Cardiac **Contractility Modulation** – An **Innovative** Therapy for Treating Heart Failure

Cardiac contractility modulation (CCM) is a new treatment approach for improving ventricular pump function in patients with advanced systolic heart failure who remain symptomatic despite optimal medical management. Unlike cardiac resynchronization therapy (CRT), cardiac contractility modulation can be used in patients with short QRS duration. With Professor Martin Borggrefe, Mannheim, Germany, and Professor Gerhard Hindricks, Leipzig, Germany, presiding, experts provided a comprehensive overview over this seminal new treatment at the 76th Annual Meeting of the German Cardiac Society (Deutsche Gesellschaft für Kardiologie) in Mannheim.

Worldwide, nearly 22 million people suffer from chronic heart failure (CHF), which is the most frequent cause of death in industrialized countries. In Germany, approximately 116,000 people are newly affected by CHF and approximately 60,000 die from this condition each year. The incidence of heart failure continues to increase in our continuously ageing population. Despite all recent advances in pharmacotherapy, many patients remain highly symptomatic.

This is one important reason why various electrical stimulation techniques for improving cardiac pump function have been under investigation for several years. Cardiac resynchronization therapy (CRT) is considered an established therapeutic option for patients with severe chronic heart failure and prolonged QRS duration. Treatment with a CRT system is useful for patients with NYHA class III-IV symptoms despite optimal medical management, an EF < 35%, sinus rhythm and left bundle branch block or echocardiographic evidence of ventricular dyssynchrony (QRS duration ≥ 120 ms). Since this criterion is met by only a small subgroup of patients, the majority of patients with CHF, but without indication for CRT, are barred from this treatment. In addition, 20–30% of patients in the treated subgroup, referred to as CRT non-responders, do not improve despite implantation of a CRT system.

Cardiac contractility modulation (CCM) is a very promising treatment option complementary to CRT. Patients who are not candidates for cardiac resynchronization because they have narrow QRS complexes and patients who do not adequately respond to CRT may benefit from CCM.

**How does CCM work?**

A small programmable implantable and percutaneously rechargeable impulse generator that resembles a pacemaker is the central part of the CCM system. Three standard pacemaker leads are transvenously inserted: One right atrial lead for atrial sensing and two right ventricular leads for both ventricular sensing and CCM signal delivery. CCM impulses differ from pacemaker signals in various respects. One distinguishing mark is that CCM impulses are nonexcitatory. CCM therapy does not aim at altering the cardiac activation sequence; it modulates contractility instead. This is accomplished by delivering high-energy electrical impulses to the myocardium during the absolute refractory period (after a programmable delay after the action potential is detected). By altering the membrane potential, these signals augment Ca²⁺ influx.

Fig.: Mechanisms of CCM: After detecting local depolarization and after a programmable time delay, an electrical stimulus of programmable polarity, duration and amplitude is delivered during the absolute refractory period. Two ventricular leads positioned on the ventricular septum and separated by at least 2 cm from each other deliver the signal.
through the L-type calcium channels, thereby increasing Ca\textsuperscript{2+}--induced calcium release from the sarcoplasmatic reticulum, which in turn augments myocardial contractility (Fig.).

CCM normalizes cardiac mRNA expression

In patients with heart failure, cardiac remodeling is associated with up-regulation of fetal and down-regulation of adult genes. Particularly affected are genes responsible for sarcoplasmic calcium cycling and contractile proteins. By reactivating the fetal pattern of gene expression, the failing myocardium attempts to adjust to lowered cardiac energy resources.

A study with a canine heart failure model has demonstrated that pathologic changes in the expression of calcium-regulating proteins (e.g. BNP, \(\alpha\)-MHC, SERCA-2A) improve under CCM (1). These results were confirmed by assessing cardiac gene expression in 11 patients participating in a randomized double-blind study on CCM (2). Both studies suggest that CCM is associated with reversal of the inappropriate cardiac fetal gene program. This reversal is one of the mechanisms potentially underlying the clinical improvements observed under CCM.

CCM improves exercise tolerance and quality of life

Safety and efficacy of the innovative CCM system (Optimizer\textsuperscript{TM} system, Impulse Dynamics) were evaluated in a randomized double-blind crossover (12 weeks ON/OFF) multicenter trial (lead investigator: Prof. Borggrefe), the FIX-CHF-4 study (3). CCM stimulation resulted in significantly improved exercise tolerance and quality of life.

Included were patients (n=164) with an EF \(\leq\) 35% and medium to severe chronic heart failure symptoms (NYHA class II [24%] or III [76%]) despite optimal medical management. Patients with atrial fibrillation, cardiac ischemia, or an indication for CRT were excluded. For the analysis, data from both groups (therapy group and sham therapy group) were lumped.

Under CCM, VO\textsubscript{2}peak increased by 0.52±1.39 ml/kg/min (p=0.03) and the Minnesota Living with Heart Failure Questionnaire (MLWHFQ) score, a measure for the quality of life, improved by 3 points (p=0.03). In addition, patients covered more distance in the 6-minute hall-walk test. The ejection fraction remained unchanged. Regular Holter recordings failed to detect any arrhythmogenic effects of this treatment modality. Due to the relatively small number of patients, significant differences with respect to mortality and number of hospital admissions were neither expected nor observed.

A total of 428 patients with NYHA class III and IV symptoms and an EF \(<\) 35% were entered into the unblinded randomized multicenter FIX-HF-5 trial (4). After randomization, patients were either implanted with an Optimizer III and received optimal medical therapy (OMT, n=215) or received OMT alone (n=213). The primary safety endpoint, a comparison of all-cause mortality and hospital admissions for any reason between both groups (as a non-inferiority analysis), was reached after one year of treatment. The primary efficacy endpoint, altered exercise tolerance measured by the O\textsubscript{2} consumption close to the anaerobic threshold, VAT [ml/kg/min], was not reached. In the entire population, VO\textsubscript{2}peak, quality of life (MLWHFQ) and NYHA class were found to improve under CCM therapy.

An increase of myocardial contractility by any therapy requires sufficient vital myocardium. A subgroup analysis of patients in NYHA class III and an EF of \(\geq\) 25% -- indicative of an adequate amount of contractile tissue -- revealed that the primary endpoint, the anaerobic threshold, as well as VO\textsubscript{2}peak, the MLWHFQ score and the NYHA class improved markedly and to a statistically significant extent under CCM therapy (Table).

Conclusions

The treatment options for patients with symptomatic heart failure but without cardiac dyssynchrony remain limited. Cardiac contractility modulation could close this therapeutic gap, because CCM differs from other device therapies as it is particularly suited for patients without ventricular dysynchrony.

At this time, further studies are required to gain more insight into the mechanisms of action of CCM and to evaluate how to use this novel and highly promising therapeutic method in the most efficient and beneficial manner.

References:
4 Abraham WT. Multicenter randomized controlled trial of cardiac contractility modulation in patients with advanced heart failure. FIX-HF-5 Trial. ACC 2009 Scientific Sessions; March 29, 2009; Orlando, FL. Late Breaking Clinical Trials I -- Congestive Heart Failure.

Source: Satellite Symposium „Cardiac Contractility Modulation: State of the Art and Future Directions“ at the 76th Annual Meeting of the German Cardiac Society – Cardiac and Circulatory Research from April 8 to April 10, 2010 in Mannheim, Germany, sponsored by Impulse Dynamics.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>OMT (n = 84)</th>
<th>OMT + CCM (n = 101)</th>
<th>Difference</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\Delta) VAT [ml/kg/min]</td>
<td>-0.54 ± 1.83</td>
<td>0.10 ± 2.36</td>
<td>0.64</td>
<td>0.024</td>
</tr>
<tr>
<td>(\Delta) Peak VO\textsubscript{2} [ml/kg/min]</td>
<td>-0.97 ± 2.31</td>
<td>0.34 ± 3.11</td>
<td>1.31</td>
<td>0.001</td>
</tr>
<tr>
<td>(\Delta) MLWHFQ score</td>
<td>-6.0 ± 21.9</td>
<td>-16.8 ± 20.2</td>
<td>-10.8</td>
<td>0.0003</td>
</tr>
<tr>
<td>(\Delta) NYHA class</td>
<td>-0.17 ± 0.64</td>
<td>-0.46 ± 0.61</td>
<td>-0.29</td>
<td>0.0011</td>
</tr>
</tbody>
</table>

\(\text{Statistically significant and clinically important differences between therapy group (OMT + CCM) and control group (OMT) for the subgroup of NYHA class III patients from the FIX-HF-5 trial (4) with EF \(\geq\) 25% and \(<\) 35 %.