Upgrade to Resynchronization Therapy

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CRT

- Cardiac resynchronization therapy (CRT) is an established therapy for patients with cardiomyopathy, ventricular dyssynchrony, and moderate-to-severe heart failure (HF) despite appropriate pharmacologic therapy.

- Randomized clinical trials have demonstrated the efficacy of CRT in this patient population.

Pacing Induced Dyssynchrony

- Extremely wide QRS complexes are frequently observed in patients who are chronically paced via a right ventricular (RV) lead for bradycardic indications.
Pacing in ICD Patients

• Retrospective analyses suggest that 15–50% of ICD patients have an accepted indication for dual chamber pacing at the time of ICD system implantation.

• Indications for dual chamber pacing may arise later in a significant portion of ICD patients who do not require pacing at implantation.


Adverse Effects of RV Pacing

• Multiple trials have shown that RV pacing may be associated with worsening of HF, even when used in conjunction with physiologic (dual-chamber) pacing modes.

• This is mostly attributed to dyssynchrony imposed on ventricular function by RV apical pacing.


Risk of Heart Failure

• The MOST study, reported a <2% hospitalization for heart failure linked to pacing over 2 years when baseline left ventricular (LV) function prior to pacing was normal and in the absence of preexisting cardiac pathology.

• Where there was preexisting pathology, there was a marked increase in the risk of heart failure hospitalization, by up to 50%.

Possible Mechanisms

- The altered pattern of activation may lead to several histological and functional adjustments of the left ventricle, including:
  - Inhomogeneous thickening of the ventricular myocardium
  - Myofibrillar disarray, Fibrosis
  - Disturbances in ion-handling protein expression
  - Myocardial perfusion defects
  - Alterations in sympathetic tone and
  - Mitral regurgitation (MR)

Dyssynchrony

- RV pacing results in **interventricular dyssynchrony**, leading to a 30–180 ms. delay in LV activation.

- **Intraventricular dyssynchrony** also results from the complete reversion of ventricular activation sequence (apex to base instead of base to apex).

Pathophysiology

• RV apical pacing leads to a heterogeneous distribution of workload:
  – Lower strain (workload), in the early-activated region than in the late-activated regions

• Early-activated regions tend to become thinner over time, as opposed to late-activated ones, which show a progressive increase in wall-thickness.

Pathophysiology

• The regional heterogeneity of myocardial hypertrophy results in remodeling of the LV, which alters its contractile and hemodynamic efficiency.

• The primary causative factor of this remodeling seems to be the alteration of force vectors, which entails an alteration of mechanical stress distribution in the ventricle.

• A role of a neuro-endocrine mechanisms cannot be excluded.
Mechanism of MR

• There appears to be a complex mechanism:
  – The altered sequence of activation of the components of the mitral apparatus and the dyssynchronized transfer of forces from the papillary muscles through the chordae tendinae to the mitral leaflets lead to poor coaptation and thus to regurgitation during ventricular systole.
  – The appearance or aggravation of pre-existing MR may contribute to the development or deterioration of HF in paced patients.
Alternative Pacing Sites

• There are reports of preservation of LV systolic function with RV septal pacing as opposed to RV apical pacing in patients without HF.

• This was not confirmed by studies in the failing heart.


RV Septal Pacing

• It has been shown that implanting the pacing lead at the site of the RV septal surface causing the shortest paced QRS may result in improved LV systolic performance.

• However, the latter findings were relatively minor and unlikely to have any significant clinical impact as in the effects on LV ejection fraction.

RVOT Pacing

• The RV outflow tract was also proposed as an alternative site of RV pacing, associated with increased cardiac output when compared with RV apical pacing in acute pacing studies.

• This was not confirmed conclusively either with long-term pacing studies.


CRT

- LV or biventricular (BiV) pacing has been proposed as an adjunctive treatment for patients with advanced HF complicated by RV pacing induced discoordinate contraction.

- Both short-term and a growing number of long-term clinical trials have reported on the mechanisms and short- and mid-term efficacy of this approach, with encouraging results.

Pacing QRS Duration

• A QRS duration over 200 ms has been arbitrarily proposed to suggest the upgrade of RV pacing in HF patients to BiV pacing.

• Such a wide QRS has been suggested to correspond with notable inter- or intra-LV mechanical dyssynchrony.

Pacing QRS Duration

• It should be noted, however, that improved mechanical synchrony and function do not necessarily require increased electrical synchrony.

• More recent data dispute the correlation between electrical features (QRS duration) and the degree of electromechanical ventricular dyssynchrony in RV paced patients.

Intraventricular Dyssynchrony

• RV pacing-induced intraventricular dyssynchrony is more common than interventricular dyssynchrony.

• The major cause of LV function impairment is likely to be the presence of intra-LV dyssynchrony.

Echocardiographic Dyssynchrony

- Echo documented dyssynchrony is an approach to patient selection and gives new insight into the possible mechanisms of improvement.
Intra-ventricular Dyssynchrony

- BiV pacing results in the improvement of intra-LV rather than of interventricular synchrony.
- RV-paced patients who present with an abnormally increased intra-LV dyssynchrony should benefit more from BiV upgrading.
CRT Upgrade Studies

- Five studies compared the clinical outcomes of patients who received an upgrade to CRT with those who received a de novo CRT implant.

- During a follow-up of 3–38 months, upgraded patients showed improvement similar to the de novo patients.
The RAFT Upgrade Substudy

- The success rate was 95.2% for de novo versus 96.3% for study upgrade and 90.0% for substudy CRT attempts (upgrade within 6 months after presentation of study results).

The Rate of CRT Upgrade

• This varies widely among studies.

• In a retrospective single center study, the upgrade rates at 1, 3, and 5 years were 0.03%, 2.4%, and 5.1%, respectively.

The Rate of CRT Upgrade

- In the European CRT Survey of 2367 implant procedures, 29.2% were identified as having an upgrade from pacemaker to CRT-P or ICD to CRT-D.

AF in Paced Patients

• Upgrading of an already implanted RV pacing system to BiV pacing in patients with HF and atrial fibrillation reversed dyssynchrony.

• It improved ventricular performance and dimensions, quality of life and symptoms of HF in the same manner as described in patients with sinus rhythm and left bundle branch block who undergo BiV pacing.


Paced Patients with AF

• Improvement in functional class, increased EF, decrease in end-systolic and end-diastolic diameters, decrease in the number of hospitalizations and improved quality of life scores were demonstrated in this patient population.

• A 40% decrease in the MR area was reported in one of the two studies

CRT-P vs. CRT-D

• The use of CRT-D already exceeds that of CRT-P in many countries.

• There is no evidence, however, from individual randomized trials nor from meta-analyses to suggest that CRT-D improves survival more than CRT-P in the primary prevention setting.
CARE-HF Study

- CRT-P improves left ventricular function and potentially reduces the risk of subsequent SCD.
- This is consistent with data from CARE-HF suggesting that CRT-P per se reduces SCD as well as total mortality.

COMPANION Study

- In the COMPANION study, survival curves between CRT-D and CRT-P were parallel beyond 9 months, suggesting that the incremental benefit of ICD may be short-lived.

CRT-P vs. CRT-D

- In deciding which device to implant in clinical practice, the physician will need to take into account clinical circumstances as well as societal, cultural, and financial factors of the individual countries.

- Keep in mind that CRT-D seems to be associated with a higher risk of device-related complications as compared with CRT-P.
### Comparative results of CRT-D versus CRT-P in primary prevention

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<tr>
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<th>CRT-D</th>
<th>CRT-P</th>
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<tbody>
<tr>
<td>Mortality reduction</td>
<td>Similar level of evidence but CRT-D slightly better</td>
<td>Similar level of evidence but CRT-P slightly worse</td>
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<tr>
<td>Complications</td>
<td>Higher</td>
<td>Lower</td>
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<tr>
<td>Costs</td>
<td>Higher</td>
<td>Lower</td>
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### Clinical guidance to the choice of CRT-P or CRT-D in primary prevention

<table>
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<th>Factors favouring CRT-D</th>
<th>Factors favouring CRT-P</th>
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<td>Life expectancy &gt;1 year</td>
<td>Advanced heart failure</td>
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<td>Stable heart failure, NYHA II</td>
<td>Severe renal insufficiency or dialysis</td>
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<td>Ischemic heart disease (low and intermediate MADIT risk score)</td>
<td>Other major co-morbidities</td>
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<td>Lack of comorbidities</td>
<td>Frailty</td>
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<td>Cachexia</td>
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Complications

• A higher risk of acute complications versus a de novo implant are reported.

• This includes venous access issues, the risk of damage or extraction of old leads, the higher risk of infection, and the additional time that may be required.
Technical Considerations

• Upgrades from RV pacing to CRT systems now comprise nearly 20% of CRT implants

• Upgrading of previously implanted RV pacing systems has been attempted in the past by the use of different techniques, either using a variety of configurations of leads and connectors or by implanting new pulse generators.

Techniques

• Most studies have involved systems connecting both ventricular leads to a common internal current source.

• This entails the risk of an impedance mismatch that could result in only RV or only LV pacing, rather than both.

• Connecting two independent channels adds further programmability of the RV–LV stimulation delay.
Need for Contralateral Lead Placement

Difficult Case
Subclavian Occlusion
Access from Right Side
Unstable Lead
Stenting of CS
Stable Lead Position
Lead Tunneled to Left Side
Lead Tunneled to Left Side
Final Position
Final Message

• Given that dyssynchrony is the problem, or at least a prominent part of it, with pacing-induced or pacing-aggravated HF, resynchronization is a theoretically sound target to pursue.

• The ‘upgrading’ approach to the treatment of already paced HF patients is at least feasible, relatively safe and most likely beneficial.
Cardiac Resynchronization Therapy in Patients With Systolic Heart Failure Who Need Pacing

CRT can be useful for patients on GDMT who have LVEF less than or equal to 35% and are undergoing new or replacement device placement with anticipated requirement for significant (>40%) ventricular pacing.


Modified recommendation (wording changed to indicate benefit based on ejection fraction and need for pacing rather than NYHA class; class changed from IIb to IIa).
Upgraded or *de novo* CRT in patients with conventional pacemaker indications and HF

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<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
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<tr>
<td>1) <em>Upgrade from conventional PM or ICD</em> is indicated in HF patients with LVEF &lt;35% and high percentage of ventricular pacing who remain in NYHA class and ambulatory IV despite adequate medical treatment.</td>
<td>I</td>
<td>B</td>
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<td>2) “<em>De novo</em>” implantation should be considered in HF patients, reduced EF and expected high percentage of ventricular pacing in order to decrease the risk of worsening HF.</td>
<td>IIa</td>
<td>B</td>
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European Heart Journal 2013;34:2281-2329
Europace 2013;15:1070–1118

www.escardio.org/guidelines