* 0.0744#
4	**RMSSD**	P=0.0029	17.14	$LFms^2$	0.0022*
5	**pNN50**	P=<.0001	25.73	$LFms^2$ $HFms^2$	0.0036* 0.0047*
6	**SD1**	P=0.0054	15.98	$LFms^2$	0.0041*
7	**SD2**	P=<.0001	29.82	$LFms^2$ $HFms^2$	<0.0001* 0.0599#

Regres-sion model	Dependent Variable	Does the regression model fit significantly? (F-statistic)	R^2 %	Significant predictors	Significance of predictor
8	**LF**	P=0.0022	17.61	$LFms^2$	0.0002*
9	**HF**	P=0.4875	NA	NA	NA
10	**LF/HF**	P=0.1310	NA	NA	NA
11	**LFnu**	P=0.0001	22.73	$LFms^2$ $HFms^2$ Sys BP	0.0005* 0.0004* 0.0117*
12	**HFnu**	P=0.0039	16.56	$LFms^2$ $HFms^2$ Sys BP	0.0046* 0.0008* 0.0780#
* P<0.05 # P<0.10					

Results from this analysis indicated that the combined influence of baseline LF, HF, BMI, VO2 max, gender and blood pressure on exercise induced change in

- **RR interval**; explained 12.83% of the variation in exercise induced change measured, but it was only the baseline $LFms^2$ value that contributed significantly (P=0.028).
- **STDRR**; explained 24.94% of the variation in exercise induced change measured, and but it was only the baseline $LFms^2$ value that contributed significantly (P<0.0001).
- **HR**; explained 19.52% of the variation in exercise induced change measured, but it was only the baseline $LFms^2$ that contributed significantly (P<0.0092).

- **RMSSD**; explained 17.14% of the variation in exercise induced change measured, but it was only the baseline $LFms^2$ value that contributed significantly (P=0.0022).
- **pNN50**; explained 25.73% of the variation in exercise induced change measured, and it was the baseline $LFms^2$ and the baseline $HFms^2$ value that contributed significantly, P=0036 and P=0.0047 respectively.
- **SD1**; explained 15.98% of the variation in exercise induced change measured, and it was only the baseline $LFms^2$ value that contributed significantly (P=0.0041).
- **$HFms^2$**; the model did not fit significantly (P=0.4875).
- **SD2**; explained 38.38% of the variation in exercise induced change measured, but was only the $LFms^2$ value that contributed significantly P<0.0001.
- **$LFms^2$**; explained 17.61% of the variation in exercise induced change measured in $LFms^2$, but it was only the baseline $LFms^2$ value that contributed significantly (P=0.0002).
- **LF/HF**; the model did not fit significantly (P=0.1310)
- **LFnu**; explained 22.73% of the variation in exercise induced change measured in LFnu, and it was the baseline $LFms^2$, baseline $HFms^2$ and baseline Sys BP that contributed significantly (P=0.0005, P=0.0004, P=0.0117).
- **HFnu**; explained 16.56% of the variation in exercise induced change measured in HFnu, and it was the baseline $LFms^2$ and baseline $HFms^2$ that contributed significantly (P<0.0046 and P=0.0008).

6.4 DISCUSSION

Conflicting results are found when the effects of exercise training on the ANS are measured with HRV during exercise, directly after exercise and after a long-term exercise programme (Chapter 1). A possible explanation for heterogeneous results on exercise induced ANS changes is that the individual's response is influenced by the baseline physiological aspects thereby producing inter-subject variation in the conventional non-spectral and spectral measures of cardiovascular variability.[1]

The aim of this chapter was to investigate the possibility that there are associations between pre-intervention blood pressure, ANS function, BMI and fitness (VO_2max), on the one hand, and the response of HRV indicator values (ΔHRV = Post HRV - Pre HRV value) to the exercise intervention, on the other. If confirmed, these associations could explain some of the conflicting HRV study results reported, as well as the large between-subject variation in the non-spectral and, especially the spectral HRV measures obtained. The fact that the individual's response may be greatly influenced by the baseline sympathetic and parasympathetic autonomic function was also investigated.

6.4.1 CORRELATION BETWEEN PRE-INTERVENTION SYSTOLIC (SYS) AND DIASTOLIC BLOOD PRESSURE (DIA) AND THE EXERCISE INDUCED RESPONSE OF HRV INDICATOR VALUES

The beneficial effects of exercise on blood pressure have been widely recognised for many years. [5-9] A meta-analysis of randomized controlled intervention trials in hypertensive and normotensive, but otherwise healthy groups, reported on

average a weighted net reduction of blood pressure in response to dynamic physical training of 3.4/2.4 mmHg ($P < 0.001$).[5] Hypertensive and normotensive participants were seen to experience reduced blood pressure, often independent of weight loss, after increased physical activity. [7,8,9] It is feasible to expect that changes in the ANS must play a role in the effect of exercise on blood pressure and that pre-intervention blood pressure could influence the ANS response to exercise. However, the effects of baseline/pre-intervention blood pressure on the ANS exercise induced response in a healthy young population, is not known. In the present study the correlations between pre-intervention Sy and Dia are shown in Table 6-1. No significant relationships were found between the pre-intervention systolic or diastolic blood pressure on the one hand, and the exercise induced changes in the HRV indicator values on the other, as measured in any of the three tachogram periods.

All of the participants from the current study were young and healthy people with a mean pre-intervention Sy of 119.03 mmHg, SD=8.52 and a mean Dia of 75.10 mmHg (SD=9.56). The fact that the intervention did not have a significant influence on the blood pressure in this normotensive group is in line with the results of Fagard,[5] reporting that exercise induced BP reductions in borderline hypertensives, as well as hypertensives, are more pronounced than in normotensives. Meredith et al. reported no exercise induced BP change in younger and older normotensive men subject to the same training programme.[6]

As no significant relationships were, in this study, found between the pre-intervention systolic and diastolic blood pressure and the response of the HRV

indicator values to the exercise intervention, it is only reasonable to assume that pre-intervention blood pressure does not play a significant role in the ANS's response to an exercise programme in young, healthy normotensive individuals on a medium to high intensity exercise intervention programme. However, it is feasible to expect that individuals with abnormal pre-intervention blood pressure may give different results.

6.4.2 Correlations between pre-intervention BMI and the exercise induced response of HRV indicator values.

It is known that increased BMI is related to reduced HRV - probably due to decreased adrenoreceptor responsiveness, withdrawal of parasympathetic tone and/or increased sympathetic activity.[7,8] In the same manner changes in weight are connected to changes in HRV,[9,10] and endurance training is said to increase HRV.[11] The question therefore is whether BMI influences the response of the ANS to exercise.

In the present study, in a group with normal BMI values (mean=22.33, SD=3.01), results indicated only two (LFnu and LFms^2), significant (P=0.03 and P=0.034), but weak correlations (r= -0.1894 and r= -0.1965) between the pre-intervention BMI and the exercise-induced responses of the HRV indicator, i.e., between BMI and ΔLFnu during the supine period (Table 6-3). However, this weak correlation between BMI and baseline sympathetic control may have been epiphenomenal and needs further investigation before any conclusion can be reached. Indications that baseline BMI is perhaps not a major predictor of the HRV response was previously published by Dietrich *et al.*[12] This study showed that improvement in

HRV as a result of regular exercise was similar for obese and normal weight subjects.[12]

Results of the current study thus indicated that, within normal BMI limits, BMI does not exert a significant effect on the response of the autonomic system to exercise and that it should not be considered a major factor in the outcome of the exercise effect on HRV. However, the possibility that stronger and more significant correlations exist between BMI in over- or under weight individuals and exercise induced responses, cannot be excluded.

6.4.3 Correlation between pre-intervention fitness as estimated by indirect measurement of VO_2 max and the exercise induced response of HRV indicator values

There can be no doubt about the association between the ANS and fitness. However, results on the relationship between fitness and ANS function, as seen from HRV indicators, are inconsistent with reports varying from significant correlations to no correlations between VO2max and HRV indicators.[13-17] Nevertheless, a number of findings does confirm the link. It is, for instance, indisputable that changes in fitness, as estimated by VO2max, is associated with vagal modulation.[18] The candidate previously found weak to moderate associations in healthy young participants, between HRV indicators and performance ability or fitness (VO_{2max}).[19] A study by Hautala et al (2003) reported baseline HRV, especially the HF power spectral component, to be related to exercise induced improved aerobic power in healthy sedentary participants,[20]

However, the question whether baseline fitness will influence the ANS response as seen by HRV analysis, is unconfirmed

Results of the present study between pre-intervention fitness, as estimated by indirect measurement of VO_2max, and the response of the HRV indicator values were shown in Table 6-4. One small (r=+0.19), but significant (P=0.044), relationship was found between the indirect measurement of VO_2max and exercise induced changes in HRV. This correlation was only seen for the period of rising and not in the results from the supine or standing periods. Although pre-intervention fitness may very well have an influence on the autonomic response to exercise, it could not be confirmed by the results of this study.

6.4.4 Correlations between pre-intervention ANS function as measured by HRV and the exercise induced response of HRV indicator values

The correlations between pre-intervention ANS function, as measured by HRV indicators, and the exercise induced effect on the HRV indicator values (Post HRV indicator - Pre HRV indicator value), were shown in Table 6-5. Highly significant negative correlations (P<0.0001) were found between pre-intervention ANS function and the exercise induced differences for most of the HRV indicators, for supine, rising, as well as for standing.

All exercise induced changes related to heart rate (ΔRR, ΔSTDRR, ΔHR) showed significant negative correlations with their pre-intervention/baseline values, indicating that the higher the initial heart rate, the larger the exercise induced

lowering of heart rate. In other words, the more unfit participant showed a larger decrease in HR than the more fit.

The results for the exercise induced changes (ΔHRV) found in pure vagal HRV indicators ($HFms^2$, RMSSD, pNN50 and SD1) followed the same pattern: the lower the vagal outflow before the exercise intervention, the larger the exercise induced increase in vagal response. As it is known that vagal-related indexes are significantly higher in fit compared to unfit subjects,[21-23] this infers that unfit participants benefit more from the exercise intervention. The mixed origin (sympathetic and vagal influence) HRV indicators SD2 and $LFms^2$, showed similar patterns, *i.e*. the lower the pre-intervention variability, the higher the response. Thus, by implication one may reason that pre-intervention vagal, as well as pre-intervention sympathetic status may influence the exercise induced changes.

For all indicators of ANS balance, LF/HF, LFnu and HFnu, baseline/pre-intervention values correlated significantly with the exercise induced changes (ΔHRV). For the supine position it was found that the higher the baseline LF/HF, the larger the exercise induced lowering of LF/HF. This lowering of LF/HF implies a shift towards the parasympathetic influence in the autonomic balance. HFnu and LFnu results for the supine position confirmed this indication by showing that a) the lower the pre-intervention vagal influence (HFnu), the higher the exercise induced increase in vagal activity (HFnu) and b) the larger the pre-intervention sympathetic (LFnu) influence, the larger the exercise induced decrease. These supine results once again indicate that the more unfit the person is before the

exercise intervention, the stronger will be the shift towards vagal control, in other words, the more beneficial the intervention.

During rising and standing results on HFnu indicated that the lower the vagal influence (more sympathetic), the smaller the exercise induced decrease in vagal influence. During rising and standing results on the ANS balance (LF/HF) ratio indicated that the more sympathetic the balance pre-intervention, the smaller the exercise induced change towards sympathetic influence. The latter suggests a favourable exercise induced response in terms of blood pressure regulation upon standing up. Rising and standing LFnu correlations showed that the larger the pre-intervention sympathetic influence, the larger the decrease in sympathetic influence. During rising and standing HFnu indicated that the lower the pre-intervention value the smaller the decrease. Exercise effects during rising and standing points to have a greater effect in individuals with the lower pre-intervention orthostatic responsiveness. This is confirmed by the standing results obtained from the indicators of ANS balance. HFnu and LF/HF, showed that the exercise induced increase in vagal withdrawal during standing is larger in the more unfit person; *i.e.* an increased response to posture change.

In short, in this study correlations were found between all pre-intervention indicators of ANS function and the response of the HRV indicator values to the exercise intervention. This applies to all three periods of recording and with all three analytical techniques. All the significant correlations were negative correlations, but the direction of changes differed, some indicators increased and

others decreased in value, largely depending on the branch of the autonomic nervous system represented by the indicator.

Even though studies on the influence of baseline ANS function on HRV response to exercise are limited, the results of this study concur with published indications. For instance, a study by Levy et al.[24] showed that in older participants with a 47% lower pre-intervention HRV than younger participants, greater HRV increases (+68%) occurred than in the younger participants (+17%). The results are also in line with suggestions that when cardiac vagal control is already high, like in trained athletes, a dissociation occurs between vagal related HRV and the exercise effects, and that this limits the use of HRV measurements as predictors of exercise outcome.[25,26]

Literature further suggests that groups with a predominant sympathetic (sympathicotonia), parasympathetic (vagotonia) or balanced (amphotonia) cardiac regulation are known to exist among people of all ages.[27] It is said that the specific type of autonomic regulation determines the type of the ANS response to exercise.[27,28] In addition, Igisheva *et al*,[27] suggested that the direction of exercise induced changes in ANS depends on the characteristics of the individual‘s baseline/pre-intervention ANS status.

The results of the present study in a healthy, young population showed that the influence of baseline HRV indicators on the response to exercise can be translated to say that the more unfit the person before the exercise intervention, the larger the exercise induced changes in HRV indicators, in other words, the

more beneficial the intervention. In this study the correlations between pre-intervention ANS function as measured by HRV indicators and the response of the HRV indicator values revealed baseline ANS function as perhaps the most significant determinant of the exercise induced responses measured by HRV.

6.4.5 REGRESSION ANALYSIS

To conclude this investigation, regression analysis was performed to determine the influence of baseline values for: $LFms^2$, $HFms^2$, BMI, VO2 max, gender and blood pressure (Systolic and Diastolic), on the exercise induced changes measured in each of the HRV indicators (Table 6-6) Regression models were fitted and were significant ($P<0.05$) in all the cases except for $HFms^2$ ($P=0.4875$) and LF/HF ($P=0.1310$).

The combined effect of baseline values for: $LFms^2$, $HFms^2$, BMI, VO2 max, gender and blood pressure, appears explain a relatively small proportion of the variation (between 12.83% and 29.82%), of the exercise induced changes in HRV indicator values (RR, STDRR, HR, RMSSD, pNN50, SD1, SD2, $LFms^2$, HFnu, LFnu). The model did not fit the exercise induced changes in LF/HF and $HFms^2$. Parameters found to be significant predictors of exercise induced changes were $LFms^2$, $HFms^2$ and Sys BP in respectively 10, 5 and 2 out of the 12 regressions performed.

It is clear that $LFms^2$ was the one HRV parameter that was consistently a significant predictor ($P<0.05$) of the exercise induced changes in the HRV indicators, followed by $HFms^2$. The HRV indicator, $LFms^2$, although considered by some as an indicator of pure sympathetic cardiac control,[31,32] is in fact of mixed

origin i.e. influenced by the sympathetic and parasympathetic branches of the ANS.

According to Hautala *et al.* the large inter-individual variation to training response as well as wide inter-subject variation found in CV autonomic regulation may be due to a common denominator other than factors such as blood pressure, blood cholesterol, cardiac dimensions, BMI, and smoking.[20] These were found to together explain only ~10% of the variation in autonomic regulation. The current study results also indicated that pre-intervention physiological aspects may play only a small role in the exercise induced changes in heart rate and HRV.

In conclusion it can thus be said that the most important determinant of the response in the supine position to an exercise intervention, as indicated in this study with normal, healthy participants, is the pre-intervention ANS status.

6.5 SUMMARY CHAPTER 6

The results on the effects of physical training on the ANS as measured by HRV are often heterogeneous, even in highly standardised exercise programs The need to standardise time and period of tachogram recordings were shown in Chapter 4. In an attempt to identify possible confounding factors, this chapter investigated the associations between pre-intervention physiological status and he exercise induced HRV responses. Regression analyses were performed to determine the combined pre-intervention influences of $LFms^2$, $HFms^2$, BMI, VO2 max, gender and blood pressure, on the exercise induced changes in HRV indicator values (RR, STDRR, HR, RMSSD, pNN50, SD1, SD2, LF, HF, LF/HF, LFnu, HFnu).

Correlation results showed that one of the most likely confounding factors in exercise intervention studies is baseline ANS functioning. Highly significant correlations were found between most pre-intervention HRV indicator values and the response to the intervention. Although very few correlations were found between the exercise-induced responses and the pre-intervention levels of the other physiological variables, it is suggested that baseline BMI, blood pressure and VO_2max may also play a role in exercise induced changes in participants with above or below normal values for these physiological aspects.

Finally, the above mentioned correlation results were confirmed by the 12 regression analyses performed; when weighing the influences of pre-intervention values for $LFms^2$, $HFms^2$, BMI, VO2 max, gender and blood pressure, on the exercise induced differences in HRV indicator values, it is the baseline ANS function that may be a significant confounder in exercise studies. However, regression results further indicated that the combined effect of the pre-intervention values for: $LFms^2$, $HFms^2$, BMI, VO2 max, gender and blood pressure, appear to explain only between 12.83% and 29.82% of the variation in exercise induced changes in the autonomic nervous system.

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CHAPTER 7 IN CONCLUSION

The study investigated the effects of a twelve week exercise intervention on autonomic nervous system function, as measured by heart rate variability analyses, and identified a number of factors that could influence the results of such analyses.

The research subjects consisted of a relatively uniform group of 183 young, healthy volunteers, 100 males and 83 females. They were between 18 and 20 years of age, of approximately similar academic level, not involved in competitive sport, with no physical or psychological problems, and not on any chronic medication. Participants were of normal weight, with a body mass index of 21.4 (SD=2.16) $kg.m^2$ for the male and 23.4 (SD=3.0) $kg.m^2$ for the female participants, and had normal values for systolic (119.03 mmHg), as well as diastolic (75.10 mmHg) blood pressures. For the period of the 12 week exercise intervention they were all subjected to the same environmental conditions and to the same high-to-medium standardised exercise regime.

For the investigation of the effect of the exercise intervention on the autonomic nervous system (Chapter 5), recordings were made in the supine, rising and standing positions. Analytical techniques used were time domain, frequency domain and non-linear (Poincaré) analysis. It was hypothesized that results of exercise induced changes on ANS are dependent on the body position and should be assessed not only in the resting position, but also during standing and during an orthostatic stressor. It was further hypothesized

that it is possible to better distinguish between exercise induced changes in the vagal and sympathetic influences by taking measurements in different body positions and that obscured information in the supine position may be gathered from assessments made during the rising and standing positions.

The results of this study, for the supine position, were in agreement with previous findings of a lowering of heart rate, an increase in resting vagal control of the heart, and a general increase in HRV by exercise programs. It also showed, with the aid of deductive reasoning, that lower post-exercise heart rate may result, not only from the exercise-induced increase in vagal activity, but that a decrease in sympathetic control of the heart contribute to it.

In contrast to the results from the supine position, it was shown that the exercise intervention increased both vagal and sympathetic variation during rising, without redistribution of the spectral frequency component. After the intervention, sympathetic activity was increased, not only during rising, but also during the standing period. This, in the face of the post-exercise increase in vagal activity during standing, would be necessary for the maintenance of blood pressure in the standing position. When the influence of the exercise intervention on the orthostatic response was assessed as the difference between the stationary standing period and supine, the exercise-improved orthostatic response was indicated as a, predominantly, increase in sympathetic control. It is thus obvious that different information is obtained depending on the period over which the orthostatic response is assessed.

The work from this study thus showed that measurement of the influence of exercise on ANS functioning are dependent on the body position and assessments should be done, not only in the resting position, but also during standing and during an orthostatic stressor. It is also possible to better distinguish between exercise-induced changes in vagal and sympathetic influences by taking measurements in different body positions and during orthostatic stress. The same should be done when testing patients with cardiovascular pathology.

The second aim of the work comprised the investigation of factors that may influence the results of HRV studies. This included assessment of the importance of tachogram length, and period of recording, as well as the influence of baseline physiological characteristics, on the response to an exercise intervention. The results from the first part of this investigation, i.e., the assessment of the influence of tachogram length and period of recording, were deemed necessary for the investigation of the influence of the exercise intervention. It was therefore completed before the latter and appears in the thesis in the chapter (Chapter 4) preceding that on the exercise intervention (Chapter 5). The second part comprised the investigation of factors that may influence the results of HRV studies. This included assessment of the influence of baseline physiological characteristics, such as BMI, VO2 max, blood pressure and baseline autonomic nervous system functioning, on the autonomic nervous system's response to exercise. Regression analyses were also performed to determine the combined pre-intervention influences of $LFms^2$, $HFms^2$, BMI, VO2 max, gender and blood pressure, on the exercise

induced changes in HRV indicator values (RR, STDRR, HR, RMSSD, pNN50, SD1, SD2, LF, HF, LF/HF, LFnu, and HFnu).

Results from the technique evaluation, investigating the influence of tachogram length and period of recording, showed that the mean HRV indicator values of vagal/parasympathetic efferent activity is not influenced by small variations in tachogram length for recordings in the supine position, but definitely during rising and standing. HRV indicators influenced by the combination of sympathetic/ parasympathetic influences were shown to be tachogram length-dependent in the supine, as well as standing positions. Results of the investigation on the length and periods of recording of tachograms thus indicated that recording times in the supine position should preferably be standardised. However, standardisation is absolutely necessary during assessment of the orthostatic stress response. Upon standing-up (orthostatic stressor), the exact starting point, as well as the length of recording, is critical due to the activation and normalisation of homeostatic mechanisms. Starting the recording too late will miss out on the initial response to a change in body position. Longer recording times during application of the orthostatic stressor will reflect the mean of HRV values obtained during the orthostatic response and that obtained after stabilisation in the standing position.

Results on the influence of pre-intervention values of physiological parameters on the outcome of exercise interventions showed one of the most likely confounding factors in exercise intervention studies to be baseline ANS

functioning. Highly significant correlations were found between most pre-intervention HRV indicator values and the response to the intervention. Very few correlations were found between the exercise-induced responses and the pre-intervention levels of the other physiological variables. It should, however, be kept in mind that the study was done on young, normal, healthy individuals with normal BMI and blood pressure values and of average fitness. The results of this part of the study thus indicate that baseline physiological variables, such as blood pressure, fitness and BMI, do not have a significant influence on the HRV response to exercise, as long as these physiological values are within normal limits. However, it is suggested that they may play a role in exercise induced changes in participants with above or below normal values.

The influences of pre-intervention physiological variables were subsequently examined by performing 12 regression analyses. When weighing the influences of pre-intervention values for $LFms^2$, $HFms^2$, BMI, VO2 max, gender and blood pressure, on the exercise induced differences in HRV indicator values, it was confirmed that baseline ANS function could be a significant confounder in the outcome of exercise study results. However, regression results indicated that the combination of pre-intervention values for: $LFms^2$, $HFms^2$, BMI, VO2 max, gender and blood pressure, contributes only between 12.83% and 29.82%, depending on the HRV variable, to the exercise induced changes in the autonomic nervous system.

In conclusion, it can be said that the work for this thesis contributes to our knowledge on HRV assessment of the influence of exercise on the autonomic nervous system by showing that assessment in the supine position alone does not give a complete picture and that additional knowledge can be obtained by simultaneous assessments in supine, rising and standing. This is also of significance for patients with cardiovascular and other problems where exercise interventions are therapeutically prescribed. It further contributes to our understanding of the role of pre-intervention physiological status on the response to exercise. It was shown that, although pre-intervention autonomic status is an important factor in the outcome, the combined effect of physiological characteristics is not big enough to account for the controversies and variations in published results. The results further contribute to our ability to predict the influence of pre-intervention values on the exercise outcome by making the connection between fitness and autonomic nervous system characteristics. The influence of baseline HRV indicators on the response to exercise can be translated, at least in a young healthy population, to say that the more unfit, in terms of HRV indicators, before the exercise intervention, the larger the exercise induced changes in HRV indicators, in other words, the more beneficial the intervention.

SUGGESTIONS FOR FURTHER STUDY

Various aspects of this study should be investigated in further detail, but it is suggested that at least the following are necessary:

- To test whether a more significant impact of pre-intervention values on the exercise response is seen in patients with abnormal values such as hypertension/hypotension or overweight/underweight. Indications to

this effect were already found in this study in the negative correlations seen between baseline HRV values and the exercise-induced responses.

- To compare, in patients with cardiovascular disorders, the value of investigations done only on supine recordings to that done over three periods (supine, rising and standing) and, based on the outcome of such studies, make recommendations for assessments in patients with cardiovascular disorders.

~The End~

APPENDIX 1 SUMMARY OF DATA

Supine

Variable	Mean	Median	Std Dev	Minimum	Maximum
PreRR	0.85	0.83	0.13	0.59	1.33
PreSTDRR	0.05	0.05	0.02	0.01	0.13
PreHR	72.81	72.58	10.94	45.38	102.73
PreSTDHR	4.99	4.83	2.04	0.78	16.57
PreRMSSD	62.82	57.35	33.36	9.40	164.70
PrepNN50	33.72	34.55	21.83	0.00	78.00
PreSD1	44.72	40.85	23.74	6.70	117.20
PreSD2	79.43	72.80	36.95	13.50	215.90
PreLFms^2	361.0	243.0	396.9	0.0	2423.0
PreHFms^2	415.8	288.5	391.3	7.0	1892.0
PreLF/HF	1.53	0.96	3.13	0.00	34.97
PreLFnu	44.99	46.45	19.99	0.00	86.20
PreHFnu	49.98	50.10	19.28	2.10	117.30
PostRR	1.01	1.00	0.16	0.66	1.40
PostSTDRR	0.07	0.07	0.03	0.01	0.19
PostHR	61.38	60.39	9.96	43.75	90.48
PostSTDHR	4.60	4.32	1.82	1.06	9.30
PostRMSSD	89.98	83.95	44.72	9.10	223.20
PostpNN50	52.48	58.45	22.03	0.00	90.20
PostSD1	64.61	60.10	31.58	6.50	158.80
PostSD2	94.42	86.10	47.15	20.40	300.30
PostLFms^2	517.6	329.5	873.2	0.0	9113.0
PostHFms^2	779.4	525.5	729.8	11.0	5023.0
PostLF/HF	2.38	0.64	10.13	0.00	94.10
PostLFnu	38.07	38.20	19.16	0.00	88.80
PostHFnu	56.89	58.95	20.38	0.00	101.00

Rising: Time = 0-180 seconds

Variable	Mean	Median	Std Dev	Minimum	Maximum
PreRR	0.70	0.67	0.11	0.53	1.01
PreSTDRR	0.05	0.05	0.02	0.01	0.11
PreHR	89.28	90.74	12.49	62.15	114.46
PreSTDHR	7.97	8.01	2.20	1.38	12.67
PreRMSSD	38.56	33.20	20.73	4.40	102.20
PrepNN50	14.20	9.40	13.96	0.00	58.60
PreSD1	27.72	24.00	14.79	3.30	72.60
PreSD2	118.4	108.0	49.0	41.7	319.5
PreLFms^2	446.0	356.0	373.8	0.0	2669.0
PreHFms^2	155.1	89.0	172.9	-25.0	753.0
PreLF/HF	5.47	3.82	17.50	-146.66	122.05
PreLFnu	73.14	76.20	19.03	0.00	104.80
PreHFnu	23.84	19.60	18.60	-5.90	114.70
PostRR	0.78	0.78	0.13	0.54	1.18
PostSTDRR	0.06	0.05	0.02	0.01	0.12
PostHR	80.12	78.84	12.14	51.15	112.27
PostSTDHR	7.54	7.58	2.27	2.06	13.37
PostRMSSD	49.67	47.10	26.26	8.80	158.40
PostpNN50	20.54	14.90	17.10	0.00	76.20
PostSD1	35.70	34.20	18.70	6.40	112.80
PostSD2	139.41	130.60	54.31	42.20	292.10
PostLFms^2	603.7	472.5	501.4	0.0	3404.0
PostHFms^2	239.5	161.0	225.3	6.0	1207.0
PostLF/HF	6.34	3.46	12.34	0.00	94.70
PostLFnu	68.75	73.55	20.86	0.00	95.20
PostHFnu	26.07	22.15	17.23	0.00	84.20

Standing: Time = 180-360 seconds

Variable	Mean	Median	Std Dev	Minimum	Maximum
PreRR	0.67	0.66	0.10	0.52	1.02
PreSTDRR	0.03	0.03	0.01	0.01	0.09
PreHR	91.83	92.08	11.69	58.96	114.78
PreSTDHR	5.06	4.86	1.69	1.58	11.69
PreRMSSD	25.81	22.20	15.49	5.00	86.90
PrepNN50	8.16	2.60	12.57	0.00	64.90
PreSD1	18.46	15.90	11.03	3.60	61.90
PreSD2	58.10	52.90	25.55	18.30	155.80
PreLFms^2	248.2	155.0	254.8	15.0	1630.0
PreHFms^2	75.7	35.0	105.9	0.0	699.0
PreLF/HF	12.76	4.91	24.07	0.15	99.00
PreLFnu	74.83	80.30	19.50	12.20	111.90
PreHFnu	22.33	16.40	18.15	0.00	83.40
PostRR	0.75	0.75	0.12	0.52	1.20
PostSTDRR	0.04	0.04	0.02	0.01	0.12
PostHR	81.95	80.54	12.40	50.50	116.47
PostSTDHR	5.46	5.06	2.18	1.88	20.89
PostRMSSD	39.36	32.00	29.23	5.10	211.10
PostpNN50	15.71	8.95	17.16	0.00	78.70
PostSD1	27.28	22.75	18.45	3.70	110.00
PostSD2	79.32	76.55	34.98	20.10	219.30
PostLFms^2	419.4	285.5	401.1	0.0	2210.0
PostHFms^2	143.0	77.5	210.6	0.0	1586.0
PostLF/HF	10.63	4.86	29.70	0.00	316.35
PostLFnu	73.88	79.75	18.73	0.00	97.80
PostHFnu	22.37	16.70	17.06	0.00	71.60

Standing: Time = 360-540 seconds

Variable	Mean	Median	Std Dev	Minimum	Maximum
PreRR	0.66	0.64	0.10	0.52	0.98
PreSTDRR	0.03	0.03	0.02	0.01	0.18
PreHR	93.10	93.79	12.31	62.05	115.27
PreSTDHR	4.99	4.70	1.86	1.18	12.58
PreRMSSD	24.51	19.65	16.53	4.80	90.20
PrepNN50	7.20	1.95	12.27	0.00	63.10
PreSD1	17.43	14.10	11.43	3.50	64.30
PreSD2	55.87	49.85	25.61	14.10	178.00
PreLFms^2	222.1	143.5	227.0	0.0	1312.0
PreHFms^2	67.6	32.5	91.5	0.0	483.0
PreLF/HF	11.28	4.47	20.67	0.00	100.00
PreLFnu	75.17	80.50	18.38	0.00	100.20
PreHFnu	21.38	17.75	16.66	0.00	73.50
PostRR	0.75	0.74	0.12	0.42	1.21
PostSTDRR	0.05	0.04	0.02	0.01	0.10
PostHR	82.46	81.77	13.62	49.68	150.45
PostSTDHR	5.62	5.01	3.22	1.80	28.10
PostRMSSD	37.64	31.15	23.44	2.40	147.40
PostpNN50	15.84	9.85	17.30	0.00	77.60
PostSD1	26.95	22.25	16.71	1.70	104.70
PostSD2	78.90	75.65	34.48	17.40	205.10
PostLFms^2	477.7	344.5	510.3	0.0	4369.0
PostHFms^2	140.6	70.0	187.0	0.0	1411.0
PostLF/HF	10.40	4.44	29.49	0.00	317.89
PostLFnu	75.74	80.00	17.05	0.00	98.90
PostHFnu	21.81	17.55	16.73	0.00	73.10