CHAPTER TWO: LITERATURE REVIEW

2.1 PATHOGENESIS AND ETIOLOGY
2.2 CLINICAL FEATURES
2.3 AUTONOMIC DYSFUNCTION IN RHEUMATOID ARTHRITIS
2.4 ROLE OF EXERCISE
Figure 2.1: Summary of Literature Review
RHEUMATOID ARTHRITIS

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

2.1 PATHOGENESIS AND ETIOLOGY

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

2.1.1 ROLE OF IMMUNITY

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

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

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

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

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

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2.1.2 GENDER (HORMONAL)

As with many other auto-immune diseases, RA has a predominance in women. The female to male ratio is 2:1 to 3:1. The specific mechanisms for this are not clear, but exposure to estradiol seems to make autoantibody producing B-cells more resistant to apoptosis. The effect on the T-cells are more difficult to explain, because estrogen tends to favour T-lymphocyte differentiation towards T-helper type 2 cells which produces anti-inflammatory cytokines\(^{(1)}\). Various methods have been utilized to explore the role of
estrogens\(^4\). RA has a reduced incidence in women on contraceptives and it appears to be less active during pregnancy with recurrence in the post-partum period.

### 2.1.3 TOBACCO

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

### 2.1.4 INFECTION

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

<table>
<thead>
<tr>
<th>Infectious Agent</th>
<th>Potential Pathogenic Mechanisms</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Mycoplasma</em></td>
<td>Direct synovial infection; superantigens</td>
</tr>
<tr>
<td>Parvovirus B19</td>
<td>Direct synovial infection</td>
</tr>
<tr>
<td>Retroviruses</td>
<td>Direct synovial infection</td>
</tr>
<tr>
<td>Enteric bacteria</td>
<td>Molecular mimicry (QKRAA)</td>
</tr>
<tr>
<td><em>Mycobacterium</em></td>
<td>Molecular mimicry (proteoglycans, QKRAA), immunostimulatory DNA</td>
</tr>
<tr>
<td>Epstein-Barr virus</td>
<td>Molecular mimicry (QKRAA)</td>
</tr>
<tr>
<td>Bacterial cell walls</td>
<td>Macrophage activation</td>
</tr>
</tbody>
</table>

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2.1.5 GENETICS

A shared epitope of the HLA-DR$_4$ cluster (HLA-DR beta *0401, 0404, or 0405) is carried by approximately 60% of patients with RA in the United States. HLA-DR$_1$ (HLA-DR beta *0101) also carries this shared epitope$^{(3)}$. Polymorphisms on many other non-HLA genes e.g. the ones associated with PADI are currently under investigation$^{(1)}$. 
2.2. CLINICAL FEATURES

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

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

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

2.2.2.3 Intermediate onset
Symptoms develop over days to weeks in 15-20% of cases. Systemic complaints are more on the foreground than in insidious type of onset\textsuperscript{(13)}.

2.2.2.4 Unusual patterns (variants) of disease\textsuperscript{(14)}
2.2.2.4.1 Palindromic
Symptoms include pain, swelling and erythema of joints or peri-articular tissues that worsen over hours to a few days. In reverse sequence, symptoms resolve without leaving residual effects. 50% of patients will continue to develop RA.
2.2.2.4.2 Rheumatoid Nodulosis
A variant disorder with subcutaneous nodules, recurrent pain and swelling in different joints, and subchondral bone cysts on imaging.

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

2.2.2.4.4 RA and Paralysis
In patients with strokes, cerebral palsy, poliomyelitis etc, joints are spared on the paralysed side.
2.2.3 CLASSIFICATION

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

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

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

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


If at least 4 of the 7 criteria are present for at least 6 weeks it is 77-95% sensitive and 85-98% specific for RA. It is however important not to exclude the diagnosis on this alone as it is not a diagnostic tool for early disease\(^{(11)}\). More recently the 2010 ACR-EULAR classification criteria for RA was published\(^{(16)}\).
2.2.4 CONSTITUTIONAL SYMPTOMS
Patients often present with constitutional symptoms including malaise, weight loss, loss of appetite, fever, fatigue and myalgia\(^{(11)}\).

2.2.5 JOINT INVOLVEMENT
Joint involvement is the characteristic feature of RA. Well-documented descriptions of specific joint involvement were mostly reported in the decades before 1980. Stress put on individual joints by the patient as well as the intensity of the disease and its chronicity determines the effect of synovitis on joints\(^{(14)}\).

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

Table 2.3: Distribution of joints involved in attacks based on a cumulative experience with 227 patients\(^{(14)}\)

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

MCP Metacarpophalangeal  
PIP Proximal interphalangeal  

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Affected joints show inflammation with warmth, swelling, tenderness and decreased range of motion (ROM). RA results in characteristic deformities if inflammation is not controlled, including:
• boutonniere and swan-neck deformities
• ulnar deviation
• hammer toes
• joint ankylosis
2.2.6 EXTRA-ARTICULAR MANIFESTATIONS

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

**Table 2.4: Extra-articular features of rheumatoid arthritis**

<table>
<thead>
<tr>
<th>Pulmonary</th>
<th>On post-mortem up to 75 %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pleural effusions/pleurisy</td>
<td>Most common. Often asymptomatic, small effusions. Unilateral or bilateral. Usually exudates - mixed cell counts, high LDH, low glucose. Presence of multi-nucleated giant cells highly specific.</td>
</tr>
<tr>
<td>Nodules</td>
<td>Mainly seropositive patients with widespread synovitis and nodules. Usually asymptomatic. Peripheral or pleural in location.</td>
</tr>
<tr>
<td>Pulmonary Fibrosis</td>
<td>Up to 6% of patients develop systematic fibrosis within 10 years of RA onset. Men &gt; women. Association with nodules. Usually bibasal. May be asymmetrical. Larger proportion may be asymptomatic. Contribution of methotrexate therapy debated.</td>
</tr>
<tr>
<td>Obstructive airways disease</td>
<td>Associated with inflammation, constrictive bronchiolitis, crico-arytenoid joint involvement. Up to 50% bronchiectasis on CT scan.</td>
</tr>
<tr>
<td>Bronchiolitis obliterans organizing pneumonia (BOOP)</td>
<td>Associated with fever and constitutional symptoms.</td>
</tr>
<tr>
<td>Shrinking lung syndrome, pulmonary arteritis and primary pulmonary hypertension are very rare.</td>
<td>On post-mortem up to 50%.</td>
</tr>
</tbody>
</table>

| Cardiac | |
| Coronary artery disease | RA is an independent risk factor, particularly with persistently elevated ESR/CRP. Increased risk of cardiovascular death - myocardial infarction. |
| Pericarditis | Mainly seropositive patients with widespread nodules. Usually asymptomatic. |
| Valvular abnormalities, myocarditis and arteritis/aortitis are rare. | |

| Haematological | |
| Anaemia | Correlates with disease activity. Abnormal iron utilization. Inhibition of erythropoiesis. |
| Thrombocytosis | Correlates with disease activity |
| Leucopenia | Felty’s syndrome - in association with splenomegaly. May also have thrombocytopenia. Variant may have neutropenia without splenomegaly. Increased risk infection and lymphoproliferative disease including malignancies. |
| Lymphadenopathy | Common with active disease, can be associated with splenomegaly. |

| Neurological | |
| Mononeuritis multiplex/sensory neuropathy | Associated with RA vasculitis (<1%) |
| Nerve impingement | Secondary to joint inflammation and destruction. Peripheral nerves and nerve roots. Secondary to atlanto-axial or sub-axial subluxation due to erosive/destructive disease of the spine. Less commonly seen with aggressive early treatment of active RA. Important to consider pre-procedures requiring sedation where the neck may be subjected to extension (e.g. intubation, endoscopy). |
| Cervical cord compression | Typically affecting smaller vessels with skin manifestations; leucocytoclastic vasculitis, capillaritis, chronic skin ulcers, infarcts (nail-fold infarct in up to 5%, does not seem to be associated with poorer outcome). Vasculitis can affect larger vessels and is more common with Felty’s syndrome. Joint disease may not be active. |
| Vasculitis (<1%) | Contributes to renal, neurological, cardiac and gastrointestinal complications. Associated with high RF levels and cryoglobulins. |

| Liver | Elevated liver function tests are not uncommon and parallel disease activity. Can be difficult to distinguish from drug effects (NSAIDs or DMARDs). Generally is due to drug treatment liver function should improve with discontinuation of the drug. Hepatomegaly can occur with Felty’s syndrome. Rarely nodular regenerative hyperplasia can occur. |

| Renal | Renal abnormalities more commonly secondary to drug effects (NSAIDs, some DMARDs). Rarely low-grade membranous nephropathy, glomerulitis or vasculitis can occur with RA. Nephrotic syndrome is seen with secondary amyloidosis - less common now with adequate inflammation control. |

| Ocular | Keratoconjunctivitis sicca is most common, associated with xerostomia from secondary Sjögren’s syndrome in up to 10% of patients. Episcleritis can occur with active RA. Scleritis indicates associated vasculitis and if persistent can result in scleromalacia, though seen less commonly with adequate inflammation control. Glaucoma and cataracts can occur as a result of drug therapy corticosteroids. |

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

2.2.6.1 **Muskuloskeletal involvement**

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

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

Most patients have muscle weakness, but only a few have muscle tenderness with elevated muscle enzymes\(^{(14)}\). Recent studies have described at least 5 different types of muscle involvement in RA:

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

Other commonly described musculoskeletal manifestations include tenosynovitis and associated tendon rupture as well as carpal tunnel syndrome\(^{(3)}\).

A further problem is bone loss due to systemic disease and/or glucocorticosteroid treatment, increasing the risk for stress fractures, fractures and generalized osteoporosis\(^{(20)}\).

2.2.6.2 **Cardiac involvement**

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

- Atherosclerosis
- Conduction defects
- Coronary arteritis
- Aortitis\(^{(14)}\).

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

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

**Figure 2.3: The complex interactions between RA characteristics, cardiovascular risk factors, genetic determinants and therapies on the development of preclinical and overt cardiovascular disease in RA\(^{(28)}\).**

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

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

2.2.6.2.1 Conventional Cardiovascular Risk Factors

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

**Table 2.5: Prevalence of traditional cardiovascular risk factors at RA incidence in RA and non-RA patients\(^{(27)}\)**

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

BMI, body mass index; RA, rheumatoid arthritis


The authors next examined the impact of conventional risk factors on cardiovascular outcome, which was defined as a combined endpoint including heart failure, myocardial infarction and cardiovascular (CV) death. Interestingly, a threelfold increased risk of CV
death was associated with a low BMI among RA patients. Lipids appeared to have a paradoxical effect, while the relative impact of the other risk factors (gender, smoking, personal- or family cardiac history, hypertension and diabetes mellitus) appeared to be significantly less in RA patients compared to non-RA patients (Figure 2.4).

The above findings were noted by other authors like Kitas and Avina-Zubieta, as well as Maradit-Kremers et al who in their study concluded that “the risk of CV disease in RA precedes the American College of Rheumatology (ACR) criteria-based diagnosis of RA, and the risk cannot be explained by an increased incidence of traditional CV disease risk factors in RA patients”, ²³,²⁹,³⁰. Myasoedova commented that RA not only represents an important modifier of conventional CV risk factors, but also has a role to play as an independent risk factor²⁸.

Figure 2.4: Relative impact of traditional CV risk factors on combined CV endpoint in RA and non-RA subjects²⁷

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²³: The American College of Rheumatology (ACR) criteria-based diagnosis.
²⁷: Relative risk comparison.
²⁸: Myasoedova's comment on RA's role as an independent risk factor.
²⁹,³⁰: Additional references.
2.2.6.2.2 Accelerated atherosclerosis and chronic inflammation

There is compelling evidence that chronic inflammation has a pivotal role in the etiopathogenesis of atherosclerosis\(^{(31)}\). Several recent studies demonstrated the independent association of inflammatory indicators and RA towards an increased risk for CV disease\(^{(27,32-35)}\). RA activity and severity, high C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), rheumatoid factor (RF), ACPA and HLA DRB\(_1\) gene are statistically significantly associated with increased risk of CV events\(^{(33,34,36-39)}\).

The Autonomic Nervous System (ANS) is one of a variety of neuronal pathways that have been implicated in modulating inflammation\(^{(40)}\). The “cholinergic anti-inflammatory pathway” is a well studied mechanism where signals transmitted via the vagus nerve control the release of cytokines, reducing the production of pro-inflammatory cytokines by an \(\alpha-7\) nicotinic acetylcholine receptor (\(\alpha7nAChR\)) dependent mechanism, and therefore ameliorating inflammatory disease\(^{(41-43)}\).

Recent studies have shown improved survival in animal models of inflammation by stimulation of the vagus nerve via electrical or pharmacological methods\(^{(42,44-46)}\). Goldstein et al in a prospective observational study found that RA patients had an increase in high mobility group box-1 (HMGB\(_1\)) – a pro-inflammatory cytokine – and a decrease in cholinergic anti-inflammatory pathway activity as measured by heart rate variability (HRV). They postulated that it would be interesting to consider if subclinical CV disease is the result of increased inflammation secondary to decreased vagus nerve activity\(^{(47)}\).

2.2.6.2.3 Conduction disorders and Arrhythmias

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

Autonomic dysfunction in patients with RA, has been studied. The literature was reviewed by searching different databases and consulting standard textbook references. The search was conducted to cover a period of 48 years (1963-2011). Databases included Ovid Medline, PubMed, Scopus, Google Scholar. Textbooks consulted included Kelly Harris’ Textbook of Rheumatology, Dieppe’s Rheumatology, Mathias CJ Bannister’s Autonomic failure: a textbook of clinical disorder of the autonomic nervous system (1999) and E Oribe’s Testing autonomic function, from Handbook of clinical neurology, 1999, p595-647. Figure 2.5 shows the route that was followed for the literature review.
Figure 2.5: Database Search (1963-February 2011)
The 27 articles will now be discussed. The measurements utilized and background of each article is summarized in Table 2.7 which can be found at the end of the chapter.

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

2.3.2 CARDIOVASCULAR REFLEX TESTS (CRT)
Ewing described a test battery to evaluate cardiac autonomic function\(^{54-56}\). This battery tested the parasympathetic nerve function as follows:

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

and the sympathetic nerve function:

i. Blood pressure response to standing
ii. Blood pressure response to sustained handgrip.
These measurements were adopted by some authors to test for autonomic dysfunction in RA patients\(^{(57-59)}\) while other used shorter or modified versions\(^{(60-68)}\).

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

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

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

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

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

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

When age was taken into account the group <60 years of age showed significant differences for the same measurements as for the whole group compared to the CG. The group >60 years of age showed a significant difference only for the blood pressure response to sustained handgrip. Contrary to previous authors’ findings, Sandhu reported a positive correlation for ANS impairment and presence of RF as well as disease duration\(^{(57)}\). A further study was performed by Stojanovich, who evaluated cardiovascular ANS function in patients with SLE, RA, Sjögren syndrome, scleroderma...
and Polymyalgia Rheumatica (PMR). They correlated the ANS function to clinical features. They reported that in all tests higher percentages of the different patient groups demonstrated abnormal results compared to the controls (p <0.05). No correlation was found between ANS dysfunction and disease duration, clinical manifestations or disease activity\(^{(58)}\).

Bidikar investigated sympathetic nervous system involvement in RA. 50 RA patients were compared to 50 healthy controls. Compared to the controls the RA patients had a significant higher resting HR and blood pressure (BP). Significant differences were also shown for the sympathetic autonomic function tests between the two groups\(^{(61)}\).
2.3.3 FOUR TASKS INDICATING AUTONOMIC FUNCTION

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

2.3.4 PRE-EJECTION PERIOD AND RESPIRATORY SINUS ARRHYTHMIA

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

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

2.3.6 PUPILLOGRAPHY

By using an infrared light reflection method, one can measure both parasympathetic function (constriction latency and latency of maximum constriction velocity) and sympathetic function (dilatation latency). Barendregt used this method to study autonomic dysfunction in 18 RA patients with ocular dryness, 18 RA patients without ocular dryness and 33 healthy controls. Constriction latency and maximum constriction velocity latency were prolonged in RA patients with ocular dryness compared to the other two groups (p <0.05). Dilation latency did not differ between the three groups, neither was any correlation found between pupillography and age, disease duration or DAS score\(^{(75)}\). Schwemmer et al used a combination of pupillography and cardiovascular reflex tests to assess the prevalence and the characteristics of autonomic dysfunction in RA. This was followed by a longitudinal study to investigate if disturbed autonomic function is linked to higher mortality. Autonomic dysfunction was demonstrated in 60% of patients, with the prevalence for pupillary autonomic dysfunction (PAD) 15 out of 30 (50%) and for cardiac autonomic dysfunction (CAD) 6 out of 30 (20%). During the longitudinal study (8 years observation), 4 out of 30 patients died. The non-survivors did not differ at baseline with regards to age, gender, disease duration, swollen joint count, tender joint count, Visual Analogue Scale (VAS) for pain, Physician’s Global Assessment, or medicine from survivors. Both CAD and PAD were
more frequent in non-survivors, perhaps indicating that autonomic dysfunction might be linked to higher mortality (76).
2.3.7 HRV

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

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

Evrengul was one of the first authors applying this method to assess the autonomic function in patients with RA. They used time domain and frequency domain analysis in 42 RA patients and 44 healthy subjects. Recordings were obtained over an hour. Results conflicted between time and frequency domain parameters, but they defended this by pointing out that frequency domain analysis are more precise than time domain analysis by referring to work done by Fei in 1996 and Howorka in 1998\(^{(78,79)}\). They concluded that their data suggested “an increase in sympathetic control of the heart rate in patients with RA”. No correlation between HRV parameters and stage of RA, disease duration or ESR was found\(^{(80)}\). Anichkov followed suit and investigated HRV parameters in RA patients, however recordings were obtained over 24 hours. Compared with controls, all time domain and Poincare parameters were significantly lower in RA patients. Contrary to most other studies already discussed they found a positive correlation between autonomic dysfunction and disease activity\(^{(81)}\).

HMGB\(_1\) is a pro-inflammatory cytokine and increased expression in synovium of RA patients has been shown. The cholinergic anti-inflammatory reflex (vagus nerve dependent) inhibits the release of HMGB\(_1\) in experimental disease models\(^{(82)}\). Goldstein
et al did a study in RA patients where the results indicated that elevated levels of HMGB₁ correlated with depressed levels of vagus nerve activity as measured by time domain and frequency domain analysis⁴⁷. The same group in another study on RA patients hypothesized that cytokine release can be suppressed by adding cholinergic agonists to whole blood cultures stimulated with endotoxin, even if vagus nerve activity is significantly reduced. Although their results showed reduced vagus nerve activity in the RA group compared to the healthy group, there was a significant age difference (p<0.05) with the RA group being older than the CG. This might have affected the result favouring the RA group, but previous authors⁵⁷,⁸¹ did not find age in RA patients to be a confounding factor. In the second phase of the study they proved their hypothesis to be correct⁸₃.

Aydemir published a study on the cardiac autonomic profile of RA and SLE patients. They utilized both cardiac reflex tests and heart rate variability parameters. The groups consisted of 36 RA, 38 SLE and 40 Control subjects. The results showed that autonomic dysfunction is common in patients compared to controls, with RA patients having abnormal results in 61-75% of cases. There was a significant association between the different methods utilised. They found no relation between autonomic dysfunction and autoantibody positivity, disease duration or disease activity, supporting other authors’ findings⁵⁸,⁵⁹,⁶₄,⁶₅,⁶₈,⁷₅,⁸₀. Another author that made use of a combination of methods to assess ANS dysfunction in RA and SLE patients, is Milovanovic. They aimed to evaluate the presence and level of ANS dysfunction as well as to identify cardiovascular risk factors associated with sudden cardiac death. In all measurements abnormal findings were significantly higher in the patient groups, but prolonged QT’s interval was only significant in SLE patients. Although both diseases were associated with depressed HRV, in the RA group vagal predominance was evident while in the SLE group it was mostly higher sympathetic activity. They pointed out that there are still great discrepancies regarding published data on autonomic nervous system function in immunologic disorders with findings ranging from normal to grossly abnormal⁶₆.

Vlcek in a small study (8 RA and 8 Control subjects) aimed to assess symphatoneural and adrenomedullary reactivity to changes in body position. Blood samples for epinephrine, norepinephrine (NE) and a sympathetic co-transmitter Neuropeptide Y
(NPY) were drawn during the course of HRV measurements. Levels for epinephrine were lower at baseline (p 0.053) and to orthostatic response (p 0.079), while NE levels were higher at baseline (p 0.034) but with no difference to orthostatic response comparing the RA group with the controls. No difference was shown for NPY or HRV parameters between the two groups. The authors concluded that their study “showed increased basal sympathetic activity and a tendency toward smaller adrenomedullary response to orthostasis in RA patients”\(^{(84)}\).

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

i. Can response to treatment be compared between different diseases (i.e. pathogenesis differ)?

ii. HRV was measured by an assessment tool (Omegawave) not previously validated in pathological conditions\(^{(85)}\).

2.3.8 HEART RATE TURBULENCE (HRT)

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

i. Turbulence onset (TO) is a measure of the initial acceleration after a premature ventricular complex due to vagal inhibition.

ii. Turbulence slope (TS) measures the rate of sinus deceleration that follows sinus acceleration with both parasympathetic and sympathetic contribution.

The response of the sinus node to premature ventricular complexes is reflected by HRT, while HRV describes variations in both RR-intervals and instantaneous heart rate. In this study of 26 RA patients and 26 healthy controls TO and TS did not show significant differences between the two study groups\(^{(86)}\).
2.3.9 SUMMARY OF LITERATURE ON AUTONOMIC DYSFUNCTION IN RA

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

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

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

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

- All studies did not comment on exclusion criteria (i.e. co-morbid diseases like diabetes$^{(56,87)}$ and hypertension$^{(68,89)}$ as well as medications used e.g. anti-arrhythmics and β-blockers will influence autonomic function). Stojanovic even included patients with HT and DM.
- Environment was not stabilized in all studies$^{(70)}$.
- Male and female subjects were used in the same study. Previous studies showed differences in HRV between males and females$^{(90-92)}$. 


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

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

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

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

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

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

No Randomised Control Trials (RCT) based on walking as the main focus have been conducted\(^{(98)}\), while studies focusing on aquatics suggest improvement of aerobic
capacity\textsuperscript{(119,140,141)}, muscle strength\textsuperscript{(106,120)} and psychological status\textsuperscript{(119)}. Studies on combination training showed positive influence on both cardiorespiratory fitness and muscle strength\textsuperscript{(126,142)}.

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

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

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

<table>
<thead>
<tr>
<th>Class</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I</td>
<td>Completely able to perform usual activities of daily living (self-care, vocational, and avocational)</td>
</tr>
<tr>
<td>Class II</td>
<td>Able to perform usual self-care and vocational activities, but limited in avocational activities</td>
</tr>
<tr>
<td>Class III</td>
<td>Able to perform usual self-care activities, but limited in vocational and avocational activities</td>
</tr>
<tr>
<td>Class IV</td>
<td>Limited in ability to perform usual self-care, vocational, and avocational activities</td>
</tr>
</tbody>
</table>

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


Iversen has shown that rehabilitation started early in disease is more effective\textsuperscript{(153)}, and Geenen et al have shown diminished ANS responsiveness in patients with early RA disease\textsuperscript{(69)}. These facts further strengthen the motivation to recruit patients with early disease (class 1 and 2 patients).
Stenstrom and Minor investigated the evidence for the benefit of aerobic and strengthening exercise in RA. They drew recommendations for exercise intervention from this evidence based approach. For aerobic exercise they concluded that in the light of the reviewed studies, the intensity level should be moderate to hard (60-85% of heart rate maximum) performed 3 times weekly for a duration of 30-60 minutes. Exercise can be land- or water based and progressive adjustment of the intensity was recommended.

For resistance training they concluded that the load level of strengthening exercises should be moderate to hard (50-80% of a maximal voluntary contraction) and performed 2-3 times per week. Exercises can be static or dynamic and performed with various types of equipment or against body weight. A progressive adjustment of load was recommended\(^{(100)}\).

A further suggestion made by them was that it is important to start documenting exercise response in terms of the individual’s characteristics, as response criteria have been published for drug trials but those are not specifically applicable to exercise studies\(^{(100)}\).
2.5 ASSESSMENT OF DISEASE ACTIVITY

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

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

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

- DAS\(_{28}\)\(^{155-157}\).
- Visual analogue scale (VAS)\(^{158-160}\).
- Health assessment questionnaire (HAQ)\(^{161,162}\).

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

2.6 CONCLUSION

The literature review has shown:

- There are extra-articular manifestations associated with increased mortality in patients with RA
- Patients with RA have cardiac involvement, and the autonomic nervous system (ANS) may play a role
- ANS dysfunction has been proven in patients with RA, but different measurements were used and there are still uncertainties left
- Exercise can improve ANS dysfunction in the general population, in cardiac patients with hypertension and ischemic heart disease as well as in patients with diabetes mellitus

- No previous exercise studies have been done in an RA population to measure the effect, if any, on autonomic function.
Table 2.7: Studies on autonomic nervous system function in rheumatoid arthritis patients

<table>
<thead>
<tr>
<th>Assessment</th>
<th>Author</th>
<th>Study Title</th>
<th>Disease duration (Mean)</th>
<th>n</th>
<th>Gender</th>
<th>Age (mean)</th>
<th>Co-Morbidity</th>
<th>Aim</th>
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<tr>
<td>Film watching (P)</td>
<td>Geenen (1996)</td>
<td>Diminished autonomic nervous system responsiveness in rheumatoid arthritis of recent onset</td>
<td>&lt;1yr</td>
<td>21</td>
<td>20</td>
<td>EG 17</td>
<td>CG 16</td>
<td>4</td>
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<tr>
<td>Sympathetic skin response (S)</td>
<td>Gozke (2003)</td>
<td>Sympathetic skin response and R-R interval variation in cases with rheumatoid arthritis</td>
<td>Not mentioned</td>
<td>10</td>
<td>14</td>
<td>EG 10</td>
<td>CG 14</td>
<td>0</td>
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</table>

ANS Autonomic nervous system
CG Control Group
EG Experimental Group
P Parasympathetic
RA Rheumatoid arthritis
S Sympathetic
<table>
<thead>
<tr>
<th>Assessment</th>
<th>Author</th>
<th>Study Title</th>
<th>Disease duration (Mean)</th>
<th>n</th>
<th>Gender</th>
<th>Age (mean)</th>
<th>Co-Morbidity</th>
<th>Aim</th>
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<tr>
<td></td>
<td>Tan (1993)</td>
<td>Sympathetic skin response and R-R interval variation in rheumatoid arthritis. Two simple tests for the assessment of autonomic function</td>
<td>90.2 months (7.5 yr)</td>
<td>30</td>
<td>30</td>
<td>3</td>
<td>4</td>
<td>51.3</td>
</tr>
<tr>
<td></td>
<td>Barendregt (1966)</td>
<td>Parasympathetic dysfunction in rheumatoid arthritis patients with ocular dryness</td>
<td>EG1 22yr EG2 10 yr</td>
<td>EG1 18 (Dryness of eyes or mouth) EG2 18 (No dryness of eyes or mouth)</td>
<td>33</td>
<td>0</td>
<td>EG1 18 EG2 18</td>
<td>57</td>
</tr>
<tr>
<td></td>
<td>Schwemmer (2006)</td>
<td>Cardiovascular and pupillary autonomic nervous dysfunction in patients with rheumatoid arthritis - a cross-sectional and longitudinal study</td>
<td>EG1 6.7 yr EG2 6.4 yr EG3 8.6 yr</td>
<td>EG1 30 (All patients) EG2 26 (Survivors) EG3 4 (non-survivors)</td>
<td>0</td>
<td>13</td>
<td>EG1 17</td>
<td>Not used</td>
</tr>
</tbody>
</table>

**Legend**

- **ANS** Autonomic nervous system
- **CG** Control Group
- **CL** Constriction latency
- **CVD** Cardiovascular disease
- **DM** Diabetes mellitus
- **EG** Experimental Group
- **MCV** Maximum constriction velocity
- **P** Parasympathetic
- **RA** Rheumatoid arthritis
- **S** Sympathetic
- **DL** Dilation latency
<table>
<thead>
<tr>
<th>Assessment</th>
<th>Author</th>
<th>Study Title</th>
<th>Disease duration (Mean)</th>
<th>n</th>
<th>Gender</th>
<th>Age (mean)</th>
<th>Co-Morbidity</th>
<th>Aim</th>
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<tr>
<td>Sweat response (S)</td>
<td>Bennett(1965)</td>
<td>Autonomic neuropathy in rheumatoid arthritis</td>
<td>Not mentioned</td>
<td>13</td>
<td>EG1 18</td>
<td>EG1 10</td>
<td>Neuropathy included</td>
<td>Determine ANS involvement in RA</td>
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<tr>
<td></td>
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<td>EG2 8</td>
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<td>CG 5</td>
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<tr>
<td>Sweat response (S)</td>
<td>Kalliomaki (1963)</td>
<td>Axon reflex sweating in rheumatoid arthritis</td>
<td>Not mentioned</td>
<td>100</td>
<td>EG 70</td>
<td>EG 70</td>
<td>CG No somatic disease</td>
<td>1) ANS involvement</td>
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<tr>
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<td></td>
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<td>CG 44</td>
<td>CG 44</td>
<td>Psychiatric hospital patients</td>
<td>2) Correlation with clinical signs of RA</td>
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<td>CG 21</td>
<td>CG 21</td>
<td>CVD</td>
<td>- disease duration</td>
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<td></td>
<td>Co-pathology likely to interfere with ANS</td>
<td>- disease activity</td>
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<td></td>
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<td></td>
<td>Drugs likely to interfere with ANS</td>
<td>- RF status</td>
</tr>
<tr>
<td>Cardiovascular reflex tests</td>
<td>Piha (1993)</td>
<td>Elevated resting heart rate in rheumatoid arthritis: possible role of physical deconditioning</td>
<td>15 (±9)</td>
<td>69</td>
<td>RA 34</td>
<td>RA 34</td>
<td>Excluded: ANS conditions</td>
<td>Assess ANS function in RA by comparing them to DM and Controls</td>
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</table>

<p>| ANS | Autonomic nervous system                      | EG  | Experimental Group | S  | Sympathetic |
| CG  | Control Group                                  | P   | Parasympathetic    |    |             |
| CVD | Cardiovascular disease                        | RA  | Rheumatoid arthritis|   |             |
| DM  | Diabetes mellitus                              | RF  | Rheumatoid factor  |   |             |</p>
<table>
<thead>
<tr>
<th>Assessment</th>
<th>Author</th>
<th>Study Title</th>
<th>Disease duration (Mean)</th>
<th>n</th>
<th>Gender</th>
<th>Age (mean)</th>
<th>Co-Morbidity</th>
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<tr>
<td>Cardiovascular reflex tests</td>
<td>Maule (1997)</td>
<td>Autonomic nervous dysfunction in systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA): possible pathogenic role of autoantibodies to autonomic nervous structures</td>
<td>9.3 (± 7.9)</td>
<td>17</td>
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<td>1) Assess ANS function in RA and SLE 2) Assess presence of Compliment fixing antibodies</td>
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<td>1) Assess ANS 2) Correlate ANS function with severity of RA</td>
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</tbody>
</table>

**ANS** Autonomic nervous system  
**EG** Experimental Group  
**RA** Rheumatoid arthritis  
**CG** Control Group  
**HT** Hypertension  
**S** Sympathetic  
**CVD** Cardiovascular disease  
**OA** Osteo-arthritis  
**SLE** Systemic lupus erythematosus  
**DM** Diabetes mellitus  
**P** Parasympathetic
<table>
<thead>
<tr>
<th>Assessment or reflex test</th>
<th>Author</th>
<th>Study Title</th>
<th>Disease duration (Mean)</th>
<th>n</th>
<th>Gender</th>
<th>Age (mean)</th>
<th>Co-Morbidity</th>
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<tr>
<td>Cardiovascular reflex tests P - Deep breathing Valsalva Orthostatic S - Orthostatic</td>
<td>Bekkelund (1996)</td>
<td>Autonomic nervous system function in rheumatoid arthritis. A controlled study.</td>
<td>13.6 (± 7.4)</td>
<td>43</td>
<td>61</td>
<td>Male</td>
<td>EG 43</td>
<td>44.4 (±8)</td>
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<td>Autonomic nervous system involvement in rheumatoid arthritis</td>
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<td>Autonomic (sympathetic) nervous system involvement in rheumatoid arthritis patients</td>
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ANS Autonomic nervous system DM Diabetes mellitus MS Multiple sclerosis CG Control Group EG Experimental Group P Parasympathetic CTD Cardiac thoracic disease HIV Human immunodeficiency virus S Sympathetic
<table>
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<th>Assessment</th>
<th>Author</th>
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<th>Age (mean)</th>
<th>Co-Morbidity</th>
<th>Aim</th>
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<td>Cardiovascular reflex tests</td>
<td>Aydemir (2010)</td>
<td>Cardiac autonomic profile in rheumatoid arthritis and systemic lupus erythematosus</td>
<td>RA 11.2 (±10) SLE 6.9 (± 5)</td>
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<td>RA 36</td>
<td>Excluded: Pregnancy DM Uraemia Hepatic failure Porphyria Amyloidosis Alcoholism Ishchemic Heart Disease Cardiomyopathy Arrhythmia Cardiovascular incident Parkinson's Disease Multiple sclerosis Drugs interfering with blood pressure and heart rate Fibromyalgia Vasculitis Secondary Sjögrens</td>
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<td>RA 6</td>
<td>SLE 38</td>
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<td>To define the frequency and spectrum of ANS dysfunction in patients with RA</td>
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<tr>
<td></td>
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<td>HRV Frequency domain</td>
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<td>SLE 37</td>
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<td>1) To evaluate cardiovascular ANS function in RA and SLE 2) To correlate ANS function with clinical features</td>
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**Legend:**
- **ANS:** Autonomic nervous system
- **HCG:** Healthy Control Group
- **S:** Sympathetic
- **CG:** Control Group
- **HRV:** Heart rate variability
- **SLE:** Systemic lupus erythematosus
- **CVD:** Cardiovascular disease
- **P:** Parasympathetic
- **SSc:** Systemic sclerosis
- **DM:** Diabetes mellitus
- **RA:** Rheumatoid arthritis
<table>
<thead>
<tr>
<th>Assessment</th>
<th>Author</th>
<th>Study Title</th>
<th>n</th>
<th>Gender</th>
<th>Age (mean)</th>
<th>Co-Morbidity</th>
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<td>RA 39</td>
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<td>1) Evaluate ANS function in RA/SLE/PMR/SSc/Sjö 2) Correlate ANS function with clinical features</td>
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<td></td>
<td>Milovanovic</td>
<td>Cardiac autonomic dysfunction in patients with systemic lupus, rheumatoid arthritis</td>
<td>SLE 52</td>
<td>41</td>
<td>SLE 43.3</td>
<td>Excluded: Pregnancy, Renal insufficiency, Cardiac insufficiency, Respiratory insufficiency, Arrhythmia, Acute thrombosis</td>
<td>To evaluate the presence and level of ANS dysfunction in patients with SLE and RA and to identify cardiovascular risk factors associated with sudden cardiac death</td>
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<td>Vlcek (2008)</td>
<td>Sympathetic nervous system response to orthostatic stress in female patients with rheumatoid arthritis</td>
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<td>Not mentioned</td>
<td>To evaluate autonomic activity in RA patients, namely sympathoneurale and adreno-medullary reactivity in changes to body position</td>
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</table>

**ANS** Autonomic nervous system  
**CG** Control Group  
**HCG** Healthy Control Group  
**HRV** Heart rate variability  
**P** Parasympathetic  
**PMR** Polymyalgia rheumatica  
**RA** Rheumatoid arthritis  
**S** Sympathetic  
**Sjö** Sjögrens  
**SLE** Systemic lupus erythemathosus  
**SSc** Systemic sclerosis
<table>
<thead>
<tr>
<th>Assessment</th>
<th>Author</th>
<th>Study Title</th>
<th>Disease duration (Mean)</th>
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<th>Age (mean)</th>
<th>Co-Morbidity</th>
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<tr>
<td>HRV</td>
<td>Holman (2008)</td>
<td>Heart rate variability predicts anti-tumor necrosis factor therapy response for inflammatory arthritis</td>
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<td>7.6 (± 6.4)</td>
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<td>26</td>
<td>7</td>
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<td>HRV (24hr)</td>
<td>Anichkov (2007)</td>
<td>Heart rate variability is related to disease activity and smoking in rheumatoid arthritis patients</td>
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<td>48</td>
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<td>4</td>
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<td>Whole blood cytokine attenuation by cholinergic agonists ex vivo and relationship to vagus nerve activity in rheumatoid arthritis</td>
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- **ANS**: Autonomic nervous system
- **DM**: Diabetes mellitus
- **CG**: Control Group
- **CVD**: Cardiovascular disease
- **EG**: Experimental Group
- **HCG**: Healthy Control Group
- **PsA**: Psoriatic arthritis
- **RA**: Rheumatoid arthritis
- **HRV**: Heart rate variability
- **rMSSD**: Root of the average squares of differences between neighbouring NN intervals
<table>
<thead>
<tr>
<th>Assessment</th>
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<td>55 ±9</td>
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<td>To determine if HRT changes in patients with RA in comparison with healthy controls</td>
</tr>
</tbody>
</table>

**TOTALS:** 1232 EG, 918 CG, 51.79 ±10 EG, 44.28 ±9 CG

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


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151. Buchheit M, Simon C, Charloux A, Doutreleau S, Piquard F, Brandenberger G. Relationship between very high physical activity energy expenditure, heart rate


157. Fransen J, Stucki G, van Riel PLCM. Rheumatoid arthritis measures: Disease Activity Score (DAS), Disease Activity Score-28 (DAS28), Rapid Assessment of Disease Activity in Rheumatology (RADAR), and Rheumatoid Arthritis Disease Activity Index (RADA1). Arthritis Care & Research 2003;49(S5):S214-S224.


