Exercise as Medicine in Rheumatoid Arthritis: Effects on Function, Body Composition, and Cardiovascular Disease Risk

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INTRODUCTION
Rheumatoid arthritis (RA) is a chronic autoimmune disease with a prevalence of 1 to 2\% worldwide which makes it the most common chronic inflammatory joint disease. RA is more frequent in women than men. It manifests with persistent joint inflammation, which, as a result, leads to joint damage and a loss of physical functioning. Therefore, it is not surprising that this disease is accompanied by a significant socioeconomic impact with 35\% work disability prevalence within 10 yr of diagnosis in both the United States and Europe (2,10). Disability remains elevated despite considerable advances in pharmaceutical treatment and improved control of disease activity and subsequent reductions in joint damage (64), suggesting that other factors are also important in the clinical management of RA.

Chronic inflammation, the main characteristic of the disease, contributes to significant alterations in the body composition of patients with RA. These changes have been termed “rheumatoid cachexia” (67), and feature muscle loss and fat mass accumulation (66,67), accompanied by increased resting energy expenditure (48,68). Among patients with RA with controlled disease, significant loss in muscle mass has been observed in about two-thirds of patients, and obesity in approximately 80\% (37,42,73). These adverse changes in body composition have been shown to be significant and independent contributors to RA disability (75). Additionally, as in other conditions, the loss of muscle mass and increased adiposity is associated with reduced immune and pulmonary function, insulin resistance, and exacerbated morbidity and mortality (33).

Since rheumatoid cachexia and disability are not adequately restored by medication (43,47), additional treatments are required. Exercise offers a potential means of optimizing management of RA, as appropriate exercise training has been shown to substantially improve body composition in these patients (38), as well as improve physical function, cardiovascular status, and disease activity (24,49,82). Moreover, exercise as well as being able to attenuate inflammation indirectly via reducing adiposity (26), has a direct anti-inflammatory effect (51) and consequently can further benefit patients with RA. Unfortunately, due to disease manifestations (joint destruction, disability, pain, fatigue) and misconceptions about the benefits and safety of exercise, most patients with RA are sedentary (49). This review will discuss existing pharmaceutical and behavioural interventions for treating rheumatoid cachexia, but will focus on the safety and beneficial effects of exercise on body composition, physical function, and cardiovascular risk in patients with RA with the intention of promoting exercise as an adjunct therapy (i.e., exercise as medicine for RA patients).

PHARMACEUTICAL AND BEHAVIOURAL INTERVENTIONS FOR TREATING RHEUMATOID CACHEXIA
Although cachexia in RA was first noted almost 150 years ago (58), rheumatoid cachexia has only received research

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attention in the last two decades. Although the lack of established diagnostic criteria for rheumatoid cachexia impairs establishing its prevalence, studies agree that even when disease activity is well-controlled, the majority of patients with RA present with adverse changes to their body composition (38,68,75). Given the combined detrimental effects of muscle mass loss (e.g., reduced function, disability, impaired immune function) and increased adiposity (e.g., increased cardiovascular disease [CVD] risk), successful interventions that reverse rheumatoid cachexia are necessary (38) and could potentially reduce the economic and social impact of RA (45).

Rheumatoid cachexia probably occurs due to an overexpression of pro-inflammatory cytokines (66–68). As a result of the inflammatory response, cytokines bind with specific receptors on cell surfaces, resulting in stimulation of pathways of signal transduction that lead to changes in transcription. One such pathway is the NF-kB pathway which is involved in inflammation-induced muscle wasting. Specifically, tumor necrosis factor alpha (TNF-α) is believed to stimulate proteolysis via an NF-kB dependent process that increases ubiquitin conjugation to muscle proteins (39). Additionally, TNF-α and other pro-inflammatory cytokines induce anabolic resistance in the muscle tissue and thereby also inhibit muscle protein synthesis (77). As such, it seemed reasonable to propose that blocking TNF-α would reverse muscle wasting in RA. However, a 6 mo study by Marcora et al. (43) found that anti-TNF-α treatment is not effective in increasing muscle mass and reducing fat mass in early, previously untreated patients with RA. These findings were confirmed in subsequent studies when anti-TNF-α treatment again failed to reverse components of rheumatoid cachexia either at 2 or 12 wk in patients with long-standing RA (47) or after 21 mo in patients with newly diagnosed RA (12). Of particular interest is the finding of the last two studies that, relative to treatment with standard disease modifying anti-rheumatic drugs (DMARDs), anti-TNF-α treatment increased fat mass, and in particular trunk fat mass; this is important, as trunk adiposity is a contributor to the increased CVD, diabetes, and metabolic syndrome risk which is evident in RA (51,77).

Similarly, preliminary unpublished data from an on-going trial investigating the effects of the current treat-to-target (T2T) strategy (AL, personal communication; RA patients n = 68, age- and sex-matched healthy controls n = 81) indicates that while this treatment is very successful in lowering disease activity [mean disease activity score 28 (DAS28) = 2.8], it is having no effect on rectifying body composition (relative muscle mass is ≈11% less, and relative fat mass is ≈15% more than sedentary matched controls) with no beneficial effect on objective functional tests (i.e., performance of knee extensor strength, handgrip strength, timed Up-and-Go, 30 s Sit-To-Stand, and 50 ft Walk tests remain 25 to 35% poorer in patients with RA compared to matched healthy controls) when compared to data collected in laboratories pre-T2T (2001–2008). Although more research is required in this area, it is apparent that even successful control of disease activity by pharmaceutical means does not reverse the adverse changes in body composition that are a common feature of RA.

Although nutritional treatment with supplementary protein has been found to be effective in inducing increases in lean muscle mass and improving objectively assessed function in patient with RA, these improvements are relatively small (41). Clearly, the adjunct intervention that conveys the most profound health benefits in these patients, including the capacity to reverse rheumatoid cachexia, is exercise. Collective research findings reveal that high-intensity exercise is effective both in increasing muscle mass and reducing adiposity in RA (5,15,16,23,37,42,76). Additionally, exercise training has repeatedly been shown to substantially improve strength, aerobic capacity, and objective measures of physical function including walk tests, stair climbing, chair tests, up-and-go test, 30 s arm curl test, vertical jump, and balance/coordination tests. Lastly, exercise may have a significant impact on reducing the increased cardiovascular burden seen in RA (30). But, given the multiple comorbidities and physical disabilities caused by RA, is exercise, and in particular, high-intensity exercise, safe in this population?

SAFETY OF EXERCISE

The significant impact of RA on different aspects of physical functioning and the extensive damage that it typically causes in musculoskeletal structures, led to a long-held, prevalent notion that exercise—especially weight-bearing exercise—was inappropriate and unsafe in this population (78). Even recently, a study demonstrated that health professionals and rheumatologists advise their patients to avoid strenuous exercises, due to fears that it would exacerbate disease symptoms (53). Good quality studies now demonstrate that these claims are unfounded. In 1990, the randomized controlled trial by Ekdahl et al. (11) was the first to demonstrate that a combined aerobic and resistance training intervention was effective in safely improving strength and physical function in patients with RA in comparison to static exercises (11). In line with these findings, van den Ende et al. (81) revealed that a high-intensity 24 wk aerobic and strength exercise intervention improved muscle strength, aerobic capacity, and joint mobility without exacerbating disease activity. These findings were confirmed in a long-term study by Hakkinen et al. (19) who, in a 2 yr randomized controlled trial utilizing high-intensity strength and aerobic exercise, observed significant improvements in strength and physical function in patients with newly diagnosed RA; notably, with a reduction in disease activity and no exacerbation of joint damage (19). These acquired beneficial effects were mostly retained when patients were reassessed 3 yr post-training (22). Similar results were also observed in a large scale randomized controlled trial, the RAPIT study, which demonstrated that a high-intensity combined strength and aerobic exercise intervention is effective in preventing radiological joint damage in patients with RA (5). It is worth noting that, although the initial results of this study led to the suggestion that patients with pre-existing damage in large joints should
avoid high-intensity exercise, in a subsequent publication investigating the 18 mo follow-up effects of exercise, this concern was retracted and it was concluded that exercise was safe for all joints, large and small, and even those already extensively damaged (6). In fact, these beneficial effects of exercise support earlier research, some of which were disregarded for many years (15,57). In a recent comprehensive review by Lemmey (38) it was noted that amongst all the available studies in RA, even those featuring prolonged high-intensity training, there was not a single report that exercise exacerbated any measure of disease activity or severity including swollen and tender joint counts (11,15,81), morning stiffness (11,81), systemic inflammation (15–17), self-reported pain or fatigue (17,32), or composite disease scores (i.e., DAS4, DAS28) (5,17,76). Additionally, two reviews by the Cochrane Library on exercise therapy for RA support the safety and benefit of high-intensity exercise for patients with RA (24,82).

Another important aspect to discuss in relation to the safety of exercise for RA is the patient’s perception of their capabilities. Although studies unanimously support the use of exercise as medicine in RA, patients fear that exercising will exacerbate their disease symptoms (36,72). These unjustified concerns about exercise are reinforced by health professionals’ lack of specific knowledge of how to prescribe exercise (85) and which physical activity regimens are appropriate for patients with RA (7,35,53). Combined, this ignorance of research findings contributes to the extreme sedentary behaviour typically observed in patients with RA. Unfortunately, increasing awareness of the benefits of exercise via relevant educational interventions does not appear, on its own, to be sufficient to make these patients more physically active (27).

**EXERCISE AND PHYSICAL FUNCTION**

The literature consistently reports beneficial effects of exercise on function in patients with RA (Table 1), with findings of improvements in a wide variety of objective physical function tests, including assessments of balance and coordination, grip strength, the vertical jump test, various sub-maximal or maximal aerobic fitness tests, and tests designed to reflect the ability to perform activities of daily living (e.g., 30 s Sit-To-Stand; timed Up-and-Go; 30 s Arm-Curl; 50 ft Walk test). Moreover, these beneficial effects are highlighted in two Cochrane reviews confirming that high-intensity aerobic and/or resistance exercise significantly improves physical function in patients with RA (24,82). In fact, a promising finding in a study by Lemmey et al. (37) revealed that although patients’ baseline physical function was significantly poorer (≈20 to 30%) compared to age- and sex-matched norms, a 24 wk high-intensity exercise intervention was sufficient to restore normal physical function in patients with long-standing disease.

It is also important to note that these benefits are recognized by patients. In support of this, studies reveal significant improvements in subjective patient-assessed function such as the McMaster Toronto Arthritis Disability Questionnaire (MACTAR), and self-reported fatigue (15,19,32,42,82).

These are indeed very promising findings and support the use of exercise as medicine in RA. Giles et al. (14) demonstrated that increasing adiposity and reduced muscle mass both independently predict poorer subjective self-assessed physical function (Health Assessment Questionnaire; HAQ) in patients with RA (14). These effects of high-intensity exercise on physical function are partly mediated by exercise-induced beneficial alterations in body composition. However, at this stage studies directly investigating this assumption are lacking.

**EXERCISE AND BODY COMPOSITION**

In patients with RA, resistance training alone has been found to significantly increase muscle mass (37,42) probably due to the increased muscle levels of insulin-like growth factor-I that coincide with the hypertrophic response to resistance training (37). Combining resistance and aerobic training also results in increases in the muscle cross-sectional area of type I and II muscle fibers in patients with RA by 6 wk (15,56), while significant improvements in electromyographic activity and quadriceps femoris cross-sectional area are evident after 21 wk (23). These findings are in line with the strengthening and hypertrophic responses seen in healthy individuals following appropriate exercise training (63). In fact, Hakkinen et al. (23) has directly compared women with RA with age-matched healthy women and showed comparable absolute and relative increases in strength as well as similar increases in quadriceps femoris thickness and reductions in quadriceps femoris subcutaneous fat thickness following completion of the same combined strength and aerobic training program (23). This similarity in training response is consistent with reports that muscle quality (i.e., muscle architecture, specific force, and voluntary activation capacity) is maintained in RA despite reductions in muscle quantity (44).

Along with increases in muscle mass, significant exercise-induced reductions in fat mass are evident in patients with RA (23,37,42). It is of particular interest that high-intensity exercise may decrease trunk fat up to 2.5 kg (37,42) which may improve arterial stiffening (25) and therefore, reduce the risk for CVD (69) in these patients. Stavropoulos-Kalinoglou et al. (76) showed that a combined aerobic and strength exercise intervention increased maximal oxygen uptake, and this increase was the sole predictor of reduced fat mass.

But how can these significant exercise-induced body composition alterations ameliorate disease activity and severity in RA? The answer to this lies in the acute and chronic effects of exercise on the function and structure of both the musculoskeletal system and adipocytes. The contracting (exercising) muscle stimulates cellular immune changes that have a significant anti-inflammatory effect. More specifically, exercise-induced muscle-derived interleukin 6 (IL-6), which is predominantly described as a pro-inflammatory cytokine in RA, may exert an anti-inflammatory and immunosuppressive effect with a down-regulating impact on the acute phase response (62).

Acute exercise also expresses anti-inflammatory effects with increased levels of anti-inflammatory cytokines such as
TABLE 1. Effects of exercise interventions on objectively-assessed physical function in patients with rheumatoid arthritis (RA).

<table>
<thead>
<tr>
<th>First Author (reference)</th>
<th>Study Design</th>
<th>Exercise Intervention</th>
<th>Frequency and Duration</th>
<th>Effects on Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>de Jong et al. (5,6)</td>
<td>RCT</td>
<td>Resistance</td>
<td>2 d wk⁻¹ 24 mo</td>
<td>Improved (KES, VO₂ max; p&lt;0.001 for each)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(70 to 90% predicted HRmax)</td>
<td></td>
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</tr>
<tr>
<td>Ekhdal et al. (11)</td>
<td>RCT</td>
<td>Resistance (≈70% 1-RM) Aerobic (≥50% VO₂ max)</td>
<td>2 d wk⁻¹ 6 wk</td>
<td>Improved (KES, KFS, VO₂ max; p&lt;0.001 for each)</td>
</tr>
<tr>
<td>Flint-Wagner et al. (13)</td>
<td>RCT</td>
<td>Resistance (70 to 85% 1-RM)</td>
<td>3 d wk⁻¹ 16 wk</td>
<td>Improved (composite strength: 46%, p&lt;0.01; walk test: p = 0.01)</td>
</tr>
<tr>
<td>Hakkinen et al. (15,16)</td>
<td>RCT</td>
<td>Resistance (70 to 80% 1-RM)</td>
<td>2-3 d wk⁻¹ 24 wk</td>
<td>Improved (strength: 11 to 49%, p&lt;0.01)</td>
</tr>
<tr>
<td>Hakkinen et al. (18,19,21,22)</td>
<td>RCT</td>
<td>Resistance (50 to 70% 1-RM)</td>
<td>2 d wk⁻¹ 24 mo</td>
<td>Improved (strength: 19 to 59%, walk test: 16%; p&lt;0.001 for each)</td>
</tr>
<tr>
<td>Hakkinen et al. (20,23)</td>
<td>Age-, gender- and weight-matched healthy controls</td>
<td>Resistance (50 to 80% 1-RM) Aerobic (≥AT, &lt;AT)</td>
<td>3 d wk⁻¹ 21 wk</td>
<td>Improved (strength: 8 to 41%, KES: 24%, walk test: 21%, VO₂ max: 15%, p&lt;0.05 for each)</td>
</tr>
<tr>
<td>Komatireddy et al. (32)</td>
<td>RCT</td>
<td>Resistance (&quot;low intensity&quot;)</td>
<td>3 d wk⁻¹ 12 wk</td>
<td>Improved (SST, GS, KES, walk test: p&lt;0.001 to 0.10)</td>
</tr>
<tr>
<td>Lemmey et al. (37)</td>
<td>RCT</td>
<td>Resistance (80% 1-RM)</td>
<td>2 d wk⁻¹ 24 wk</td>
<td>Improved (composite strength: 119%, p&lt;0.001; SST, KES, ACT, walk test: 17 to 30%, p = 0.001 to 0.027)</td>
</tr>
<tr>
<td>Lyngberg et al. (40)</td>
<td>RCT</td>
<td>Resistance (50% 1-RM)</td>
<td>3 d wk⁻¹ 3 wk</td>
<td>Improved (strength: 21%)</td>
</tr>
<tr>
<td>Marcora et al. (42)</td>
<td>Age-, gender-matched RA</td>
<td>Resistance (80% 1-RM)</td>
<td>3 d wk⁻¹ 12 wk</td>
<td>Improved (composite strength: 57%, p&lt;0.01; SST, KES, ACT, HG: 17 to 39%, p = 0.001 to 0.073)</td>
</tr>
<tr>
<td>McMeeken et al. (46)</td>
<td>RCT</td>
<td>Resistance (70% 1-RM)</td>
<td>14 sessions in 6 wk</td>
<td>Improved (KES: 25 to 28%, p = 0.003 to 0.018; KFS: 38 to 41%, p = 0.003 to 0.008; TUG: 11%, p = 0.01)</td>
</tr>
<tr>
<td>Nordemar et al. (55)</td>
<td>No controls</td>
<td>Resistance (50 to 70% VO₂ max) Aerobic</td>
<td>5 d wk⁻¹ 6 wk</td>
<td>Improved (KES: 23%, walk test: 6%, VO₂ max: 12%, p&lt;0.05 for each)</td>
</tr>
<tr>
<td>Nordemar et al. (55)</td>
<td>Disease-, sex-, and body size matched RA</td>
<td>Resistance Aerobic</td>
<td>1 time per 2 wk 4-8 years</td>
<td>Improved (KES: 13%, p&lt;0.05; walk test: 6%, NS; step test: 16%, p&lt;0.05; stair test: 6%, NS)</td>
</tr>
<tr>
<td>Rall et al. (65)</td>
<td>Comparisons with healthy aged and young subjects</td>
<td>Resistance (80% 1-RM)</td>
<td>2 d wk⁻¹ 12 wk</td>
<td>Improved (composite strength: 57%, walk test: 20%, p&lt;0.01 for each)</td>
</tr>
<tr>
<td>Stavropoulos-Kalinoglou et al. (76)</td>
<td>Gender-BMI matched RA</td>
<td>Resistance (70% 1-RM) Aerobic (70% VO₂ max)</td>
<td>3 d wk⁻¹ 24 wk</td>
<td>Improved (VO₂ max: 17%, p = 0.001)</td>
</tr>
<tr>
<td>van den Ende et al. (81)</td>
<td>RCT</td>
<td>Resistance Aerobic (70 to 85% predicted HRmax)</td>
<td>3 d wk⁻¹ 12 wk</td>
<td>Improved (composite strength: 17%, p = 0.02; VO₂ max: 17%, p&lt;0.001)</td>
</tr>
</tbody>
</table>

1-RM = one repetition maximum; ACT = 30 s arm curl test; AT = anaerobic threshold; GS = grip strength; HRmax = maximum heart rate; KES = knee extensor strength; KFS = knee flexor strength; NS = not significantly different versus baseline; RCT = randomized controlled trial; SST = Sit-To-Stand Test; TUG = timed Up-and-Go; VO₂ max = maximal oxygen uptake.
IL-10 and IL-1 receptor antagonist (80). These phenomena may have a profound effect on the inflammatory response in patients with RA in whom the disease-driven overexpression of these cytokines leads to increased disease activity and severity. In addition, amongst the long-term effects of exercise are increased muscle mass and improved balance and coordination; which have a beneficial impact on physical function and thus, disease severity (28). With regards to the effects of exercise on adipocytes, it is accepted that exercise reduces inflammation via the inhibition of adipocyte-derived pro-inflammatory cytokines and improvement in adipocyte oxidative capacity (61). The latter may also be linked with the significant reduction in the cardiovascular risk of patients with RA as a result of exercise (52,76).

EXERCISE AND CARDIOVASCULAR DISEASE RISK

It is well established that RA is associated with an increased risk for CVD, with cardiovascular events typically occurring approximately a decade earlier in patients with RA compared to the general population (30). This increased risk may be partly due to the increased prevalence of hypertension (59,60), hypercholesterolemia (79,80), vascular dysfunction (70,71) and insulin resistance (8,9) seen in patients with RA. In addition, the significant inflammation-induced alterations in body composition (rheumatoid cachexia) have been implicated in this increased CVD risk (74,77). However, all these factors collectively can only partly explain the increased CVD risk in RA. This suggests that an interplay of these factors with other parameters may exist which contribute to the 50 to 100% increased prevalence of CVD in RA (42).

One such parameter is exercise. Lack of exercise and/or physical activity can result in low cardiorespiratory fitness, a major risk factor for CVD (54). Metsios et al. (50) demonstrated that physical inactivity in RA is associated with an inferior cardiovascular profile characterized by exacerbations of both classical and novel CVD risk factors. It appears, however, that high-intensity combined aerobic and resistance exercise can reverse this phenomenon. Results from a recent trial revealed that such an intervention significantly improved blood pressure, body fat, blood lipid profile, vascular function, markers of oxidative stress, and the 10 yr risk of a CVD event among patients with RA (52,76,84). Interestingly, the increase in cardiorespiratory fitness was the strongest predictor for each of these observed improvements. This observation is consistent with effects seen in the general population, with meta-analyses revealing that increased cardiorespiratory fitness leads to improvements in blood pressure (4), high-density lipoprotein (HDL) levels (31), insulin resistance (3), and body fat (83).

The reasons why high-intensity exercise has such profound effects on the cardiovascular profile in RA warrants further investigation in appropriately designed trials. However, in patients with RA, exercise-induced reductions in fat mass were independently associated with the beneficial changes in blood pressure and inflammatory biomarkers (76). So again, the significant exercise-induced changes in body composition may account for this and, hence, exercise holds significant promise in improving the cardiovascular profile of patients with RA.

RECOMMENDATIONS

Exercise has multiple health benefits for patients with RA, supporting the use of exercise as medicine in RA. The different training programmes and modes utilized in the literature, along with the reported compliance rates, indicate that patients with RA can safely perform different types of high intensity exercise programs, and enjoy the same range and magnitude of benefits as age- and sex-matched healthy individuals.

To achieve and maintain the significant benefits of exercise, apart from following the same training progression principles as in the general population (34), specific attention needs to be given to devising tailored programmes for these patients because RA affects patients differently. It is also important to incorporate patient’s preferences in order to devise an effective exercise programme. Doing so will very likely increase adherence to regular structured physical activity and reduce the sedentary behaviours seen in RA (29). An example of developing a tailored exercise programme appears in Table 2. The following specific principles are suggested for exercising in RA:

1. Using existing infrastructure and/or a home-based approach (where possible), exercise should be part of the overall management of RA in combination with pharmacological and behavioural interventions, which is consistent with previously published recommendations.
2. The main targets of exercise in RA should be initially to restore functional ability with the intention to initiate exercise programmes that aim at improvement of CVD risk as well as

<table>
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<tr>
<th>TABLE 2. Steps for developing effective exercise programs for patients with rheumatoid arthritis.</th>
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<tbody>
<tr>
<td>1. Patient History: Take into account previous/current extra-articular comorbidities.</td>
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<td>2. Functional Ability: Evaluate during initial patient interview and via Disease Activity Score 28.</td>
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<tr>
<td>3. Patient Preferences: Discuss during initial patient interview and incorporate in the program.</td>
</tr>
<tr>
<td>4. Training Principles: Similar to the general population Frequency: 3 d·wk⁻¹. It is advised that the patients learn to perform all exercises (warm-up, main session, and recovery) using appropriate technique to avoid injury. Supervision during the first three sessions may be required. Intensity: Aerobic training should be applied first for 4 wk. Aerobic exercise intensity = 60 to 80% of maximum heart rate. Resistance exercise intensity = 50 to 80% of 1-repetition maximum. Consider the lower end of these percentages at the start of a program to avoid injury. Higher percentages can be applied, later in the program as per training principles and/or in patients with good functional ability. Type: Three to four aerobic exercises (walking, cycling, rowing) in intervals of 3 to 4 min. Following each aerobic exercise, perform resistance exercise (10 to 15 repetitions) using exercises for large muscle groups (e.g., leg press, chest press, shoulder press). Total time: 60 min: 10 min warm-up, 30 to 40 min main session, 10 min cooldown.</td>
</tr>
</tbody>
</table>
REFERENCE


64. Pincus T, Castrejon I. Evidence that the strategy is more important than the agent to treat rheumatoid arthritis. Data from clinical trials of combinations of non-biologic DMARDs, with protocol-driven intensification of therapy for tight control or treat-to-target. Bull Hosp Jt Dis (2013). 2013;71 Suppl1:S33–40.
