#### CLINICAL REVIEW

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## Aerobic exercise prescription in heart failure patients with cardiac resynchronization therapy

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#### Abstract

Exercise for heart failure patients had been shown to be beneficial in improving functional status, and was reviewed to be safe. In cases of advanced heart failure, Cardiac Resynchronization Therapy (CRT) is a promising medical option before being a heart transplant candidate. CRT itself is a biventricular pacing device, which could detect electrical aberrance in the failing heart and provide a suitable response. Studies have shown that exercise has clear benefits toward improving an overall exercise capacity of the patients. Despite its impacts, these randomized clinical trials have varying exercise regime, and until now there has not been a standardized exercise prescription for this group of patients. The nature of CRT as a pacemaker, sometimes with defibrillator, being attached to a heart failure patient, each has its own potential exercise hazards. Therefore, providing detailed exercise prescription in adjusting to the medical condition is very essential in the field of physical medicine and rehabilitation. Being classified as a high-risk patient group, exercise challenges for the complex heart failure with CRT patients will then be discussed in this literature review, with a general aim to provide a safe, effective, and targeted exercise regime.

#### **KEYWORDS**

aerobic exercise prescription, cardiac resynchronization therapy, functional capacity, heart failure, rehabilitation

#### **1** | INTRODUCTION

Cardiac resynchronization therapy (CRT) is indicated by the European Society of Cardiology (ESC) as a treatment given to patients with advanced heart failure, before consideration of heart transplantation.<sup>1,2</sup> There lies two main classification of CRT device, the default CRT-P (CRT-Pacemaker), and the addition of implantable cardioverter defibrillator (ICD), which form-up CRT-D (CRT-Defibrillator). One unique property of the CRT device is the presence of biventricular pacing system, in which CRT-D additionally allows the device to identify electrical activity in both ventricles and

responds accordingly. Initial CRT candidate screening includes those diagnosed with heart failure, New York Heart Association (NYHA), functional class of III and IV, wide QRS segment (≥120 ms), and the presence of Left Bundle Branch Block (LBBB), which signifies cardiomyopathy.<sup>1</sup> Cardiologists would then determine which device is suitable for the patients' condition, in which the National Institute for Health and Care Excellence (NICE) guideline had clearly shown CRT-D is more indicated for those with wider QRS and NYHA functional class below IV, thus, showing better life expectancy.<sup>3</sup>

The functional impact of CRT implantation has been reported to be satisfactory. It was shown that 59% of CRT patients will improve

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1 level of NYHA functional class in 6 months, along with improvements in exercise capacity.<sup>4</sup> In the context of exercise capacity improvement, CRT led to faster  $VO_2$  kinetics towing to enhanced stroke volume response and faster heart rate kinetics with cardiac adaptation.<sup>5,6</sup> Other improvement of cardiac conduction caused by chronotropic restoration after unloading ventilatory sensory receptors was also reported.<sup>6</sup> It is then evident that CRT effectively improves the central cardiac function through chronotropic resynchronization, as well as peripheral sympathetic tone recovery, ultimately providing a general improvement in exercise capacity.<sup>5,7,8</sup>

Over the years, the role of exercise in CRT patients had been highlighted to improve the central cardiac enhancements even further through beneficial effects of peripheral circulatory restoration.<sup>7,9,10</sup> Exercise training was consistently shown to be safe and also effective in maintaining the changes brought about by CRT.<sup>10,11</sup> One of the commonly assessed outcome is the  $VO_2$  peak, in which studies have shown the increase in VO<sub>2</sub> peak in exercise CRT groups as compared to control, accruing up to 40% increase against 16% in the control CRT group.<sup>12</sup> Similar exercise results after CRT were also constantly brought about by other studies over the years.<sup>10,11,13-15</sup> These exercise capacity augmentations may be caused by improvements in peripheral blood flow toward skeletal muscles, which resulted in a more efficient aerobic or even anaerobic metabolism process.<sup>14</sup> On a biomolecular level, regular exercise improves formation basal endothelial nitric oxide and also vasodilation response of skeletal muscle vessels.<sup>16,17</sup> Additionally, more recent studies utilize flow-mediated dilation (FMD) to assess arterial response to shear stress in the peripheral circulation, with concurring results of peripheral endothelial function improvement.<sup>18</sup> Nevertheless, macroscopic improvements of the exercise were also evident in the peripheral skeletal muscles conversion of type II to type I muscle fiber, ultimately resulting in improvements of both exercise capacity and quality of life in performing activities of daily living.<sup>13,16</sup> Studies have consistently shown that regular exercise may be the key to reversing the muscle atrophy and exercise adaptation of skeletal muscles in heart failure patients, reflected in increased maximal workload.<sup>18-21</sup>

In the context of exercise in CRT-D recipients, it is essential to determine shock threshold as it was mentioned that ICD shocks are associated with reduced quality of life, hence, would affect exercise compliance and physical activity.<sup>10,22,23</sup> Recent Cochrane meta-analysis had shown that studies on exercise in ICD recipients have better effects toward receiving appropriate shocks, however, this result was still inconclusive because of low level of available evidence.<sup>10,11</sup> Studies had mentioned that resting parasympathetic tone was found to raise along with exercise, and this would further protect against ventricular arrhythmias.<sup>8,10</sup> It could then be drawn out that exercise in implantable cardiac device recipients would provide its beneficial effects through amelioration of autonomic tone.<sup>8,22</sup>

With all these facts unfolded, it could be seen that exercise is safe and beneficial for CRT patients, and what lies beyond is how to effectively prescribe these exercise training. Being the core of physical medicine and rehabilitation field, in order to achieve targeted goals with tailor-made exercise regimen, a detailed exercise prescription should comprise of exercise frequency, intensity, type, and time. This review was made with an aim to discuss and bring forward the present evidence on the complete exercise prescription for CRT patients that had been used in the existing randomized controlled trials, beginning from initial assessment after implantation, exercise testing, exercise training, and home exercise safety. Therefore, with all these, physicians would be able to achieve a comprehensive care in this essential CRT patient group, ultimately improving their quality of life.

#### 2 | INITIAL ASSESSMENT

Exercise prescription for Cardiac Resynchronization Therapy (CRT) patients would firstly require local examination of operative outcome. This includes skin healing, which then should be responded by restriction of upper extremity motions.<sup>22</sup> However, after 24 hours of device implantation, light upper extremity motion will be required to obtain a positive effect on joint immobilization.<sup>24</sup> It was shown through a meta-analysis of exercises in patients with CRT and CRT-D that there is a 5% chance of device malfunction during the first 12 months after implantation, and 1.8% chance of infection at the implantation site, which then highlights the need of wound monitoring.<sup>4,9</sup> The next step is the assessment of the implanted cardiac device, which will also influence the prescription of the exercise.

For patients with CRT-D devices, it is important to know the shock threshold and trigger (at a certain pulse rate).<sup>22</sup> Thus, it can be seen that the concept of exercise prescription in this group of patients can adapt to the ICD exercise protocol.<sup>25</sup> For years, it has been stated by the American Association of Cardiovascular and Pulmonary Rehabilitation (AACVPR) that the exercise protocol is safe when performed on ICD users.<sup>25</sup> However, training supervisors, including physiatrists, need to know the device settings. Normally, the device is programmed to recognize the abnormal pulse rate when there are shockable rhythms, such as ventricular tachycardia or ventricular fibrillation (VT/VF).<sup>22</sup> Exercise will generally continue to use pulse rate as a marker of exercise effectiveness (in achieving target heart rate). It is very important to note that the exercise must be targeted to only reach a pulse rate 10-15 times below the rate that will trigger shock.<sup>22,24,25</sup> Despite the fact that current CRT-D and ICD devices are more advanced in detecting aberrant rhythms, such as the dual-chamber discriminator of PR Logic™ algorithm, informing the patients regarding shock threshold and shock appropriacy were proven to improve their quality of life.<sup>26,27</sup> Comprehensive discussion with cardiologists regarding medication is important in order to set endpoints as well as exercise prescription, knowing the fact that CRT patients are mostly in an advanced heart failure stage.<sup>22</sup> In cases where neurohumoral blockers are used, utilizing Borg would then be the most fitting.<sup>20,28,29</sup>

Aside from shock burden, rate responsiveness of the device should be carefully observed in prescribing exercise in CRT patients.<sup>20,23,30</sup> As stated by AACVPR, the increase in pulse rate during exercise is a very important factor to consider because of its

relationship with cardiac output and oxygen uptake.<sup>25</sup> This could be the case only if the patient uses a pacemaker with a rate-responsive mode, which means an increase in pulse frequency as a response to increased activity.<sup>31,32</sup> It is also important to note that some sensors from pacemakers can be triggered with body movements (through accelerometers detecting body vibration), as well as metabolic and physiological changes, all of which could change during exercise period.<sup>24,25,31,32</sup> Thus, extra attention must be given during exercise testing before personalized exercise prescription is given to this special population.<sup>22</sup>

The main distinctive feature of CRT devices is the presence of three sensor leads, located in the right atrium, right ventricle, and coronary sinus, as well as the ability to pace both ventricles (biventricular pacing).<sup>24</sup> Studies had shown that not all heart failure patients may have good response to CRT, some group is acknowledged as 'nonresponders' and this accrues up to 20%-30% of the candidates.<sup>22,33</sup> Whereas response to CRT device is generally evaluated in 3-6 months postimplantation, studies had shown that exercise training could safely be done in all phases of CRT implantation, even prior to its implantation, regardless of their response to the CRT as evaluated in future visits.<sup>13,33-35</sup> Several recent studies on heart failure have shown that exercise training by itself would be beneficial through a series of peripheral changes, even in those receiving mild central cardiac function improvement from CRT.<sup>36,37</sup> One particular study had successfully proven that significant  $VO_2$  peak improvement in CRT 'nonresponders' was highly correlated with knee extensor muscle strength, consequently displaying the role of peripheral improvements.<sup>35</sup> In a glance, these peripheral effects that are exerted by exercise training include histologic peripheral skeletal muscle changes, muscle sympathetic nerve activity through mechanoreflex and metaboreflex sensitivity, and finally improving nitric oxide endothelial reactivity, leading to enhancement of heart rate variability.8,22,38,39

#### 3 | IDEAL TRAINING TIME

Taking reference to the exercise prescription after recent intervention for implantation of intracardiac pacing devices by American College of Sports Medicine (ACSM), there are two after implantation timings to be considered. The first is 24 hours after implantation, as it has been shown that light exercises could prevent complications of immobilization in prolonged bed rest or other complicated cases. Adhering to the exercise guidelines of heart failure patients, it should be noted that light exercises could be initiated when the patient is hemodynamically stable, and could tolerate daily activities without severe restriction caused by symptoms. Whereas the second timing is 3-4 weeks after implantation, with the prohibition to heavy upper extremity activities, such as swimming, bowling, heavy lifting, or golf. On the other hand, exercise or lower extremity physical activity is permitted.<sup>24</sup>

There are still few controlled trials that investigates the impact of exercise training in CRT patients, and even fewer that clearly describes the exercise prescription.<sup>9,22,40</sup> Patwala et al uses stable criteria for heart failure within 1 month, these includes no admission to hospital with heart failure symptoms, no change in treatment, and no change in NYHA class, only if all these criteria are met would the training begin.<sup>13</sup>

The same stable criteria within 1 month were also used by Conraads et al, and subsequent research by Belardinelli et al used a longer stable criteria for 2 months before their study inclusion.<sup>12,14</sup> The patients must also have no postoperative complications to upper extremity motions, as strenuous upper extremity training may dislodge the recently implanted leads.<sup>9,24</sup> Although there are no studies that indicate the ideal timing, it can be concluded from existing studies that patients must reach clinical stability before initiating exercise, preferably 1 week after the implantation to account for postimplantation healing and familiarization.<sup>9,12-14,24</sup>

#### 4 | EXERCISE TESTING

Generally, it is known that the target of exercise testing is to evaluate maximal functional capacity and provide a specific exercise prescription.<sup>28,41</sup> However, there lies another specific purpose of testing in CRT patients who are essentially patients with heart failure, which is to observe their chronotropic response.<sup>42</sup> More objective outcome measurement such as VO<sub>2</sub> peak (the peak rate of oxygen consumption recorded from the average consumption within the last 15 seconds of testing) could be attained only by using cardiopulmonary exercise testing (CPET), and its applicability in heart failure subjects require some endpoint modifications.<sup>41,43,44</sup>

Although exercise protocols in CRT patients are usually identical with management of heart failure, the presence of pacemaker itself is an unique characteristic in this group of patients.<sup>41</sup> Thus, a study has shown that there is a specified exercise testing that can be used by CRT patients, namely, the Chronotropic Assessment Exercise Protocol (CAEP) with treadmill.<sup>9</sup> This protocol is specifically designed to assess patients with rate-responsive pacemakers.<sup>45</sup>

The CAEP protocol will start with 1.5 METs, with a calculation of 1 MET (3.5 ml  $O_2/kg/min$ ). The patient will go through 2 minutes at each stage with an increase of 1 MET at each stage for the first 10 minutes.<sup>9</sup> Thus, this protocol will give patients the opportunity to complete several stages of exercise, and test chronotropic responses to the submaximal capacities that exist in the range of common daily activities. That study had also obtained a conversion formula with comparison to the Bruce protocol, in obtaining predicted heart rate at each stage under the following formula:<sup>46</sup>

$$HRstage = \frac{[220 - age - HRrest] \times [METSstage - 1]}{METSpeak - 1} + HRrest$$

In addition, Haennel et al also showed the importance of noticing changes in heart rate within 3-5 minutes of the recovery time after exercise testing.<sup>9</sup> Essentially, changes in heart rate have been shown to be related to hemodynamics during postexercise recovery.<sup>9</sup> Other

	CAEP			Naughton			Modified Balke			Bruce		
Time (min)	Grade (%)	Stage (#)	Speed (mph)	Grade (%)	Stage (#)	Speed (mph)	Grade (%)	Stage (#)	Speed (mph)	Grade (%)	Stage (#)	Speed (mph)
0-1	0	0	1.0	0	1	1.0	0	1	0.5	10	1	1.7
1-2	0	0	1.0	0	1	1.0	0	2	1.0	10	1	1.7
2-3	2	1	1.0	0	1	1.0	0	3	1.7	10	1	1.7
3-4	2	1	1.0		Rest		0	4	2.2	12	2	2.5
4-5	3	2	1.5		Rest		0	5	2.7	12	2	2.5
5-6	3	2	1.5		Rest		0	6	3.3	12	2	2.5
6-7	4	3	2.0	0	2	1.5	1	7	3.3	14	3	3.4
7-8	4	3	2.0	0	2	1.5	2	8	3.3	14	3	3.4
8-9	5	4	2.5	0	2	1.5	3	9	3.3	14	3	3.4
9-10	5	4	2.5		Rest		4	10	3.3	16	4	4.2
10-11	6	5	3.0		Rest		5	11	3.3	16	4	4.2
11-12	6	5	3.0		Rest		6	12	3.3	16	4	4.2
12-13	8	6	3.5	0	3	2.0	7	13	3.3	18	5	5.0
13-14	8	6	3.5	0	3	2.0	8	14	3.3	18	5	5.0
14-15	10	7	4.0	0	3	2.0	9	15	3.3	18	5	5.0
15-16	10	7	4.0		Rest		10	16	3.3	20	6	5.5
16-17	10	8	5.0		Rest		11	17	3.3	20	6	5.5
17-18	10	8	5.0		Rest		12	18	3.3	20	6	5.5
18-19	10	9	6.0	3.5	4	2.0	13	19	3.3	22	7	6.0
19-20	10	9	6.0	3.5	4	2.0	14	20	3.3	22	7	6.0
20-21	10	10	7.0	3.5	4	2.0				22	7	6.0
21-22	10	10	7.0									
22-23	15	11	7.0									

than CAEP, treadmill exercise testing could also utilize the modified Naughton or Balke protocol, which is also considered safe in CRT patients.<sup>15,28,47</sup> It is challenging for heart failure subjects to achieve maximal capacity as a result of their symptoms, therefore, often times in cardiopulmonary exercise testing (CPET) environment, patients with low peak respiratory exchange ratio (pRER) of <1.05 will have self-interrupted test termination.<sup>44</sup> Nevertheless, subjective symptoms such as leg fatigue and breathlessness can be readily utilized for a test termination criteria, as reported by other studies.<sup>43,44,47</sup>

A scientific statement from American Heart Association regarding exercise testing standard have shown that the use of cycle ergometer for exercise testing is also viable, especially in the advanced, aging population of CRT patients.<sup>28,29</sup> Although the Naughton protocol is treadmill based, it could also be used in a cycle ergometer.<sup>47</sup> It was shown that pedaling speeds of 50-80 rpm could achieve the highest values of VO<sub>2</sub> and heart rate, with initial output of 10 or 25 W, followed by increase of 25 W every 2 or 3 minutes until endpoints are attained.<sup>28</sup> One drawback of the cycle is that oxygen uptake is significantly higher in treadmill testing as proven by a cross-over study.<sup>47</sup> This may be caused by the presence of steady state between stages which allows recovery, as compared to a continuous 10-W/min step protocol for cycle ergometer, and also the presence of local leg muscle fatigue which is reached before  $VO_2max$  is achieved.<sup>28,45,47</sup>

Another modality which could be used for exercise testing is the 6-minute walking test, which requires subjects to walk continuously on a 30-m track for a whole duration of 6 minutes.<sup>28</sup> Despite the fact that VO<sub>2</sub>max correlates of this test are only modest ( $r \approx 0.50$ ), this test is better implemented in the clinical setting and could routinely be performed during follow-up.<sup>15,28</sup> Additionally this test could be readily used in ambulatory patients with chronic disease, and it is evident that CRT recipient population is highly suitable, owing to aging frailty and heart failure.<sup>19,28</sup>

Obese individuals or other comorbidities that disallow patients to sustain relatively high-power output in the early stages of the protocol, the Naughton protocol will not be possible.<sup>45</sup> Other studies have mentioned the use of modified Balke protocol, where instead of a steady speed of 3.3 mph (5.31 km/h) along all the stages, a slow increments of speed at 0% grade in the first 5 minutes at the start of the test are used.<sup>45</sup> It was shown that protocols which have a more linear or ramp pattern of workload increase have been found to produce a more continuous increase in cardiorespiratory response, leading to more accurate measurement of VO<sub>2</sub>max.<sup>45</sup> Table 1 shows

differences between the three safe protocols and standardized Bruce protocol.

In patients with a set rate mode of CRT-P, it is very important to remember that the exercise testing cannot always be monitored with heart rate.<sup>9,25</sup> Therefore, the safe exercise test to be carried out is a submaximal capacity testing, namely, the 6-minute walk test by American Thoracic Society.<sup>48</sup> Exercise test termination will be subjective complaints, quantitatively assessed by the Borg scale.<sup>20</sup> This 6-minute walk submaximal exercise testing protocol is in accordance with the *European Society of Cardiology* (ESC) statement on exercises for patients with heart failure, and is applicable when treadmill testing is not possibly performed.<sup>20</sup> Table 2 sums the contraindications from the exercise tests (A), exercise (B), and increased risk (C) in heart failure exercises, which should be noted before prescribing.<sup>20</sup>

#### 5 | PRESCRIBING AEROBIC EXERCISE

Although there are lack of evidence on aerobic endurance training prescription for CRT patients, heart failure patients could undergo both continuous and interval training. However, the existing evidence shows that continuous training seems to be safe, whereas not much controlled trials have been performed on interval training.<sup>22</sup> The discussion in this section will summarize and explore existing studies on the aerobic exercise protocols used.

In general, the recommended exercise frequency is 3-5 days/ week.<sup>9,22</sup> The three existing controlled trials have also shown that all of these programs must be supervised, and are safely carried out in a hospital-based gym setting. This frequency is found the same in all three studies, namely, three times per week.<sup>12-14</sup> Additionally, there is one report that shows efficacy of a protocol which is slightly milder from those for heart failure patients with ICD, which is twice every week for 2 hours.<sup>49</sup> The protocol may be considered more safe as it has lesser frequency than the commonly prescribed 3-5 days/week, instead it requires a longer exercise time of 2 hours. Therefore, a critical review from Haennel et al does not recommend that particular prescription of 2 hours per session as a result of lack of evidence-based safety.<sup>9</sup>

For heart failure patients, ESC had stated that exercise intensity should obtain range of exercise Heart Rate Reserve (HRR), which could be calculated by taking the difference of basal heart rate and peak heart rate. It has been said that the main objective of this exercise is to achieve 40%-70% of exercise HRR and 10-14/20 on the Borg scale RPE (rating of perceived exertion).<sup>20</sup> Taking the statement in mind. Haennel et al recommend that the target of the exercise in CRT-P device patients to be modified to the resting heart rate added with 40%-60% of HRR.<sup>9</sup> The use of training targets range would vary in between. Patwala et al used a target that increases in each exercise phases, ie, the first phase of 4 weeks will aim to reach 80% of peak HR, the next 4 weeks is 85%, and the last 4 weeks reaching 90%.<sup>13</sup> Bellardinelli on the other hand had used VO<sub>2</sub> as exercise target. That particular study mentioned that exercise intensity should reach 60% of the VO<sub>2</sub> peak.<sup>14</sup> Another alternative as shown by Conraads et al, with target heart rate of 90% exercise heart rate achieved in ventilatory threshold during CPET.<sup>12</sup> Two of these three studies had used gas analyzers in their CPET protocol, but it could be seen that 6-minute walk test is still appropriate for use, and heart rate or Borg scale is sufficient to obtain good exercise intensity.<sup>9,20</sup> Maximal heart rate determination is also required, especially in patients with CRT-D implanted, where shock thresholds may differ between patients. As mentioned earlier, the general rule is to have the exercise heart rate to be 10-20 beats below the threshold.9,14,20,50

Another general guide for aerobic modality in post device implantation heart failure patients would be to maintain the standing

(A) Contraindications to exercise testing & training	(B) Contraindications to exercise training	(C) Increased risk for exercise training
1. Early phase after acute coronary syndrome (up to 2 days)	<ol> <li>Progressive worsening of exercise tolerance or dyspnea at rest over previous 3-5 days</li> </ol>	1. >1.8 kg increase in body mass over the previous 1-3 days
2. Untreated life-threatening cardiac arrhythmias	2. Significant ischemia during low-intensity exercise (<2 METs, <50 W)	2. Concurrent, continuous, or intermittent dobutamine therapy
3. Acute heart failure (during the initial period of hemodynamic instability)	3. Uncontrolled diabetes	3. Decrease in systolic blood pressure with exercise
4. Uncontrolled hypertension	4. Recent embolism	4. NYHA functional class IV
5. Advanced atrioventricular block	5. Thrombophlebitis	5. Complex ventricular arrhythmia at rest or appearing with exertion
6. Acute myocarditis and pericarditis	6. New-onset atrial fibrillation/atrial flutter	6. Supine resting heart rate >100 b.p.m.
7. Symptomatic aortic stenosis		7. Pre-existing co-morbidities limiting exercise tolerance
8. Severe hypertrophic obstructive cardiomyopathy		
9. Acute systemic illness		
10. Intracardiac thrombus		

TABLE 2 Summary table of various contraindications and risks to exercise testing and training<sup>20</sup>

3 Suggested exercise protocol

	CRT exercise protocol	<b>TABLE 3</b> Sug in CRT patients		
Frequency	<ul><li> 3-5 days/week</li><li> 30-50 minutes/session</li></ul>			
Intensity	<ul> <li>80% of Heart Rate Reserve</li> <li>Maximal intensity in Borg scale of 14 of 20</li> <li>10-20 beats below shock threshold for CRT-D</li> </ul>			
Туре	<ul> <li>5- to 10-minute warm-up stretches (lower extremities)</li> <li>20- to 30-minute aerobic ergocycle</li> <li>5- to 10-minute cooling down</li> </ul>			
Time	After 1 month medically stable preceding the implantation of CRT			
CRT mode	Rate adaptive pacing mode			

position, hence, walking would be more preferred.<sup>22</sup> As body motion detected by accelerometer would trigger rate-adaptive pacing, it is important to initially test and supervise these exercises, before safely prescribing them.<sup>9,23</sup> These three prospective studies have also shown a mutual exercise goal of achieving overall endurance, which eventually leads to walking and cycling exercise being the most effective.<sup>12-14</sup> It also appears that these exercise modes do adhere to the training recommendations by ESC in patients with heart failure, with the properties of medium to high intensity, and the presence of steady-state conditions.<sup>20</sup>

# 6 | SAFETY OF HOME-BASED EXERCISE PROGRAM

The next step that ensues after prescribing hospital-based exercise is also to prepare a personalized home-based exercise program. To begin with, strenuous and strengthening exercise in upper extremities is usually not recommended for CRT patients. Whereas not many studies had shown efficacy of home-based program, Smolis Bak et al have shown direct improvement in endurance and quality of life after home-based telemonitoring. Exercise duration is 5 times a week for a total of 8 weeks, comparing the effects of home based with monitoring against control (no monitoring).<sup>15</sup>

Smolis Bak administered home exercise regimen which includes extremities range of motion exercise, strengthening isometric exercise for small muscle groups, coordination, and respiratory exercises. Before beginning the regimen, electrocardiography (EKG) results must first be sent to the monitoring center, as well as queries on subjective symptoms and drug compliance. During exercise, the EKG is recorded and sent to the monitoring center for a direct interactive feedback. The study did not show any data on number of shocks that occurred during exercise, but up to half of the total sample (n = 52) in each groups had undergone a condition that requires hospitalization (43.8% in monitoring and 51.7% in control group).<sup>15</sup>

The study had also shown improvements in Left Ventricular Ejection Fraction (LVEF) in both groups, with and without monitoring. Interestingly, in 12 months, LVEF improvement in control group (24.9  $\pm$  7.2 to 31.7  $\pm$  10.6, P = .001) was found to be slightly higher

than in the exercise group ( $25.3 \pm 7.4$  to  $28.9 \pm 9.1$ , P = .0213), although intergroup differences did not seem to be statistically significant.<sup>15</sup> Despite the fact that the study had not shown impacts toward prognosis, the rate of readmission should be a general concern, and monitoring could improve exercise safety at home.

#### 7 | ADVERSE EVENTS OF EXERCISE

Despite most studies have revealed safety of mild-to-moderate exercise training in the heart failure population, several adverse events have been reported by HF-ACTION, being the largest multicenter, randomized, controlled trial on exercise intervention in heart failure patients.<sup>7,10,22,51</sup> The most prevalent cardiac-related adverse event was worsening of heart failure, whereas for general adverse event, the most common is inappropriate shocks.<sup>19,51</sup> Additionally, all of these prevalence were not significantly different in the usual care as compared to the exercise intervention group.<sup>51</sup> Therefore, it could be drawn out that these adverse events may not be particularly caused by exercise, instead it is a multifactorial events occurring in the course of heart failure. The FRAIL-HF cohort had reported that hospitalized congestive heart failure patients were 70.2% frail, hence, there is a superimposition of progressive CHF symptoms and aging frailty.<sup>19</sup> Therefore, it would be essential to perform multidisciplinary care in CRT patients to achieve the best functional outcome.29

#### 8 | CONCLUSION

It can be concluded that exercise provides significant improvement in heart failure patients after implantation of CRT.<sup>4</sup> Prescribing exercise to this patient group was also found to be safe, and thus is recommended for CRT patients who have been medically stable for the past 1 month.<sup>9</sup> Regardless of response to the CRT device, aerobic exercise training has been shown to both be safe and effective to provide adequate functional capacity improvement, therefore, is highly recommended.<sup>13,33-35</sup>

To date, there are still no standard guidelines for providing aerobic exercise to patients with CRT, but this current literature review has included an exercise protocol which could safely be performed for the patient group.<sup>12-14</sup> Generally, exercise frequency is 3-5 days/ week, with exercise duration of 30 minutes to 1 hour. Although there are various ways of determining exercise intensity, achieving 80% of the patients' HRR is a sufficient target, which could be assessed by performing 6-minute walk test.<sup>20</sup> Because CRT patients are principally heart failure patients with pacemakers, the Borg scale could always be used, in which achieving exercise intensity up to 10-14 of 20 would result in a positive exercise effect.<sup>20</sup> Exercise modalities that could be used are walking aerobic exercises (either a treadmill or normal walking) and static cycling (ergocycle). It is also important to note that in CRT-D (defibrillator) patients, an additional exercise testing will be needed to determine the maximum heart rate during exercise, which should be targeted 10-20 beats below the shock threshold.<sup>9,12-14,20,50</sup> Table 3 depicts the general exercise prescription for CRT patients.

Exercise can be given for 8-12 weeks, where home exercise can also be given to provide more sustained effects. However, existing evidence on the home-based program safety must be accompanied by telemonitoring, especially in monitoring EKG before and during exercise.<sup>15</sup> Further studies will be required in examining the effectiveness of other types of exercises, such as breathing and mild strengthening exercises, that are safe for CRT patients.

#### DISCLOSURE

The authors have no conflicts of interest to disclose.

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#### REFERENCES

- Vardas PE, Auricchio A, Blanc J-J, Daubert J-C, Drexler H, Ector H, et al. Guidelines for cardiac pacing and cardiac resynchronization therapy. The Task Force for Cardiac Pacing and Cardiac Resynchronization Therapy of the European Society of Cardiology. Developed in collaboration with the European Heart Rhythm Association. Eur Heart J. 2007;9(10):959–98.
- Brignole M, Auricchio A, Baron-Esquivias G, Bordachar P, Boriani G, Breithardt O-A, et al. 2013 ESC guidelines on cardiac pacing and cardiac resynchronization therapy: the task force on cardiac pacing and resynchronization therapy of the European Society of Cardiology (ESC). Developed in collaboration with the European Heart Rhythm Association. Europace. 2013;15(8):1070-118.
- Normand C, Linde C, Singh J, Dickstein K. Indications for cardiac resynchronization therapy: a comparison of the major international guidelines. JACC Heart Fail. 2018;6(4):308–16.
- McAlister FA, Ezekowitz J, Hooton N, Vandermeer B, Spooner C, Dryden DM, et al. Cardiac resynchronization therapy for patients with left ventricular systolic dysfunction: a systematic review. JAMA. 2007;297(22):2502-14.
- Tomczak CR, Paterson I, Haykowsky MJ, Lawrance R, Martellotto A, Pantano A, et al. Cardiac resynchronization therapy modulation of exercise left ventricular function and pulmonary O₂ uptake in heart failure. Am J Physiol Heart Circ Physiol. 2012;302(12):H2635 -H2645.

- Auricchio A, Kloss M, Trautmann SI, Rodner S, Klein H. Exercise performance following cardiac resynchronization therapy in patients with heart failure and ventricular conduction delay. Am J Cardiol. 2002;89(2):198–203.
- Chen Z-B, Fan L-B, Liu Y-J, Zheng Y-R. Meta-analysis of the effects of cardiac rehabilitation on exercise tolerance and cardiac function in heart failure patients undergoing cardiac resynchronization therapy. Biomed Res Int. 2019;2019:3202838.
- Kuniyoshi RR, Martinelli M, Negrão CE, Siqueira SF, Rondon M, Trombetta IC, et al. Effects of cardiac resynchronization therapy on muscle sympathetic nerve activity. Pacing Clin Electrophysiol. 2014;37(1):11–8.
- Haennel RG. Exercise rehabilitation for chronic heart failure patients with cardiac device implants. Cardiopulm Phys Ther J. 2012;23(3):23.
- Steinhaus DA, Lubitz SA, Noseworthy PA, Kramer DB. Exercise interventions in patients with implantable cardioverter-defibrillators and cardiac resynchronization therapy: a systematic review and meta-analysis. J Cardiopulm Rehabil Prev. 2019;39(5):308–17.
- Nielsen KM, Zwisler A-D, Taylor RS, Svendsen JH, Lindschou J, Anderson L, et al. Exercise-based cardiac rehabilitation for adult patients with an implantable cardioverter defibrillator. Cochrane Database Syst Rev. 2019;2:CD011828.
- Conraads VMA, Vanderheyden M, Paelinck B, Verstreken S, Blankoff I, Miljoen H, et al. The effect of endurance training on exercise capacity following cardiac resynchronization therapy in chronic heart failure patients: a pilot trial. Eur J Cardiovasc Prev Rehabil. 2007;14(1):99–106.
- Patwala AY, Woods PR, Sharp L, Goldspink DS, Tan LB, Wright DJ. Maximizing patient benefit from cardiac resynchronization therapy with the addition of structured exercise training a randomized controlled study. JAC. 2009;53(25):2332–9. https://doi.org/10.1016/j. jacc.2009.02.063
- 14. Belardinelli R, Capestro F, Misiani A, Scipione P, Georgiou D. Moderate exercise training improves functional capacity, quality of life, and endothelium-dependent vasodilation in chronic heart failure patients with implantable cardioverter defibrillators and cardiac resynchronization therapy. Eur J Cardiovasc Prev Rehabil. 2006;13(5):818–25.
- 15. Smolis-Bąk E, Dąbrowski R, Piotrowicz E, Chwyczko T, Dobraszkiewicz-Wasilewska B, Kowalik I, et al. 1 Hospital-based and telemonitoring guided home-based training programs: effects on exercise tolerance and quality of life in patients with heart failure (NYHA class III) and cardiac resynchronization therapy. A randomized, prospective observation. Int J Cardiol. 2015;199:442-7.
- JCS Joint Working Group. Guidelines for rehabilitation in patients with cardiovascular disease (JCS 2012). Circ J. 2014;78(8):2022–93.
- Hambrecht R, Fiehn E, Weigl C, Gielen S, Hamann C, Kaiser R, et al. Regular physical exercise corrects endothelial dysfunction and improves exercise capacity in patients with chronic heart failure. Circulation. 1998;98(24):2709–15.
- Pearson MJ, Smart NA. Effect of exercise training on endothelial function in heart failure patients: a systematic review meta-analysis. Int J Cardiol. 2017;231:234–43.
- Vigorito C, Abreu A, Ambrosetti M, Belardinelli R, Corrà U, Cupples M, et al. Frailty and cardiac rehabilitation: a call to action from the EAPC Cardiac Rehabilitation Section. Eur J Prev Cardiol. 2017;24(6):577-90.
- Piepoli MF, Conraads V, Corrà U, Dickstein K, Francis DP, Jaarsma T, et al. Exercise training in heart failure: from theory to practice. A consensus document of the Heart Failure Association and the European Association for Cardiovascular Prevention and Rehabilitation. Eur J Heart Fail. 2011;13(4):347-57.
- 21. Santoso A, Maulana R, Alzahra F, Prameswari HS, Ambari AM, Hartopo AB, et al. The effects of aerobic exercise on N-terminal

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pro-B-type natriuretic peptide and cardiopulmonary function in patients with heart failure: a meta-analysis of randomised clinical trials. Heart Lung Circ. 2020;29(12):1790–8.

- 22. Ambrosetti M, Braga SS, Giada F, Pedretti RFE. Exercise-based cardiac rehabilitation in cardiac resynchronization therapy recipients: a primer for practicing clinicians. Monaldi Arch Chest Dis. 2017;87(3):791.
- Rhodes T, Weiss R. Device therapy in the heart failure. In Feldman DS, Mohacsi P, editors. Heart Failure. Cham, Switzerland: Springer, 2019; p. 129–53.
- Pescatello LS. Exercise prescription for patients with cardiovascular and cerebrovascular disease. In: Pescatello LS, Arena R, Riebe D, Thompson PD, editors. ACSM's Guideline for Exercise Testing and Prescription, 9th edn. Baltimore, MD: Wolters Kluwers Lippincott Williams & Wilkins; 2014. p. 236–59.
- AACVPR. Special populations. In: Williams MA, Roitman JL, editors. Guidelines for Cardiac Rehabilitation and Secondary Prevention Programs, 5th edn. Champaign, IL: HumanKinetics; 2013. p. 143-92.
- Perini AP, Kutyifa V, Veazie P, Daubert JP, Schuger C, Zareba W, et al. Effects of implantable cardioverter/defibrillator shock and antitachycardia pacing on anxiety and quality of life: A MADIT-RIT substudy. Am Heart J. 2017;189:75–84.
- 27. Fleeman BE, Aleong RG. Optimal strategies to reduce inappropriate implantable cardioverter-defibrillator shocks. J Innov Card Rhythm Manag. 2019;10(4):3623–32.
- Fletcher GF, Ades PA, Kligfield P, Arena R, Balady GJ, Bittner VA, et al. Exercise standards for testing and training: a scientific statement from the American Heart Association. Circulation. 2013;128(8):873-934.
- 29. Martens P, Jacobs G, Dupont M, Mullens W. Effect of multidisciplinary cardiac rehabilitation on the response to cardiac resynchronization therapy. Cardiovasc Ther. 2018;36(6):e12467.
- Iliou MC, Alonso C, Cristofini P, Salah O, Lavergne T, Charon O, et al. Exercise training after cardiac resynchronization in chronic heart failure. Results of a pilot study. Eur J Cardiovasc Prev Rehab. 2003;10:402.
- Lau C-P, Tse H-F, Camm AJ, Barold SS. Evolution of pacing for bradycardias: sensors. Eur Hear J Suppl. 2007;9(suppl\_l):111–122.
- 32. Korpas D. Implantable cardiac devices technology. Springer; 2013.
- Sinagra G, Proclemer A, Zecchin M. Resynchronization therapy in heart failure: the "nonresponder". J Cardiovasc Med (Hagerstown). 2018;19(Suppl 1):e112–e115.
- Auricchio A, Prinzen FW. Non-responders to cardiac resynchronization therapy. Circ J. 2011;75(3):521–7.
- Yanagi H, Nakanishi M, Konishi H, Yamada S, Fukui N, Kitagaki K, et al. Effect of exercise training in heart failure patients without echocardiographic response to cardiac resynchronization therapy. Circ Reports. 2019;1(2):55–60.
- Abreu A, Clara HS. Imaging predictive factors and exercise training in patients submitted to cardiac resynchronization. Monaldi Arch Chest Dis. 2016;86(1–2):760.
- Iliou MC, Blanchard JC, Lamar-tanguy A, Cristofini P, Ledru F. Cardiac rehabilitation in patients with pacemakers and implantable cardioverter defibrillators. Monaldi Arch Chest Dis. 2016;86:1–7.
- Radi B, Santoso A, Siswanto BB, Mansyur M, Ibrahim N, Kusmana D. Early exercise program for patients with heart failure after hospital discharge. Int J Phys Med Rehabil. 2017;5:392.

- Enomoto K, Yamabe H, Toyama K, Matsuzawa Y, Yamamuro M, Uemura T, et al. Improvement effect on endothelial function in patients with congestive heart failure treated with cardiac resynchronization therapy. J Cardiol. 2011;58(1):69–73.
- Santos GL, Alcântara CC, Silva-Couto MA, García-Salazar LF, Russo TL. Decreased brain-derived neurotrophic factor serum concentrations in chronic post-stroke subjects. J Stroke Cerebrovasc Dis. 2016;25(12):2968–74. https://doi.org/10.1016/j.jstrokecerebrov asdis.2016.08.014
- Malhotra R, Bakken K, D'Elia E, Lewis GD. Cardiopulmonary exercise testing in heart failure. JACC Heart Fail. 2016;4(8):607–16.
- 42. Jamil HA, Gierula J, Paton MF, Byrom R, Lowry JE, Cubbon RM, et al. Chronotropic incompetence does not limit exercise capacity in chronic heart failure. J Am Coll Cardiol. 2016;67(16):1885–96.
- Piepoli MF, Corra U, Agostoni P. Cardiopulmonary exercise testing in patients with heart failure with specific comorbidities. Ann Am Thorac Soc. 2017;14(Supplement 1):S110–S115.
- 44. Corrà U, Agostoni P, Piepoli MF, Giordano A, Mezzani A, Giannuzzi P, et al. Metabolic exercise data combined with cardiac and kidney indexes: MECKI score. Predictive role in cardiopulmonary exercise testing with low respiratory exchange ratio in heart failure. Int J Cardiol. 2015;184(1):299–301.
- 45. Flo GL, Glenny RW, Kudenchuk PJ, Dougherty CM. Development and safety of an exercise testing protocol for patients with an implanted cardioverter defibrillator for primary or secondary indication. Cardiopulm Phys Ther J. 2012;23(3):16–22.
- Wilkoff BL, Corey J, Blackburn G. A mathematical model of the cardiac chronotropic response to exercise. J Electrophysiol. 1989;3(3):176–80.
- 47. Goldraich L, Ross HJ, Foroutan F, Walker M, Braga J, McDonald MA. Reevaluating modality of cardiopulmonary exercise testing in patients with heart failure and resynchronization therapy: relevance of heart rate-adaptive pacing. J Card Fail. 2017;23(5):422-6.
- ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. ATS statement: guidelines for the six-minute walk test. Am J Respir Crit Care Med. 2002;166(1):111–7.
- Fitchet A, Doherty PJ, Bundy C, Bell W, Fitzpatrick AP, Garratt CJ. Comprehensive cardiac rehabilitation programme for implantable cardioverter-defibrillator patients: a randomised controlled trial. Heart. 2003;89(2):155–60.
- Fletcher GF, Balady GJ, Amsterdam EA, Chaitman B, Eckel R, Fleg J, et al. Exercise standards for testing and training: a statement for healthcare professionals from the American Heart Association. Circulation. 2001;104(14):1694–740.
- O'Connor CM, Whellan DJ, Lee KL, Keteyian SJ, Cooper LS, Ellis SJ, et al. Efficacy and safety of exercise training in patients with chronic heart failure: HF-ACTION randomized controlled trial. JAMA. 2009;301(14):1439–50.

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