

SDC Table 2: Studies Included with Pacemaker (CRT)

Study	Design/Sample	Intervention	Outcomes	Results	Summary/Conclusions
<p>Greco et al (1998)⁴⁸</p>	<p>Design: Single group; Pre/post (n=11)</p> <p>Sample: patients with rate responsive pacemakers, implanted for high degree atrioventricular AV block and chronotropic incompetence; no CRT devices used</p> <p>Pacemaker type: Medtronic =5 Guidant=4 St. Jude=1 Biotronic=1</p> <p>Activity sensors: 5; temperature sensors: 4; dual sensors: 2</p> <p>Gender: n(%): M: 7 (63.6%) F: 4 (36.4%)</p> <p>Age: (mean, range) 60 y (18-83)</p>	<p>EX: Formal or informal aerobic training program, (3-5 d/wk at aerobic workloads (30-45min) at home or in outpatient setting</p> <p>The f/u duration: 2-7 mo (mean 3.9 mo)</p>	<p>4 mo: Exercise capacity</p> <ul style="list-style-type: none"> - Peak VO₂ (mL/kg/min) - Anaerobic threshold time (ATT) min - Exercise time (ET) min 	<p>4 mo: Exercise capacity</p> <p>PeakVO₂ Pre: 20.54±7.69 Post: 25.32±10.97 P=.002</p> <p>ATT Pre: 6.86±2.24 Post: 13.18±4.22 P<.001</p> <p>ET Pre: 11.50±2.73 Post: 17.14±5.14 P<.001</p> <p>Adverse events Not reported (NR)</p>	<p>Level of Evidence: VI</p> <p>Jadad score = NR</p> <p>Strength - Tailoring of CPET was done for the type of rate response pacemaker</p> <p>Weakness - Small sample size - Not all exercise programs were the same, some were done at home and others supervised - Not all follow-up times were at the same time following training.</p>

	<p>LVEF% (mean ± SD): NR</p> <p>Dropout rate: NR</p>				
Conraads et al (2007) ²²	<p>Design: prospective RCT (n=8) who got exercise, matched to CRT no exercise (n=9), compared to historical controls (n=19) who got no exercise</p> <p>Sample: patients with LV systolic dysfunction and LBBB, cardiac resynchronization therapy CRT and dyssynchrony 1 month after CRT implanted, EF<35%,</p> <p>CRT device: Guidant CRT-P= 13 Guidant CRT-D=4 Settings in DDD mode</p> <p>Gender (M/F): CRT group CRT+: 3/5 CRT- :5/4 C group HF+:7/2</p>	<p>EX: Supervised ambulatory endurance exercise program 1h x 3x/wk x 4 mo at HR 90% of the ventilatory threshold. (n=17)</p> <p>CRT+ Standard pharmacological therapy plus 4-mo endurance exercise training program with CRT (n=8)</p> <p>HF+ Standard pharmacological treatment plus 4 mo endurance exercise training-<u>no CRT</u> (n=9)</p> <p>Control: (n=19)</p> <p>CRT- Standard pharmacological therapy with CRT</p>	<p>5 mo: Exercise capacity - Peak VO₂ (mL/kg/min) - Peak Watts (maximal workload (wattmax))</p> <p>LV remodeling - LVEF - Left ventricular end-diastolic (LVEDD) - Left ventricular end-systolic diameter (LVESD)</p> <p>QOL MLHFQ</p> <p>Biomarker NT-pro brain natriuretic peptide (NT-proBNP)</p>	<p>5 mo: Exercise capacity Peak VO₂ CRT+: 19.3±1.2 CRT- : 13.8 ±0.9 P=.005</p> <p>Watt peak CRT+: 113±12 CRT- : 87 ±9 P=0.0005</p> <p>LV remodeling LVEF CRT+: 36±5 CRT- : 34 ± 6 P=.50</p> <p>LVEDD CRT+: 59±3 CRT- : 68 ± 4 P=.30</p> <p>LVESD CRT+: 47±3 CRT- : 54±5 P=.30</p> <p>QOL MLHFQ CRT+: 30±6</p>	<p>Level of Evidence: II</p> <p>Jadad score = 3</p> <p>Strength - 4 group design - 2 historical group controls used with no CRT</p> <p>Limitations - Small patient groups - relative short follow-up time - There are no comparisons done between those with CRT who exercised and HF patients without CRT who exercised, to determine the benefits of exercise and CRT.</p>

	<p>HF-:7/3</p> <p>Age (mean ± SD) CRT group CRT+: 57±2 CRT- :61±4 C group HF+:65±3 HF-:64±4</p> <p>LVEF (mean ± SD): CRT group CRT+: 27±5 CRT-: 28±5 C group HF+: 28±3 HF-: 26±2</p> <p>Dropout rate: NR</p>	(n=9) <p>HF-: standard pharmacological treatment no CRT (n=10)</p>	levels	<p>CRT- :24 ±7 P=.50</p> <p>Biomarker NT-proBNP CRT+: 1698±802 CRT- : 711±198 P=.70</p> <p>Adverse events No lead dislodgement Normal LV thresholds</p>	
Patwala et al (2009) ⁴⁹	<p>Design: prospective RCT (n=50) 3 mo after CRT</p> <p>Groups: NYHA functional class III to IV who received CRT, QRS>120 msec, LVEF%< 35%,</p> <p>Gender %: M: 92%</p> <p>Age (mean): 64.4y</p>	<p>EX: Physician-supervised exercise training (30min/3visit/wk at intensity 80% of the peak heart rate (HR) achieved at the 3-mo test for the first 4 wk, 85% for the next 4 wk, and 90% for the final 4 wk) n=25</p> <p>C: No specific advice on exercise training and underwent no</p>	<p>6 mo: Exercise capacity Peak VO₂ (mL/kg/min) Peak cardiac power output (CPO) Maximum RER %Peak VO₂ at the anaerobic threshold</p> <p>Echocardiogram Left ventricular end-diastolic</p>	<p>6 mo: Exercise capacity Peak VO₂ EX: 20.10±3.84 C: 18.07±3.89 P=.02</p> <p>%peak VO₂ at the anaerobic threshold EX: 62.1±10.0 C: 70.0±11.3 P=.11</p> <p>Echocardiographic LVEDD EX: 6.40±0.53</p>	<p>Level of Evidence: II</p> <p>JADAD=3</p> <p>Strength: - Randomization delayed to determine effects of CRT alone until the 3 mo - Exercise training in a nonclinical setting and by using a physician not involved in the pacemaker implant or follow up</p>

	<p>CRT-P: Biventricular pacer set to 60 bpm, AV delay 120 msec,</p> <p>LVEF%: 23.67</p> <p>Dropout rate: NR</p>	<p>supervised training (n=25)</p> <p>Randomization to EX or C occurred 3 mo post-CRT implant</p>	<p>dimension (LVEDD)</p> <p>LVEF%</p> <p>QOL MLHFQ</p> <p>Peak skeletal muscle torque Isokinetic dynamometry with 2 sets of knee extensions</p>	<p>C: 6.34 ± 0.57 P=.96</p> <p>LVEF% EX: 37.3±5.4 C: 35.0±7.2 P=.37</p> <p>QOL MLHFQ EX: 26.2 ±20.5 C: 29.5 ±17.8 P=.02</p> <p>Peak muscle torque right leg EX=144.8+57.6 C=131.5+49.5 P=.13</p> <p>Adverse events NR</p>	<p>Weakness:</p> <ul style="list-style-type: none"> - Relatively small sample - Control group not receiving CRT but randomized to exercise training would have improved the methodology
Smolis-Bak et al (2015) ³	<p>Design: prospective randomized observation (n=52)</p> <p>Sample HF of ischemic or another etiology, NYHA class III</p> <p>Gender: % (n): Male: EX=96.1% C=84.6%</p>	<p>EX: Initial aerobic exercise training in the hospital setting (3 wk) and continued training program at home with telemonitoring. Large and small muscle isometric exercises, respiratory exercises, ROM exercises both in hospital and at home up to 3 mo; n=26.</p>	<p>4 mo: Exercise capacity Peak VO₂ (ml/kg/min) -Exercise time (min) -METs -6MWD (meters)</p> <p>QOL - NHP-EL - NHP-LM</p>	<p>4 mo: Exercise capacity PeakVO₂ EX: 17.2±3.9 C: 13.4±4.2 P=.03 Ex time EX: 7.98±2.80 C: 5.22±2.7 P=.007</p> <p>METs EX:5.47±1.76</p>	<p>Level of Evidence: II</p> <p>Jadad score =1</p> <p>Strengths</p> <ul style="list-style-type: none"> - 12 mo follow-up - Home telemonitoring used to monitor safety while exercising at home <p>Limitations</p> <ul style="list-style-type: none"> - No aerobic exercise training provided

	<p>Age 62±9.3y EX: 60+8.5y C: 65.1+8.2y</p> <p>CRT device: CRT-D</p> <p>Disease: Ischemic cardiomyopathy EX=42.6% C=50%</p> <p>LVEF% (mean ± SD) EX: 25.3±7.4 C:24.9±7.2</p> <p>Dropout rates: NR</p>	<p>C: Hospital rehabilitation (3 wk), but no training program after discharge (n=26)</p>	<p>Depression Beck Depression Inventory</p> <p>12 mo: Same as 4 mo</p> <p>Echocardiogram - Left ventricular end-diastolic dimension-LVDD - Left ventricular end systolic dimension-LVSD - LVEF</p>	<p>C:4.13±1.80 P=.41</p> <p>6MWD EX=460+99 C=435+107 P=NR</p> <p>QOL NHP-EL EX: 1+0.8 C:1.2+1.0 P=.43</p> <p>NHP-LM EX:1.5±1.2 C:2.3±1.4 P=.03</p> <p>Depression BDI EX: 10.3±6.9 C: 12.0±7.3 P=.41</p> <p>12 mo: Exercise capacity PeakVO₂ EX: 13.1±4.1 C:14.2±3.1 P=.94</p> <p>Time EX: 7.34±3.07 C:5.42±3.09 P=.38</p>	
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Zeitler et al (2015) ⁵⁰	<p>Design: prospective RCT</p> <p>Sample (n=1118) Outpatients with HF and LVEF ≤35%. NYHA 2-4, with implanted ICD or CRT device Comparison group = no device (n=1200)</p> <p>CRT Device: - ICD: single and dual-chamber ICD (n=683) -Biventricular lead: CRT-D (n=435) Gender: n(%) Female 430(35%) RV=137 (20%) CRT-D 94 (22%) Age: 58y ICD = 61y</p>	<p>EX: Supervised cardiac rehab 18 sessions 40 min 5x per wk, at 60% to 70% of heart rate reserve, followed by home exercise 5x/ wk 40 min 60-70% of HRR for 9 mo; n=1149</p> <p>C: No restricted activity n=1160</p>	<p>3 mo: Exercise Capacity Exercise time (min) Peak VO₂ (mL/kg/min)</p> <p>QOL KCCQ</p> <p>Pro BNP</p> <p>Adverse Events: All cause mortality</p> <p>Composite of CV death or CV hospitalization</p> <p>Composite of CV death or HF hospitalization</p>	<p>3 mo: Exercise Capacity Peak VO₂ ICD EX:15.1 C: 14.5</p> <p>CRT-D EX:14.9 C:13.9</p> <p>No device EX= 15.9 C=15.6 P=NS</p> <p>Exercise time ICD EX: 10.8 C: 9.8</p> <p>CRT-D EX: 10.6 C:9.3</p> <p>No device</p>	<p>Level of Evidence: II</p> <p>Jadad score = 3</p> <p>Strengths - Largest HF exercise trial completed to date</p> <p>Limitations - Not blinded to collection of outcome data - Complete data not reported, no mean±SD data, no P values. - Considerable missing data</p>

	<p>CRT-D=61 y</p> <p>Ethnicity AA 483 (40%) ICD 173(20%) CRT-D 93(22%)</p> <p>Diagnosis Ischemic cardiomyopathy n=512 (42%) ICD 456(67%) CRT-D 229 (53%)</p> <p>LVEF 25±21.31 ICD 24% CRT-D 23%</p> <p>Dropout rate: No device 19.9% ICD: 15.1% CRT-D: 17.1%</p>			<p>EX 11.6 C=10.5 P=NS</p> <p>KCCQ total RV lead EX: 73 C: 72</p> <p>CRT-D EX:72 C:71</p> <p>No device EX=69 C=70 P=NS</p> <p>Pro-BNP RV lead EX: 998.2 C: 959.8</p> <p>CRT-D EX: 1197 C:881.5</p> <p>No device EX=480.8 C=558 P=NS</p> <p>Difference among device groups: All cause mortality P=.33</p>	
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				<p>All cause death or hospitalization P=.06</p> <p>CV death or CV hospitalization P=.19</p> <p>Hospitalization rates Higher for those with devices vs no device, 26% vs 15%.</p> <p>Adverse events NR</p>	
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Final List: Pacemaker

Total: 5 Studies

Greco EM, Guardini S, Citelli L. Cardiac rehabilitation in patients with rate responsive pacemakers. *PACE-Pacing Clin Electrophysiol.* 1998;21(3):568-575.

Conraads VM, Vanderheyden M, Paelinck B, 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 DF, Tan LB, Wright DJ. Maximizing patient benefit from cardiac resynchronization therapy with the addition of structured exercise training: a randomized controlled study. *J Am Coll Cardiol.* 2009;53(25):2332-2339.

Smolis-Bąk E, Dąbrowski R, Piotrowicz E, et al. 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;199:442-447.

Zeitler EP, Piccini JP, Hellkamp AS, et al. Exercise training and pacing status in patients with heart failure: results from HF-ACTION. *J Card Fail.* 2015;21(1):60-67.

Table abbreviations: AV, atrioventricular; BDI, Beck Depression Inventory; C, control group; CPET, cardiopulmonary exercise test; CRT, cardiac resynchronization therapy; CRT-D, cardiac resynchronization-defibrillator; CRT-P, cardiac resynchronization-pacemaker; CRT+, with cardiac resynchronization therapy; CRT-, no cardiac resynchronization therapy; CPR, cardiopulmonary resuscitation; CV, cardiovascular; EF, ejection fraction; EX, exercise intervention; f/u, follow-up; HF, heart failure; HF+, with heart failure; HF-, no heart failure; HR, heart rate; ICD, implantable cardioverter defibrillator; KCCQ, Kansas City Cardiomyopathy Questionnaire; LV, left ventricular; LVEF, left ventricular ejection fraction; METs, metabolic equivalents; MLHFQ, Minnesota Living with Heart Failure Questionnaire; NHP-EL, Nottingham Health Profile-Energy Level; NHP-LM, Nottingham Health Profile-Limited Mobility; NYHA, New York Heart Association; NR, not reported; QOL, quality of life; RCT, randomized controlled trial; RV, right ventricle; SD, standard deviation; VO₂, oxygen uptake; 6MWD, 6-minute walk distance.