Cardiac Contractility Modulation (CCM)

Jürgen Kuschyk
Departement of Cardiology-Electrophysiology
University Hospital Mannheim
Germany
Disclosure slide

Honoraria Fees:
• Medtronic, SJM, Boston Scientific, Impulse Dynamics, Biocontrol Medical

Advisory boards and Procter activities:
• SJM, Boston Scientific, Medtronic, Impulse Dynamics

Emotional support:
• My wife
Mild to Severe Symptomatic Heart Failure, EF ≤ 35%, Optimal Medical Therapy

- Broad QRS complex (dyssynchrony)
- Normal QRS complex

- CRT (~ 30% of Pts)
- CCM (> 50% of Pts)

RETHIN-Q-Study –
ECHO-CRT-Study?
Cardiac Contractility Modulation (CCM)

IPG

Atrial Lead

ICD Lead

Millar $(dP/dt_{\text{max}})$

CCM Leads

[Image of a medical device and cardiac lead system]
CCM System (Impulse Dynamics)

Optimizer III IPG

Optimizer III Charger

Programmer
Cardiac Contractility Modulation

CCM signals are applied during the absolute refractory period and drive cell properties towards normal.
Cardiac Contractility Modulation - ECG
Heart Failure

- Dysfunction und Dephosphorylation of key regulatory proteins
- Switch to fetal gene program
  - Increased oxygen consumption
  - Apoptosis
  - LV-Remodeling

Neurohumoral and Mechanical Stress
Mechanisms of Action

- Normalization of the activity of key regulatory proteins (Phospholamban) - seconds
- Reversal of the Fetal Gene Program - hours
- Reverse Remodeling - months
CCM effects

- 4 x 7 cm myocardial area
- Normalization of key proteins (PLB)
- Acute improvements in regional function
CCM acute effects (seconds)

Phosphorylation of Phospholamban

Imai JACC, 2007
CCM – Phosphorylation of Phopholmaban

- CCM signals increase phospholamban phosphorylation in cells in vitro within seconds
- This indicates that CCM has a direct effect on intracellular molecular processes

P-PLB @ Serin -16
P-PLB @ Threonin-17

P-PLB = Phosphorylated Phospholamban
Reversal of the fetal gene program (hours)

Imai JACC, 2007
Remote Effects of CCM

- Sustained improvements in regional function improve global ventricular function and reduce stress on remote regions

- Improved electrotonic intercellular coupling (Connexin 43)
SERCa2a expression is normalized at near site and remote site from CCM signal delivery after 3 months of treatment.

**Near Site of CCM Delivery**

- Normal
- HF - Sham
- HF + CCM

**Remote Site of CCM Delivery (3 months)**

- Normal
- HF - Sham
- HF + CCM

*P < 0.05 vs.*

Imai JACC, 2007
CCM – Reverse Remodeling

Yu et al., 2009 JACC Cardiovascular Imaging
Goal:

- Reduction of CHF Symptoms
- Improvement in Quality of Life in CHF Patients

Potential Candidates for CCM Therapy:

- CHF - NYHA II-III by systolic LV-Dysfunction
- Subgroups?
Randomized, double blind study of non-excitatory, cardiac contractility modulation electrical impulses for symptomatic heart failure

Martin M. Borggreffe\textsuperscript{1*}, Thomas Lawo\textsuperscript{2}, Christian Butter\textsuperscript{3}, Herwig Schmидinger\textsuperscript{4}, Maurizio Lunati\textsuperscript{5}, Burkert Pieske\textsuperscript{6}, Anand Ramdat Misier\textsuperscript{7}, Antonio Curnis\textsuperscript{8}, Dirk Böcker\textsuperscript{9}, Andrew Remppis\textsuperscript{10}, Joseph Kautzner\textsuperscript{11}, Markus Stühlinger\textsuperscript{12}, Christophe Leclercq\textsuperscript{13}, Miloš Táborský\textsuperscript{14}, Maria Frigerio\textsuperscript{5}, Michael Parides\textsuperscript{15}, Daniel Burkhoff\textsuperscript{15,16}, and Gerhard Hindricks\textsuperscript{17}
Inclusion Criteria:

- EF ≤ 35%
- NYHA II/III
- OMT

Exclusion Criteria:

- Peak VO2 < 10
- Active ischemia
- Persistent AF
- Eligible for CRT
Results FIX-HF-4

**VO2 max**
- Group 1 (ON to OFF)
- Group 2 (OFF to ON)

**6MW**
- Group 1 (ON to OFF)
- Group 2 (OFF to ON)

**MLWHFQ**
- Group 1 (ON to OFF)
- Group 2 (OFF to ON)

On vs. Off: $p=0.03$
On vs. Off: $p=0.05$
On vs. Off: $p=0.03$
Results FIX-HF-4

Event free survival - hospitalisations

- Control
- CCM
A randomized controlled trial evaluating the safety and efficacy of cardiac contractility modulation in advanced heart failure

Alan Kadish, MD, a,s Koonlawee Nademanee, MD, b,s Kent Volosin, MD, c,s Steven Krueger, MD, d,s Suresh Neelagaru, MD, e,s Nirav Raval, MD, f,s Owen Obel, MD, g,s Stanislav Weiner, MD, h,s Marc Wish, MD, i,s Peter Carson, MD, j,s Kenneth Ellenbogen, MD, k,s Robert Bourge, MD, l,s Michael Parides, PhD, m,s Richard P. Chiacchierini, PhD, n,s Rochelle Goldsmith, PhD, o,s Sidney Goldstein, MD, p,s Yuval Mika, PhD, q,s Daniel Burkhoff, MD PhD, r,s and William T. Abraham, MD s,e Chicago, IL; Inglewood, CA; Philadelphia, PA; Lincoln, NE; Amarillo, Dallas, and Tyler, TX; Atlanta, GA; Fairfax, and Richmond, VA; Birmingham, AL; New York, and Orangeburg, NY; Detroit, MI; and Columbus, OH

AHJ 2011
Inclusion Criteria

- EF ≤ 35%
- Class III or IV
- Narrow QRS complex
- Optimal medical therapy
- ICD required
- No permanent AF

Endpoints

- Efficacy (6 months)
- Safety (12 months)
Fix-CHF-5: Overall Results

- **Delta Anaerobic Threshold (ml/kg/min)**
  - Control
  - Treatment
  - Difference
  - p=ns

- **Delta Peak VO2 (ml/kg/min)**
  - Control
  - Treatment
  - Difference
  - p=0.024

- **NYHA (% Patients with ≥ 1 Point Reduction)**
  - Control
  - Treatment
  - Difference
  - p=0.0026

- **Six Minute Walk (m)**
  - Control
  - Treatment
  - Difference
  - p=0.108

- **ΔMLWHFQ**
  - Control
  - Treatment
  - Difference
  - p<0.0001
<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>ΔVAT (ml/kg/min)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischemic Cardiomyopathy</td>
<td>205</td>
<td>0,15</td>
<td>0,75</td>
</tr>
<tr>
<td>Idiopathic Cardiomyopathy</td>
<td>104</td>
<td>-0,24</td>
<td>0,73</td>
</tr>
<tr>
<td>EF&lt;25</td>
<td>144</td>
<td>-0,59</td>
<td>0,09</td>
</tr>
<tr>
<td>EF≥25</td>
<td>165</td>
<td>0,53</td>
<td>0,15</td>
</tr>
<tr>
<td>NYHA III</td>
<td>276</td>
<td>0,13</td>
<td>0,55</td>
</tr>
<tr>
<td>NYHA IV</td>
<td>33</td>
<td>-1,21</td>
<td>0,10</td>
</tr>
<tr>
<td>NYHA III + EF≥25</td>
<td>206</td>
<td>0,69</td>
<td>0,04</td>
</tr>
<tr>
<td>NYHA IV + EF&lt;25</td>
<td>18</td>
<td>-1,17</td>
<td>0,19</td>
</tr>
</tbody>
</table>
Subgroup NYHA III, EF > 25%

Effect maintained through 50 weeks

Follow Up (Weeks)

Treatment

Control

Δ VAT (ml/kg/min)

0.75

0.50

0.25

0.00

-0.25

-0.50

-0.75

-1.00

12

24

50

p=0.04
IN PRESS – JOURNAL OF CARDIAC FAILURE

Subgroup Analysis of a Randomized Controlled Trial Evaluating the

Safety and Efficacy of Cardiac Contractility Modulation

in Advanced Heart Failure

Authors: William T Abraham MD,1 Koonlawee Nademanee MD,2 Kent Volosin MD,3
Steven Krueger MD,4 Suresh Neelaguru MD,5 Nirav Raval MD,6 Owen Obel MD,7
Stanislav Weiner MD,8 Marc Wish MD,9 Peter Carson MD,10 Kenneth Ellenbogen
MD,11 Robert Bourge MD,12 Michael Parides PhD,13 Richard P Chiacchierini
PhD,14 Rochelle Goldsmith PhD,15 Sidney Goldstein MD,16 Yuval Mika PhD,17
Daniel Burkhoff MD PhD,15, 17 and Alan Kadish, MD18 on Behalf of the FIX-HF-5
Investigators and Coordinators*
**Additional Patient Population**

- CCM therapy has a high potential to improve exercise tolerance and quality of life in a cohort of heart failure patients with preserved EF (EF > 35%)
Patient Selection for CCM

• Current patient population eligible for CCM are patients with symptomatic heart failure and normal QRS duration despite optimal medical therapy.

• Recent findings show that CCM is more effective in patients in class III heart failure and EF > 25% or preserved EF.
Are two leads better than one?

A single center experience
Nina Schoene, Martin Borggrefe, Juergen Kuschyk
Universitätsmedizin Mannheim, Department of Cardiology, Mannheim, Germany

Background:
Cardiac contractility modulation is an effective treatment for patients (pts) with chronic heart failure (CHF) due to severely depressed left ventricular function despite optimal pharmacological therapy and narrow QRS. So far, CCM is delivered via two electrodes to the right ventricular septum. Due to the position of the electrodes and the high stimulation amplitude, phrenic nerve stimulation may occur in some pts requiring deactivation of one lead.

....In this study we were able to demonstrate, that improvement in ejection fraction and NYHA class is similar in patients being treated via one lead compared to two leads .....
Implantation Technique
Ideal Septal Positioning

Septal Position
Septal Lead Positioning
Lead Positioning

a.p.

LAO 45%
Millar-Catheter

Procedure

a.p.
$\frac{dp}{dt}$

LV Pressure

ECG

$\frac{dP}{dt}$
Implantation
Take Home Message

- CCM is safe and improves exercise tolerance and quality of life in CHF patients
- Recent findings show that CCM is more effective in patients in class III heart failure and EF > 25% or preserved EF
- The mechanisms of action are multiple
- Further studies are warranted
Can we save a patient’s life with a single device?

Yes we can!!!
Thank you very much for your attention

Jürgen Kuschyk
Departement of Cardiology-Electrophysiology
University Hospital Mannheim

juergen.kuschyk@umm.de
CCM versus CRT

CCM effect comparable in magnitude to CRT in a different population
Myokardialer Sauerstoffverbrauch

![Chart showing the relationship between MVO2/HR and dP/dt_max (mmHg/s). The chart includes three lines representing LV Stimulation, 2 h CCM, and Dobutamin.](chart)

Butter, JCF 2007
Sabbah, Heart Rhythm 2005
Measurements

- **RV:**
  - Red: Ring
  - Black: Tip

- **LS:**
  - Green: Ring
  - Yellow: Tip

- **Atrium**
  - White: Ring
  - Blue: Tip
Vereinfachung des Optimizer-Systems?

• Verkleinerung des Gerätes (aktuell 58 cc, 115 g)
• Integration in ICD-System? Clip on device?
• Die atriale Elektrode dient zum Sensing und Timing -> Algorithmusänderung?
• Effektivität nur einer Septumelektrode?

Aktuell Fix-CHF-18 Studie
## Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Group I (n=80)</th>
<th>Group II (n=84)</th>
<th>NR (n=17)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td>58.9±9.8</td>
<td>59.9±10</td>
<td>57.4±11.4</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td>71 (88.8%) M</td>
<td>68 (81%) M</td>
<td>15 (88.2%) M</td>
</tr>
<tr>
<td></td>
<td>9 (11.2%) F</td>
<td>16 (19%) F</td>
<td>2 (11.8%) F</td>
</tr>
<tr>
<td><strong>CHF Etiology:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic</td>
<td>51 (63.8%)</td>
<td>47 (56%)</td>
<td>13 (76.5%)</td>
</tr>
<tr>
<td>Idiopathic</td>
<td>28 (35%)</td>
<td>32 (38%)</td>
<td>4 (23.5%)</td>
</tr>
<tr>
<td>Other</td>
<td>1 (1.2%)</td>
<td>5 (6%)</td>
<td></td>
</tr>
<tr>
<td><strong>Resting HR (bpm)</strong></td>
<td>71±11.3</td>
<td>72.6±12.7</td>
<td>74.2±12.2</td>
</tr>
<tr>
<td><strong>Systolic BP (mmHg)</strong></td>
<td>114.7±17</td>
<td>117.1±17.9</td>
<td>120±19.6</td>
</tr>
<tr>
<td><strong>QRS Duration (ms)</strong></td>
<td>119.9±28.3</td>
<td>116.3±26.6</td>
<td>121.5±33.5</td>
</tr>
<tr>
<td><strong>NYHA</strong></td>
<td>II 22 (27.5%)</td>
<td>17 (20%)</td>
<td>4 (23.5%)</td>
</tr>
<tr>
<td></td>
<td>III 58 (72.5%)</td>
<td>67 (80%)</td>
<td>13 (76.5%)</td>
</tr>
<tr>
<td><strong>MLWHFQ</strong></td>
<td>38.9±27.4</td>
<td>36.5±27.1</td>
<td>40.8±26</td>
</tr>
<tr>
<td><strong>6 minute walk (M)</strong></td>
<td>386±103</td>
<td>394±102</td>
<td>406±88</td>
</tr>
<tr>
<td><strong>Peak VO2 (ml O2/min/kg)</strong></td>
<td>14.1±3</td>
<td>13.6±2.7</td>
<td>13.2±2</td>
</tr>
<tr>
<td><strong>EF (%)</strong></td>
<td>29.3±6.6</td>
<td>29.8±7.8</td>
<td>25.3±11.7</td>
</tr>
<tr>
<td><strong>LV EDD (mm)</strong></td>
<td>69.3±9.1</td>
<td>68.3±7.7</td>
<td>69.77±10.2</td>
</tr>
</tbody>
</table>
## Baseline Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control (n=213) Mean (SD) or n (%)</th>
<th>Treatment (n=215) Mean (SD) or n (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>58.55 (12.23)</td>
<td>58.09 (12.79)</td>
<td>0.51091</td>
</tr>
<tr>
<td>Male</td>
<td>151 (70.9%)</td>
<td>158 (73.5%)</td>
<td>0.59012</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>142 (66.7%)</td>
<td>154 (71.6%)</td>
<td>0.50263</td>
</tr>
<tr>
<td>Black</td>
<td>45 (21.1%)</td>
<td>36 (16.7%)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>26 (12.2%)</td>
<td>25 (11.7%)</td>
<td></td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>93.30 (22.16)</td>
<td>91.17 (23.27)</td>
<td>0.16321</td>
</tr>
<tr>
<td>BMI (kg/m2)</td>
<td>30.95 (6.53)</td>
<td>30.44 (7.04)</td>
<td>0.21791</td>
</tr>
<tr>
<td>Resting HR (bpm)</td>
<td>73.74 (12.19)</td>
<td>73.98 (13.13)</td>
<td>0.96811</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>115.61 (17.61)</td>
<td>116.65 (19.48)</td>
<td>0.86951</td>
</tr>
<tr>
<td>CHF Etiology</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic</td>
<td>142 (66.7%)</td>
<td>139 (64.7%)</td>
<td>0.64653</td>
</tr>
<tr>
<td>Idiopathic</td>
<td>48 (22.5%)</td>
<td>58 (27.0%)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>23 (10.8%)</td>
<td>18 (8.3%)</td>
<td></td>
</tr>
<tr>
<td>NYHA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Class I</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0.17203</td>
</tr>
<tr>
<td>Class II</td>
<td>1 (0.47%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>Class III</td>
<td>183 (85.92%)</td>
<td>196 (91.16%)</td>
<td></td>
</tr>
<tr>
<td>Class IV</td>
<td>29 (13.62%)</td>
<td>19 (8.84%)</td>
<td></td>
</tr>
</tbody>
</table>
Baseline Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control (n=213)</th>
<th>Treatment (n=215)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>QRS Duration (ms)</strong></td>
<td>101.51 (12.81)</td>
<td>101.63 (15.30)</td>
<td>0.59684</td>
</tr>
<tr>
<td>PVCs/24hr (Holter)</td>
<td>1365.1 (2000.9)</td>
<td>1323.3 (1930.6)</td>
<td>0.51131</td>
</tr>
<tr>
<td><strong>LVEF (%)</strong></td>
<td>26.09 (6.54)</td>
<td>25.74 (6.60)</td>
<td>0.56411</td>
</tr>
<tr>
<td>LVEDD (mm)</td>
<td>63.01 (8.56)</td>
<td>62.41 (9.22)</td>
<td>0.77151</td>
</tr>
<tr>
<td>MLWHFQ</td>
<td>57.38 (22.62)</td>
<td>60.49 (23.00)</td>
<td>0.11091</td>
</tr>
<tr>
<td>6MW (meters)</td>
<td>323.99 (92.44)</td>
<td>326.38 (82.10)</td>
<td>0.59711</td>
</tr>
<tr>
<td><strong>CPX (core lab)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration (minutes)</td>
<td>11.50 (3.46)</td>
<td>11.34 (3.20)</td>
<td>0.48141</td>
</tr>
<tr>
<td>Peak SBP (mmHg)</td>
<td>138.8 (24.6)</td>
<td>139.7 (27.1)</td>
<td>0.97141</td>
</tr>
<tr>
<td>Peak HR (bpm)</td>
<td>121.2 (20.5)</td>
<td>122.1 (20.2)</td>
<td>0.52231</td>
</tr>
<tr>
<td>Peak RER</td>
<td>1.13 (0.09)</td>
<td>1.14 (0.10)</td>
<td>0.51891</td>
</tr>
<tr>
<td>Peak VO2 (ml/kg/min)</td>
<td>14.71 (2.92)</td>
<td>14.74 (3.06)</td>
<td>0.85751</td>
</tr>
<tr>
<td>AT (ml/kg/min)</td>
<td>10.97 (2.18)</td>
<td>10.95 (2.24)</td>
<td>0.97194</td>
</tr>
</tbody>
</table>
Table 2. Hemodynamic and Ventriculographic Findings in Dogs with Heart Failure Obtained at Baseline and 2 hours After Initiating CCM Therapy (n = 6)

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>2 Hours of CCM</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (beats/min)</td>
<td>79 ± 3</td>
<td>75 ± 3</td>
<td>.26</td>
</tr>
<tr>
<td>Peak LVP (mm Hg)</td>
<td>101 ± 5</td>
<td>107 ± 8</td>
<td>.23</td>
</tr>
<tr>
<td>LV EDP (mm Hg)</td>
<td>14 ± 1</td>
<td>9 ± 1</td>
<td>.005</td>
</tr>
<tr>
<td>Stroke volume (mL)</td>
<td>18 ± 1</td>
<td>21 ± 1</td>
<td>.004</td>
</tr>
<tr>
<td>LV EDV (mL)</td>
<td>71 ± 8</td>
<td>68 ± 7</td>
<td>.001</td>
</tr>
<tr>
<td>LV ESV (mL)</td>
<td>53 ± 7</td>
<td>47 ± 6</td>
<td>.001</td>
</tr>
<tr>
<td>LV EF (%)</td>
<td>26 ± 1</td>
<td>31 ± 2</td>
<td>.001</td>
</tr>
<tr>
<td>LV CBF (mL/min)</td>
<td>35 ± 4</td>
<td>27 ± 3</td>
<td>.017</td>
</tr>
<tr>
<td>LV Power (watts)</td>
<td>0.32 ± 0.02</td>
<td>0.37 ± 0.03</td>
<td>.040</td>
</tr>
<tr>
<td>MVO2 (umol/min)</td>
<td>257 ± 41</td>
<td>180 ± 34</td>
<td>.12</td>
</tr>
</tbody>
</table>

Abbreviations are same as in Table 1. CCM, cardiac contractility modulation; P value = probability value of baseline versus CCM.

CCM
Verbesserte EF ohne Steigerung des O2 Verbrauchs

Sabbah, Heart Rhythm 2005

Butter, JCF 2007