Does Cardiac Resynchronization Therapy and Aerobic Exercise Improve Exercise Tolerance / Ability in Heart Failure Patients Better Than Either Intervention Alone or no Intervention at All?

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Does Cardiac Resynchronization Therapy and Aerobic Exercise Improve Exercise Tolerance / Ability in Heart Failure Patients Better Than Either Intervention Alone or no Intervention at All?

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December 17, 2010
Abstract

OBJECTIVE: The objective if this systematic review is to determine whether or not cardiac resynchronization therapy with aerobic exercise improves exercise tolerance / ability better then either treatment alone or no intervention at all.

STUDY DESIGN: Review of 4 English language primary studies. 2 Investigator Blinded and 2 Double Blind Crossover studies were used.

DATA SOURCES: Articles were found utilizing OVID and COCHRANE databases.

OUTCOME MEASURED: 4 outcomes were considered in this review. Dyspnea, leg comfort, exercise time / AT, and V02 (exercise tolerance).

RESULTS: The Wasserman article concludes that those individuals who are beginning with a baseline Peak V02 of < 50% of predicted benefit greatly from BVP-ON w/exercise while those with BVP-OFF or BVP-ON (Peak V02 > 50% predicted) show no statistically significant different. The Laveneziana article concludes patients with CRT-ON during exercise showed marked improvement in dyspnea and leg discomfort (typically leg discomfort is seen as the major limiting symptom in patients with CHF [as seen in this study]). The Schlosshan article concludes that CRT in long term therapy (post remodeling) continues to confer benefit to the heart. The Conraads article concludes that the combination of CRT with endurance training show a synergistic effect on exercise tolerance (better then either alone).

CONCLUSION: The results of all 4 articles express similar conclusion. Exercise and CRT therapy are both beneficial on exercise tolerance and perhaps even reduction of cardiac remodeling. However, Exercise with CRT therapy provides benefit beyond either therapy alone.

KEY WORDS: CRT (cardiac resynchronization therapy), LVEF (left ventricular ejection fraction), peak VO2, NYHA (new york heart association), BVP (bi-ventricular pacing), CHF (congestive heart failure), CPET (cardiopulmonary exercise testing), LVF (left ventricular failure), AT (anaerobic threshold).
INTRODUCTION

Congestive heart failure is a condition where the heart is no long able to pump an adequate amount of blood throughout the body. It affects millions of people world wide. CHF is more prevelant with age which makes it an increasingly important issue as our aged population continues to enlarge. There are many causes such as coronary artery disease, HTN or any condition that alters / damages heart tissue (MI, viruses, toxic exposures). There are different types of heart failure: systolic dysfunction, diastolic dysfunction. Systolic function involves impairment in heart contraction such as in a dilated cardiomyopathy. Diastolic dysfunction involves impairment in ventricle filling such as in a ventricular hypertrophy. CHF can be classified according to symptoms experienced during everyday activities using the New York Heart Association classification.

Table 1: NYHA Classifications

<table>
<thead>
<tr>
<th>NYHA Class</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>No symptoms and no limitation in ordinary physical activity, e.g. shortness of breath when walking, climbing stairs etc.</td>
</tr>
<tr>
<td>II</td>
<td>Mild symptoms (mild shortness of breath and/or angina) and slight limitation during ordinary activity.</td>
</tr>
<tr>
<td>III</td>
<td>Marked limitation in activity due to symptoms, even during less-than-ordinary activity, e.g. walking short distances (20–100 m). Comfortable only at rest.</td>
</tr>
<tr>
<td>IV</td>
<td>Severe limitations. Experiences symptoms even while at rest. Mostly bedbound patients.</td>
</tr>
</tbody>
</table>

There are many signs and symptoms of congestive heart failure. There are non side specific symptoms such as tachycardia, hypotension, diaphoresis, cachexia, cyanosis, clubbing. There are left sided heart failure signs and symptoms such as shortness of breath, orthopnea, chronic non-productive cough and exercise intolerance. There are right sided heart failure signs and symptoms such as loss of appetite, (pitting) edema, ascites, nausea, jugular venus pressure increse, hepatic enlargement. It is important to remember that most patients suffer a combination of both left and right sided heart failure with one predominating. Right sided heart failure is most commonly caused by left sided heart failure.
Diagnoses can be made by analyzing multiple areas of health: CBC, renal function tests, BNP, EKG, chest radiography, echo cardiography, angiography and cardiac catheterization. While there are multiple avenues for diagnosing; effective treatments / cures still elude us. There are a multitude of both pharmacological and non-pharmacological treatments. The current standard medicines are diuretics, ACE inhibitors, ARB's, beta blockers, digitalis, nitrates, neseritide and hydralazine. Other pharmacological treatments include inotropic agents, antiarhythmics, statins, anticoagulation and CCB's. Non-pharmacological treatments involve revascularization, cardiac transplant, diet, exercise and pacing. Exercise and ventricular pacing our the focus of this paper. The importance of research and evidence based treatments can be seen in the sequelae of congestive heart failure: organ failure (kidney / liver), pulmonary edema, decrease in physical capacity and death.

Physician assistants are highly valued instruments in the care of CHF patients. CHF is a non-reversible disease that requires enormous amounts of care and money. PA's, rather than doctors, are able to spend longer periods of time with patients aiding them in understanding their disease and employing treatments that are best suited to them at a lower cost. The treatments highlighted in this paper are time consuming and require discipline, however as you will see in this paper are effective.

**OBJECTIVE**

The objective if this systematic review is to determine whether or not cardiac resynchronization therapy with aerobic exercise improves exercise tolerance / ability better then either treatment alone or no intervention at all. The hypothesis is that the above two treatments do indeed improve exercise tolerance better then either treatment alone or not at all.

**METHODS**

All 4 studies met the following criteria for population selection. Patients were aged 50-80 with a NYHA class II or greater. Left ventricular ejection fraction (LVEF) was < 35% in all selected patients and the QRS complex width was > 120ms. Two of the studies were investigator blinded [Wasserman, Conraads] and 2 of the studies were double blind crossover studies [Laveneziana, Schlosshan]
The general interventions were CRT on or off during aerobic exercise. Essentially pts with CRT on during exercise were compared to patients with CRT off during exercise. In one experiment CRT with exercise is compared to CRT alone [Conraads]. Four questions were analyzed to determine treatment outcome. Do patients feel exercise tolerance is improved? Do patients experience less dyspnea? Do patients experience less leg pain? Peak oxygen uptake was also used as a way to measure exercise tolerance.

The 1st study [Wasserman] was conducted throughout the United States at many different facilities. Every site abided by a workout protocol on either a bike or a treadmill. Baseline and 6 month protocols were the same. The 2nd study [Conraads] is a European study that utilized a rigorous endurance training protocol for the CRT with ET and not training protocol for CRT without ET. There were baseline and 5 month measurements in this study. The 3rd study [Schlosshan] is a crossover study conducted in Europe. Patients were evaluated with CRT either on or off and then on a separate day evaluated again with their CRT setting changed to the opposite setting. The 4th study [Lavenezia] is a crossover study conducted in Canada. This study was a three days study with the first day being part of the learning curve and days 2 – 3 generating the results. Pt's were randomized to CRT on or off and switched the next day to the opposite setting. Pt were tested under incremental cycle exercising.

Key words used in searches were: CRT (cardiac resynchronization therapy), LVEF (left ventricular ejection fraction), peak VO2, NYHA (new york heart association), BVP (bi-ventricular pacing), CHF (congestive heart failure), CPET (cardiopulmonary exercise testing), LVF (left ventricular failure), AT (anaerobic threshold). All articles were published in peer review journals in English. Articles were found using Ovid and Cochrane databases and were chosen based on relevant and patient oriented evidence. Articles included were from 2007 or later due to a pending review in 2006. All articles were RCTs and investigator blinded.
### Table 2: Demographics

<table>
<thead>
<tr>
<th>Study</th>
<th>Type</th>
<th>#Pts</th>
<th>Age (yrs)</th>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
<th>W/D</th>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wasserman, USA, 2007</td>
<td>Investigator Blinded RCT</td>
<td>239</td>
<td>60-80</td>
<td>NYHA Class II-IV LVF pts with wide (&gt;120ms) QRS complexes and w/o BVP</td>
<td>NYHA class I with narrow QRS complex</td>
<td>0 (18 crossed over from BVP-OFF to BVP-ON</td>
<td>Randomized to BVP-ON or BVP OFF</td>
</tr>
<tr>
<td>Conraads, Europe, 2007</td>
<td>Investigator Blinded RCT</td>
<td>17</td>
<td>50-68</td>
<td>Ischaemic or dilated cardiomyopathy; NYHA &gt; III; LVEF &lt; 35%; LVEDD &gt; 55mm; LBBB &gt; 120ms; permanent sinus rhythm</td>
<td>&lt; 1 month stable pharmacological drug treatment; minimal inter-ventricular dyssynchrony</td>
<td>0</td>
<td>Randomized to CRT (+) [w/exercise training] or CRT (-) [w/o exercise training]</td>
</tr>
<tr>
<td>Schlosshan, Europe, 2009</td>
<td>Randomized Double Blind Crossover Trial</td>
<td>15</td>
<td>54-72</td>
<td>Before CRT: NYHA &gt; III, QRS &gt; 120, LVEF &lt; 35% After CRT: NYHA I – III (ie symptomatic benefit from CRT)</td>
<td>Inability to do treadmill, exercise beyond anaerobic threshold, angina, coexisting lung, other systemic diseases</td>
<td>0</td>
<td>CRT ON or OFF (order pt did the test on or off was blinding since it was a crossover)</td>
</tr>
<tr>
<td>Laveneziana, Europe, 2009</td>
<td>Randomized Double Blind Crossover Trial</td>
<td>7</td>
<td>69-73</td>
<td>CRT &gt; 6m; NYHA III – IV; LVEF &lt; 35%; QRS &gt; 120ms</td>
<td>Major cardiovascular event in previous 6w, HF needing continuous IV TX, resting O2 &lt; 90% or 4% decrease during exercise, other illness / inability to perform exercise</td>
<td>0</td>
<td>CRT ON or OFF (order pt did the test on or off was blinding since it was a crossover)</td>
</tr>
</tbody>
</table>
OUTCOMES MEASURED

The key outcome measured in 3 / 4 studies [Laveneziana excluded] was V02 (peak oxygen uptake). Peak oxygen uptake measures the patients maximum capacity to use and transport oxygen during exercise. This measurement translates into the individuals physical fitness level. Another primary outcome [included by Wasserman, Schlosshan] was anaerobic threshold. Anaerobic threshold marks exercise that is rigorous enough to trigger anaerobic metabolism. Both V02 and AT are essential POEMs (patient oriented evidence that matters) in that improving values for both indicate the pt is able to exercise longer and harder without pain or fatigue.

[Laveneziana] utilized dyspnea and pain ratings to characterize the effects of exercise and CRT therapy. Pain was rated using the Borg scale. Other secondary measurements included heart rate, ventilation ratio and exercise time. The importance of all these measurements is that they can all show in both a subjective and physiologic way the patients exercise tolerance.

RESULTS

Three of the four studies were convertible into dichotomous data [except Conraads]. The study data were compiled with intention-to-treat analysis in all four studies. All patients who began the study finished it.

Wasserman et al reported a 28% risk reduction when CRT was turned on (with a number need to treat of 4). The p-value was 0.0001 with a paired t test. The relative risk reduction could not be measured since the CER was 0.

Laveneziana et al reported that both leg discomfort and dyspnea were higher in the CRT off group. The p-value was 0.05. RRR and ARR could not be calculated in this study. Data shows an average dypsnea / pain rating (borg units) for CRT-OFF and CRT-ON but does not specify an n value. Pts were repeatedly used but randomized as to whether they were receiving CRT for each exercise session.
Schloshman et al showed that CRT-on during exercise led to an 8% improvement in exercise time and a 9% improvement in aerobic capacity. The p-value was 0.04 and 0.01 respectively. RRR and ARR could not be calculated in this study. The results show data averages +- deviations.

Conraads et al showed the CRT therapy plus exercise translated to a synergistic effect on VO2 increase. The p-value was 0.00003. Breath-by-breath gas exchange measurements were performed using a metabolic cart. Ventilation (VE) oxygen uptake (VO2) and carbon dioxide production VC02 were determined on-line every 15s resulting in continuous data that could not be transformed into dichotomous data.

*Table 3: Dichotomous Results*

<table>
<thead>
<tr>
<th>Study</th>
<th>CER</th>
<th>EER</th>
<th>RBI</th>
<th>ABI</th>
<th>NNT</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wasserman</td>
<td>0.00%</td>
<td>28.00%</td>
<td>NA</td>
<td>28.00%</td>
<td>~4</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

Table 3 shows the results of calculations to determine benefit increases. Of the results, only one area of data was significantly significant. Only that data was included in the calculation. 54 of 192 individuals who were evaluated with CRT on showed a statistically significant improvement in their peak VO2. Those 54 individuals started with a baseline VO2 of < 50% expected. There was no statistically significant data in the CRT off group resulting in n=0 for those with improved VO2. Consequently, the relative benefit increase cannot be calculated due to a CER of 0. Likewise the anaerobic threshold improved in 40% of those with CRT on (p-value 0.0001) and could not be evaluated in CRT off due to a lack of statistical significance (study records 28% of persons improved).

*Table 4: Lavenezia Results*

<table>
<thead>
<tr>
<th>POEM</th>
<th>CRT On</th>
<th>CRT Off</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyspnea</td>
<td>2.7 +- 0.9*</td>
<td>4.6 +- 1.2</td>
</tr>
<tr>
<td>Leg Discomfort</td>
<td>4.7 +- 1.1*</td>
<td>6.7 +- 0.7</td>
</tr>
</tbody>
</table>

* P < 0.05

Table 4 shows the POEM results of the lavenezia et al study. Utilizing the Borg scale (0 no breathlessness – 10 max breathlessness) pt rated their dyspnea and leg discomfort while at rest, each
minute of exercise and at peak exercise. A trend that can be noticed is CRT on values are often associated with statistical significance while CRT off values are not. Table 4 shows this trend. Both CRT on result in lower borg scale ratings (ie less dyspnea and leg discomfort) then CRT off. Lavenezia et al also measured value shared by the other studies such as VO2, pulse, etc... The results of these other parameters show general improvement when CRT was set to on.

Table 5: Schlosshan Results

<table>
<thead>
<tr>
<th>POEM</th>
<th>CRT On</th>
<th>CRT Off</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>VO2</td>
<td>17.2 +- 4.9</td>
<td>15.6 +- 4.3</td>
<td>0.005</td>
</tr>
<tr>
<td>Exercise Time</td>
<td>587 +- 212</td>
<td>542 +- 204</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Table 5 shows the results of the Schlosshan et al study. Both VO2 and exercise time were statisticall significant and showed improvement in those who had CRT set to on. Because this was a crossover study there were no n values assigned. Like the other studies, there were multiple parameters measured, however VO2 and exercise time are the most compatible when using as comparison to the other studies.

The Conraads et al study compared 4 groups of individuals to compare CRT with exercise and pharmacology, CRT with pharmacology, exercise and pharmacology and pharmacology alone. The study shows that the combination of CRT, exercise and pharmacology together resulted in the best outcome when measuring VO2. CRT with pharmacology and pharmacology with exercise were similar in result. Pharmacology alone proved to be the least effective treatment protocol. VO2 measured at baseline and post the endurance training timeline.

The number needed to harm has not been calculated in this paper for the reason that we are examining the synergistic effects of exercise when combined CRT therapy. Both therapies are inherently safe (aside from the complications of the implanting the pacer) are not known for causing harm. The purpose of this paper was to emphasize the clinical importance of utilizing both therapies
DISCUSSION

There are many therapies for heart failure, however there is a lack of evidence for definitive treatments aside from cardiac transplant. Therapies aim to accomplish two big tasks in the heart failure patient: prevent remodelling of the heart, improve ADLs. While we have taken a closer look at the pt's ADLs (i.e., POEMs) it's important to remember that the studies do mention there appears to be improvement in the prevention of remodeling, though more studies are needed. CRT therapy aids the CHF patient by synchronizing the ventricles to work together providing stronger and more efficient contractions. Increased efficiency translates to better oxygenation throughout the body and therefore less cardiac demand. The results in less stress by the heart and a reduction in remodeling. Exercise in a normal healthy individual improves all of the different parameters we have studied in this paper such as VO₂, exercise time, etc... With CRT therapy, even a heart failure pt can gain the full effects of exercise that a healthy heart can.

There are limitations to this review. The parameters between utilized RCTs vary, however they all point to the same generalized concept of exercise ability. Unfortunately evidence must be repeatable and better conclusions could be drawn with RCTs operating under the same study design. Population size was another limitation to the studies. For example [Conraads] represented 17 individuals. The results perhaps would have more statistical significance given a bigger set of individuals. CRT on is often statistically significant in the studies whereas CRT off is not. Consequently CRT off is usually the smaller subset such as in [Wasserman] where 192 were set to CRT on and 47 to CRT off. The condition of the pt entering the study may also play a role in how much of an impact the therapies have to offer. For example [Wasserman] deduces that those with a baseline VO₂ < 50% of the expected value seemed to benefit the most from the therapies. In future studies it might be beneficial to categorize the pts with a little more rigor rather than just NYHA classifications. [Conraads] pointed out that their study may have suffered from bias since they utilized data from a different trial and evaluated it while looking at a
different variable.

CONCLUSION

Cardiac resynchronization therapy and aerobic exercise does improve exercise tolerance / ability in heart failure patients better than either intervention alone. More study is needed to evaluate the best exercise regimen for the heart failure pt and also which type of heart failure patients benefit the most from a combination CRT / exercise regimen.
REFERENCES


