

# Clinical effects of cardiac contractility modulation (CCM) as a treatment for chronic heart failure

Martin Borggrefe<sup>1\*</sup> and Daniel Burkhoff<sup>2</sup>

<sup>1</sup>Department of Medicine (Department of Cardiology), Medical Faculty Mannheim, University of Heidelberg, Germany; and <sup>2</sup>Division of Cardiology, Columbia University, New York City, NY, USA

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Cardiac contractility modulation (CCM) signals are non-excitatory signals applied during the absolute refractory period that have been shown to enhance the strength of left ventricular contraction without increasing myocardial oxygen consumption in studies carried out in animals and humans with heart failure and reduced ejection fraction. Studies from myocardial tissue of animals and humans with heart failure suggest that the mechanisms of these effects is that CCM drives expression of many genes that are abnormally expressed in heart failure towards normal, including proteins involved with calcium cycling and the myocardial contractile machinery. Clinical studies have primarily focused on patients with normal QRS durations in view of the fact that cardiac resynchronization (CRT) is a viable option for patients with prolonged QRS duration. These studies show that CCM improves exercise tolerance as indexed by peak oxygen consumption ( $\text{VO}_2$ ) and quality of life indexed by the Minnesota Living with Heart Failure Questionnaire. The device is currently available for clinical use in countries recognizing the CE mark and is undergoing additional testing in the USA under a protocol approved by the Federal Drug Administration.

**Keywords** Heart failure • Cardiac contractility modulation • Electrical treatment of heart failure

Cardiac resynchronization therapy (CRT) improves symptoms, quality of life, and exercise tolerance, and reduces hospitalizations in patients with advanced heart failure and increased QRS duration.<sup>1,2</sup> The results of a recent study showed that patients with mechanical dyssynchrony detected by tissue Doppler imaging but a normal QRS duration did not benefit from CRT.<sup>3</sup> Thus, QRS duration remains the primary criterion for selecting patients for CRT. Also, since ~60% of patients with heart failure have a normal QRS duration<sup>4</sup> and since at least 30% of patients receiving CRT do not respond,<sup>1</sup> development of new device-based treatments for patients with persistent symptoms despite optimal medical therapy (OMT) remains an important quest.

Cardiac contractility modulation (CCM) signals are non-excitatory signals applied during the absolute refractory period that have been shown to enhance the strength of left ventricular (LV) contraction and improve exercise tolerance and quality of life.<sup>5,6</sup> This paper will review the concept and available evidence demonstrating the clinical effects of CCM in patients with heart failure.

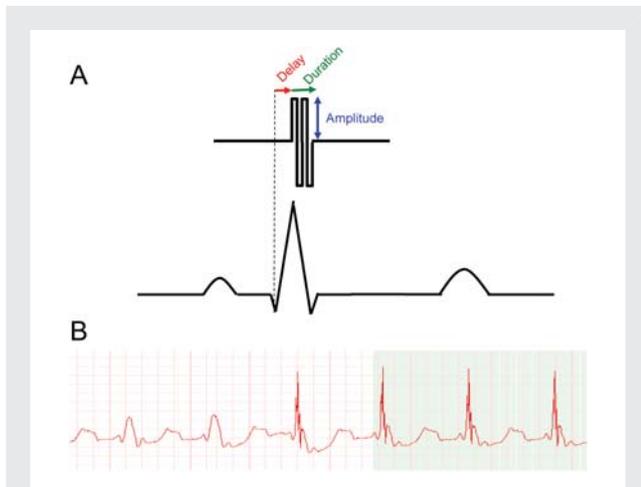
## Concept of cardiac contractility modulation and its effects on haemodynamics and myocardial energetics

Cardiac contractility modulation signals are electrical impulses delivered during the absolute refractory period (*Figure 1A*). CCM signals used in clinical practice today are delivered ~30 ms after detection of the onset of the QRS complex and consist of two biphasic  $\pm 7.7$  V pulses spanning a total duration of ~20 ms. These signals do not elicit a new action potential or contraction (as is the case with extra- or post-extrasystolic contractions), and they do not affect the electrical or mechanical activation sequence. CCM signals are thus referred to as 'non-excitatory'.

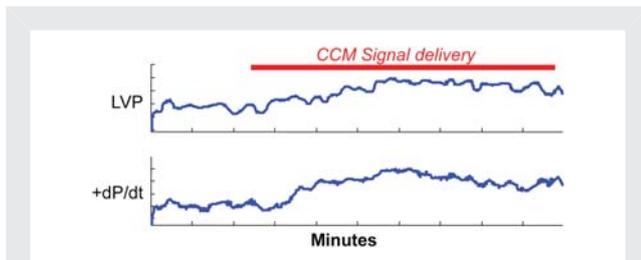
Cardiac contractility modulation signals are provided by a pacemaker-like impulse generator (OPTIMIZER III, IMPULSE Dynamics, Orangeburg, NY, USA) that connects to the heart via two standard active fixation leads placed on the right ventricular (RV) septum. An additional right atrial lead is used to detect the

\* Corresponding author. Tel: +49 621 383 2204, Fax: +49 621 383 3821, Email: martin.borggrefe@umm.de

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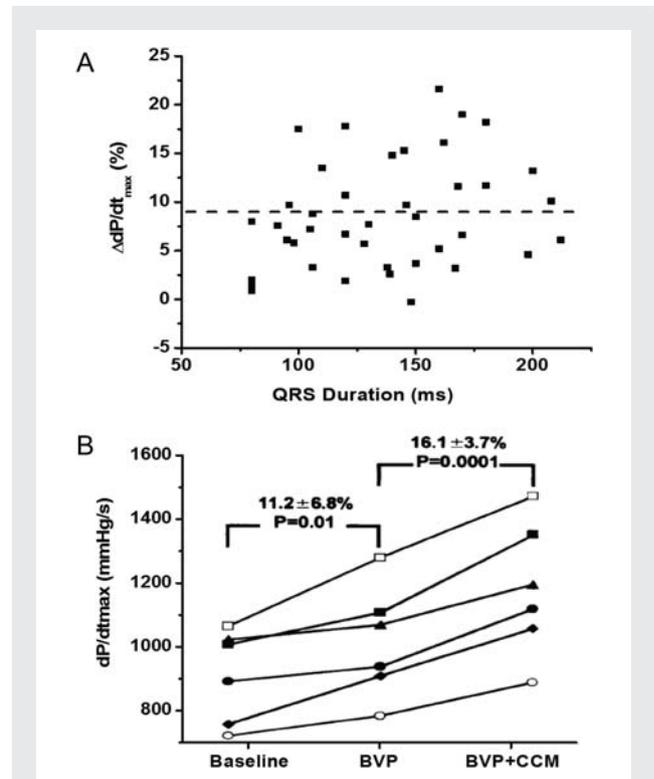
**Figure 1** (A) Cardiac contractility modulation (CCM) signals employed in clinical study are biphasic pulses delivered after a defined delay from detection of local electrical activation. (B) Body surface electrocardiogram showing two beats prior to initiating CCM signals and the first four beats of CCM signal application.



**Figure 2** Effects of cardiac contractility modulation (CCM) signals on global function assessed by left ventricular pressure (LVP) and the rate of rise of LVP ( $+dP/dt$ ) in a patient undergoing an acute OPTIMIZER III device implant.

timing of atrial activation; this information is used in an algorithm to ensure proper timing of CCM signal delivery and also to suspend CCM delivery in the event of ventricular arrhythmias. CCM pulses contain 50–100 times the amount of energy delivered in a standard pacemaker impulse and are readily identified on the body surface electrocardiogram (Figure 1B).

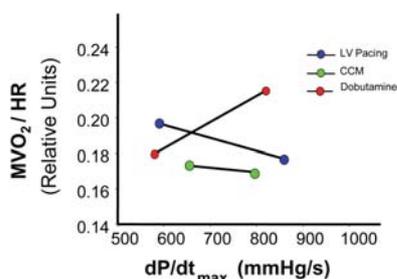
Within several minutes of acute CCM signal application, a mild increase in ventricular contractile strength can be detected as indexed by increases in LV pressure (LVP) and the rate of rise of LVP (LV  $dP/dt_{max}$ , Figure 2).<sup>6–10</sup> Interestingly, the acute change  $dP/dt_{max}$  is independent of QRS duration (Figure 3A).<sup>11,12</sup> Also, in patients with prolonged QRS duration, the acute contractile effects of CCM are additive to those of CRT (Figure 3B),<sup>11</sup> which is due to the fact that the mechanisms of action are different. It is important to note that the magnitude of the acute CCM haemodynamic effect can depend on electrode position within the right ventricular septum. It has been recommended that during CCM implantation, a Millar catheter be inserted into the left ventricle



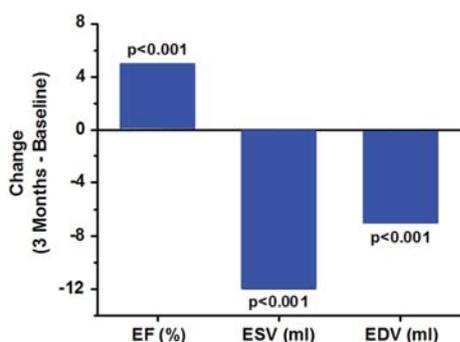
**Figure 3** (A) Changes in  $dP/dt_{max}$  in individual patients as a function of their respective QRS durations showing that the cardiac contractility modulation (CCM) effect is independent of QRS duration. (B) Individual patient responses and average percentage changes ( $\pm$  SD) in  $dP/dt_{max}$  in response to acute biventricular pacing (BVP; also known as cardiac resynchronization therapy, CRT) and in response to acute, simultaneous BVP plus CCM in patients with prolonged QRS duration. Reprinted from reference<sup>11</sup> with permission from Elsevier.

to measure the impact of CCM on LV  $dP/dt_{max}$  and that, if a significant effect (e.g.  $>5\%$ ) is not achieved, the electrodes be repositioned. In previous studies, there has not been any correlation between the acute haemodynamic effects of CCM and the chronic effects on clinical symptoms or exercise tolerance. A similar lack of correlation between acute haemodynamic and chronic clinical effectiveness has also been noted for CRT.<sup>13</sup> The purpose of measuring the acute effects is therefore not necessarily to optimize the chronic effects, but rather simply to ensure that the electrodes are in a position on the septum from which LV properties can be influenced.

Since many investigators believe that the impact of heart failure therapy on myocardial energetics is an important factor in long-term safety and efficacy, a clinical study was undertaken to investigate the acute effects of CCM on myocardial oxygen consumption ( $MVO_2$ , Figure 4).<sup>14</sup>  $MVO_2$  and LV  $dP/dt_{max}$  were measured in nine patients exposed to acute CCM signals. In this study, as shown by the green dots in Figure 4, acute CCM was associated with an increase in  $dP/dt_{max}$  from  $\sim 630$  to  $\sim 800$  mmHg/s (an  $\sim 20\%$  increase). Despite the acutely increased contractility, there was no detectable increase in  $MVO_2$ . These data were compared with



**Figure 4** Impact of acute dobutamine infusion and left ventricular (LV) pacing (i.e. cardiac resynchronization therapy, CRT) on LV  $dP/dt_{max}$  in patients with prolonged QRS duration as described by Nelson *et al.*<sup>15</sup> in comparison with the same data in patients receiving acute cardiac contractility modulation (CCM) treatment. Reprinted from reference<sup>14</sup> with permission from Elsevier. MVO<sub>2</sub>, myocardial oxygen consumption.



**Figure 5** Cardiac contractility modulation (CCM)-induced changes in ejection fraction (EF), end-systolic volume (ESV), and end-diastolic volume (EDV) following 3 months of treatment as detected by 3D echocardiography. Reprinted from reference<sup>17</sup> with permission from Elsevier.

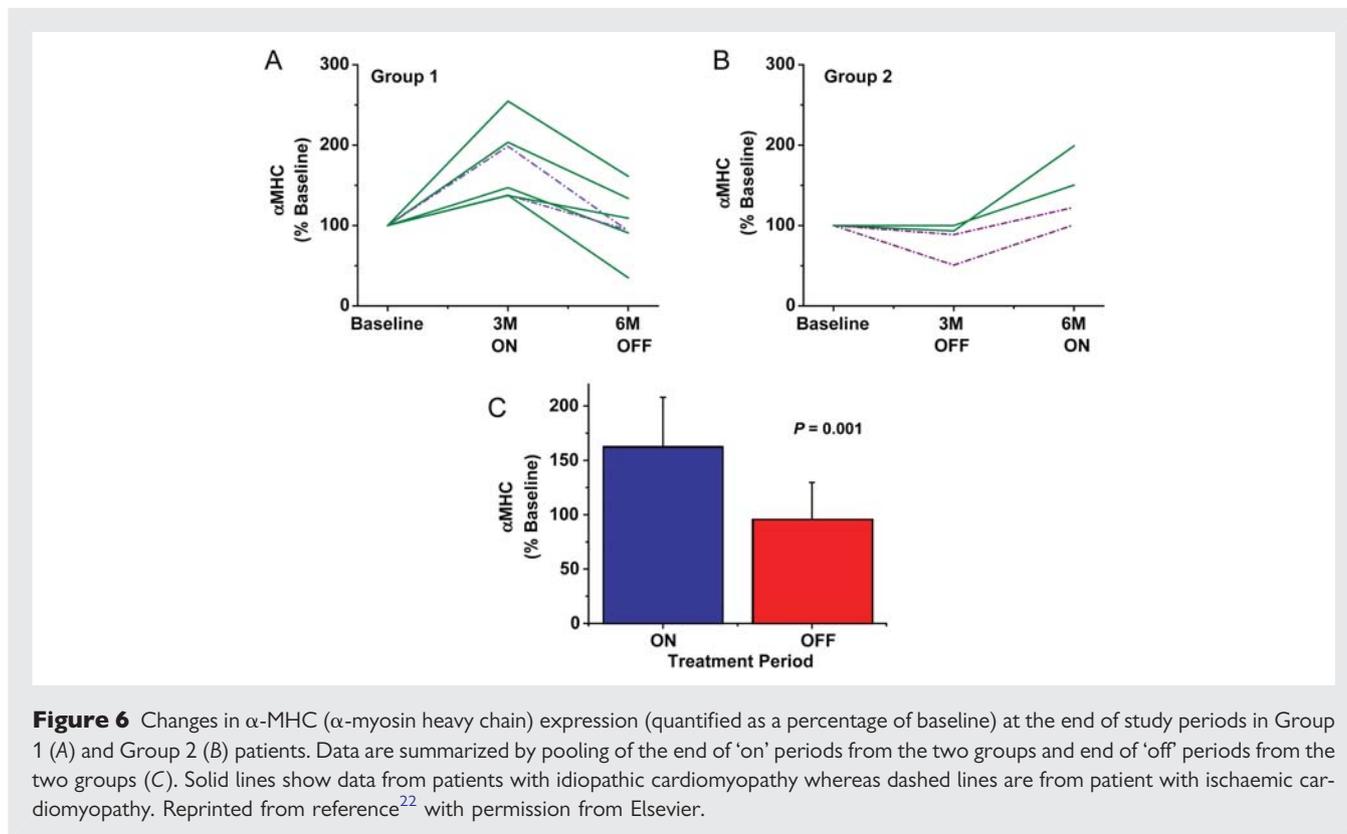
those of Nelson *et al.*,<sup>15</sup> who had previously measured MVO<sub>2</sub> and  $dP/dt_{max}$  when contractility was increased first by applying CRT (blue dots) and then dobutamine (red dots) to achieve a comparable increase in  $dP/dt_{max}$ . As shown, dobutamine increased both  $dP/dt_{max}$  and MVO<sub>2</sub>, consistent with its mechanism of action, among other things, to increase calcium cycling. In contrast, the increase in  $dP/dt_{max}$  achieved by CRT was not associated with an increase in MVO<sub>2</sub>. Thus, like CRT, the acute, modest increase in contractility achieved by CCM does not increase energy demands.

In addition to these acute haemodynamic effects, improvement in global ventricular function has also been reported during chronic CCM signal application (Figure 5).<sup>16,17</sup> In one study,<sup>17</sup> 30 patients with an ejection fraction (EF) <35% and New York Heart Association (NYHA) functional class III symptoms despite OMT underwent 3D echocardiography at baseline and for the following 3 months of CCM treatment. The LVEF increased by ~5%

(absolute points) and end-diastolic and end-systolic volumes decreased by ~12 and ~7 mL, respectively, indicating reverse remodelling. This degree of reverse remodelling has been shown to be similar to what is observed with CRT.<sup>18</sup>

## Mechanisms of action

Several recent studies sought to define the mechanisms by which CCM signals impact on regional and global myocardial function. Many of these studies have been reviewed recently.<sup>19</sup> In view of previous literature showing that electromagnetic fields can impact on protein–protein interaction and gene expression<sup>20</sup> and considering that the CCM-induced increases in contractility were not associated with an increase in MVO<sub>2</sub>, CCM signals may have a direct impact on cellular physiology beyond typical acute effects on calcium handling that underlie pharmacological inotropic effects. To explore this hypothesis, myocardial samples were initially obtained for molecular (northern blot) and biochemical (western blot) analyses from an animal model of heart failure in both acute and chronic studies.<sup>10,21</sup> Samples were taken from the interventricular septum (near the site of CCM signal delivery) and in a remote area on the LV free wall. The impact of CCM on a variety of genes and proteins was explored; for illustrative purposes, emphasis was placed on genes and proteins of high abundance whose tissue contents were known to be significantly altered in heart failure. It was demonstrated that one of the most rapid effects of CCM is that near the site of signal delivery there is, within minutes, an increase in phosphorylation of phospholamban (PLB), a key protein that modulates the activity of sarcoendoplasmic reticulum calcium ATPase type 2a (SERCA2a) which in turn modulates calcium handling by the sarcoplasmic reticulum.<sup>10</sup> Shortly thereafter, changes in gene expression can be demonstrated. For example, the expression of SERCA2a was decreased in animals with untreated heart failure in both the interventricular septum ('near') and far from the LV free wall ('remote'). For tissue obtained from animals with acute (4 h) CCM treatment, SERCA2a expression increased in the region near the site of CCM stimulation, but not in the remote region. In the chronic setting, however, SERCA2a expression was improved in both near and remote regions. These findings are representative of findings obtained with other genes whose expression is decreased in chronic heart failure. Brain natriuretic peptide (BNP) expression was also examined but, in this case, BNP was overexpressed in untreated heart failure, decreased acutely only in the region near the CCM pacing site, and decreased in both the near and remote sites with chronic CCM treatment. The fact that gene expression is improved in the short term only near the area of treatment implies that the effects of CCM treatment are local and direct. However, in the long term, where expression is improved in both near and remote sites, two possible factors may contribute. First, changes in gene expression in remote areas may be secondary to the global haemodynamic benefits provided by chronic regional CCM treatment. Alternatively, there may be some direct effect that is transmitted to remote sites via gap junctions. Which, if either, of these is contributory or dominant remains to be elucidated.



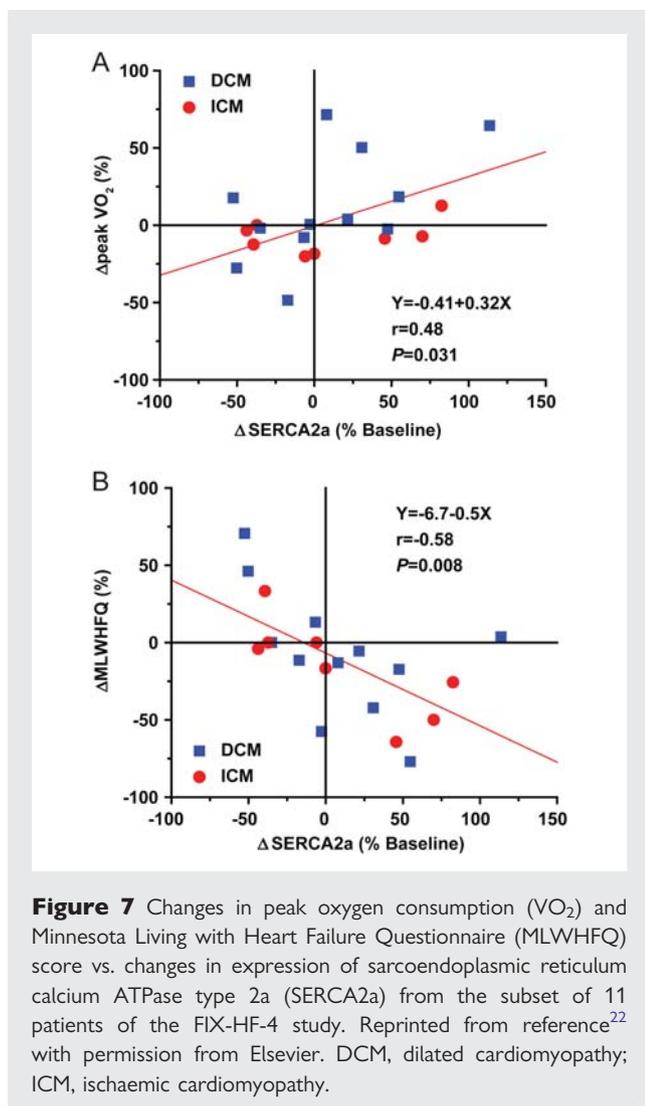
These findings concerning the molecular effects of CCM treatment in an animal model of heart failure were confirmed in a biopsy study performed in 11 patients with heart failure. Endomyocardial biopsies were obtained at baseline (prior to CCM therapy) and 3 and 6 months thereafter.<sup>19</sup> Patients were randomized either to receive CCM therapy for the first 3 months followed by sham treatment (Group 1) or to receive sham treatment first followed by active treatment (Group 2). mRNA expression was analysed in a core lab blinded to the treatment sequence. Expression of atrial natriuretic peptide (ANP), BNP,  $\alpha$ -myosin heavy chain (MHC), the sarcoplasmic reticulum genes SERCA2a, phospholamban (PLB), and ryanodine receptor (RYR), and the stretch response genes p38 mitogen-activated protein kinase (MAPK) and p21ras was measured using reverse transcription-PCR (RT-PCR) and bands quantified in densitometric units. The 3 months therapy off phase was associated with increased expression of ANP, BNP, p38-MAPK, and p21ras, and decreased expression of  $\alpha$ -MHC, SERCA2a, PLB, and RYR. In contrast, the 3 months on therapy phase resulted in significantly decreased expression of ANP, BNP, p38-MAPK, and p21ras, and significantly increased expression of  $\alpha$ -MHC, SERCA2a, PLB, and RYR.

A detailed analysis of the findings pertaining to  $\alpha$ -MHC is shown in Figure 6. mRNA content was determined from northern blot band intensities which were normalized to their respective values obtained in the baseline heart failure state. Data from patients with ischaemic and idiopathic cardiomyopathy are shown with dashed and solid lines, respectively. At the end of Phase 1,  $\alpha$ -MHC expression increased in Group 1 patients

(device on, Figure 6A) and stayed the same or decreased in Group 2 patients (device off, Figure 6B). After crossover, expression decreased in Group 1 patients when the device was switched off, and increased in Group 2 patients when the device was switched on. The overall comparisons are summarized in Figure 6C where results from on periods are pooled and results from off periods are pooled. As shown, there was a statistically significant  $\sim 62.7 \pm 45.3\%$  increase in  $\alpha$ -MHC expression above the heart failure baseline state in response to CCM treatment. As shown in this typical example, there was no substantive difference in the response identified in hearts with idiopathic and ischaemic cardiomyopathies. These findings were representative of those obtained with the other genes examined, except, as detailed above, expression of ANP, BNP, p38-MAPK, and p21ras which is up-regulated in chronic heart failure and whose content was decreased during CCM therapy.

Most interestingly, there were significant correlations between improvements in gene expression and improvements in peak  $\text{VO}_2$  and the Minnesota Living with Heart Failure Questionnaire (MLWHFQ).<sup>22</sup> As one example, the correlations between changes in these parameters of functional status and changes in SERCA2a expression are summarized in Figure 7. As shown, these correlations were present for both ischaemic and idiopathic cardiomyopathy.

These findings indicate that CCM treatment reversed the cardiac maladaptive fetal gene programme and normalized expression of key sarcoplasmic reticulum  $\text{Ca}^{2+}$  cycling and stretch response genes. These findings, which are confirmatory of those



identified in response to CCM treatment in animals with heart failure discussed above, support a novel mechanism of action by which CCM improves LV function in patients with heart failure.

In addition to looking at mRNA expression, myocardial protein expression was also examined in the myocardium from the animal studies noted above at sites both near to and remote from the site of CCM signal application.<sup>10</sup> Protein levels of  $\beta_1$ -adrenoreceptor, SERCA-2a, PLB, and RyR decreased and those of ANP and BNP increased significantly in sham-operated controls compared with normals. CCM therapy restored the expression of all measured proteins except for total PLB. The restoration of genes and proteins after 3 months of CCM therapy was the same in LV tissue obtained from the interventricular septum, the site nearest to the CCM signal delivery leads, and the LV free wall, a site remote from the CCM leads.

Although protein levels of total PLB did not change with CCM, levels of PLB that was phosphorylated (P-PLB) at Ser16 and Thr17 in tissue obtained from both the interventricular septum and the LV free wall were significantly lower in sham-operated dogs with heart failure compared with normal dogs and returned to near

normal levels after 3 months of CCM therapy. In both the interventricular septum and LV free wall, the ratio of P-PLB at Ser16 to total PLB and the ratio of P-PLB at Thr17 were also significantly lower in sham-operated dogs with heart failure compared with normal dogs. Thus, long-term CCM therapy resulted in a significant increase of both ratios in the interventricular septum and the LV free wall, respectively.

## Chronic signal application in heart failure patients

Following three small pilot studies of chronic CCM signal application,<sup>16,23,24</sup> a multicentre randomized, double-blind, double crossover study was performed in heart failure patients with  $EF \leq 35\%$  and NYHA class II or III symptoms despite OMT (the FIX-HF-4 study).<sup>25</sup> A total of 164 subjects with  $EF < 35\%$  and NYHA class II (24%) or III (76%) symptoms received a CCM pulse generator. Patients were randomly assigned to Group 1 ( $n = 80$ , CCM treatment 3 months, sham treatment second 3 months) or Group 2 ( $n = 84$ , sham treatment 3 months, CCM treatment second 3 months). The co-primary endpoints were changes in peak  $VO_2$  and MLWHFQ score. Baseline  $EF$  ( $29.3 \pm 6.69\%$  vs.  $29.8 \pm 7.8\%$ ), peak  $VO_2$  ( $14.1 \pm 3.0$  vs.  $13.6 \pm 2.7$  mL/kg/min), and MLWHFQ score ( $38.9 \pm 27.4$  vs.  $36.5 \pm 27.1$ ) were similar between groups. Peak  $VO_2$  increased similarly in both groups during the first 3 months ( $0.40 \pm 3.0$  vs.  $0.37 \pm 3.3$  mL/kg/min). This was interpreted as evidence of a prominent placebo effect. During the next 3 months, however, peak  $VO_2$  decreased in the group switched to sham treatment ( $-0.86 \pm 3.06$  mL/kg/min) and increased in patients switched to active treatment ( $0.16 \pm 2.50$  mL/kg/min). At the end of the second phase of the study, the difference in peak  $VO_2$  between groups was  $\sim 1$  mL/kg/min. After performing statistical testing for carryover effects and period effects, data from both study phases could be formally combined to arrive at a net mean ( $\pm$  SD) treatment effect on peak  $VO_2$  of  $0.52 \pm 1.39$  O<sub>2</sub>/kg/min ( $P = 0.032$ ).

The MLWHFQ score behaved similarly, trending only slightly better with treatment ( $-12.06 \pm 15.33$  vs.  $-9.70 \pm 16.71$ ) during the first 3 months (again consistent with a large placebo effect). During the second 3 months, the MLWHFQ score increased in the group switched to sham treatment ( $+4.70 \pm 16.57$ ) and decreased further in patients switched to active treatment ( $-0.70 \pm 15.13$ ). As was the case for peak  $VO_2$ , formal statistical testing of data from a crossover study design confirmed that these differences represent a statistically significant positive treatment effect ( $P = 0.030$ ).

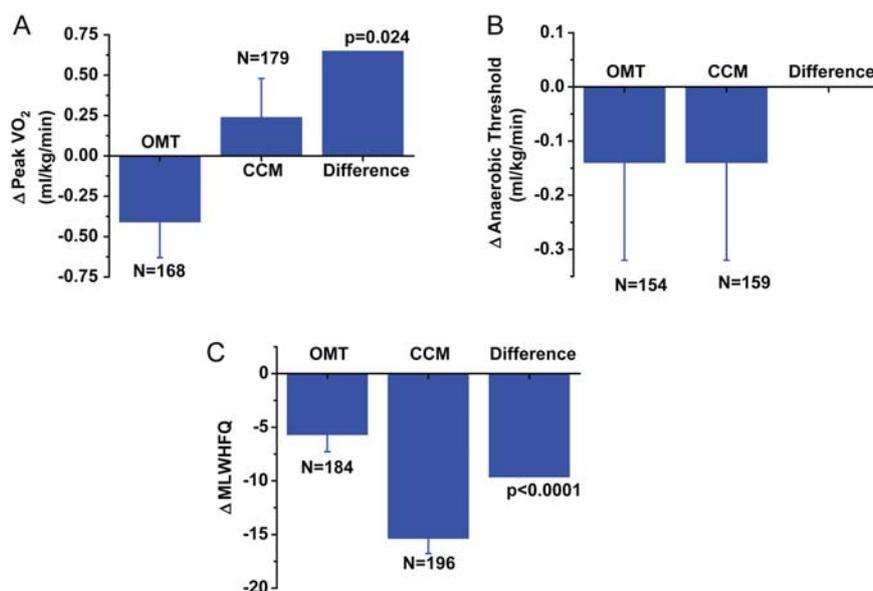
The study met its primary endpoint using the formal analysis of a crossover study design; both exercise tolerance and quality of life improved significantly during the on periods compared with the off periods. Serious cardiovascular adverse events were tracked carefully in both groups. The most frequently reported adverse events were episodes of decompensated heart failure, atrial fibrillation, bleeding at the OPTIMIZER System implant site, and pneumonia. Importantly, there were no significant differences between on and off phases in the number or types of adverse events.

The next study of CCM was a multicentre study involving 428 patients recruited from 50 sites in the USA (FIX-HF-5 study).<sup>26</sup> Patients were characterized by NYHA class III (89%) or IV (11%), QRS duration averaging 101 ms, and EF averaging 25%. Patients were required to be receiving stable OMT, defined as a beta-blocker, angiotensin-converting enzyme inhibitor, or angiotensin receptor blocker and a diuretic for at least 3 months (unless intolerant); the daily dose of each medication could not vary by more than a 50% reduction or 100% increase over the previous 3 months. Patients were randomized (1:1 and stratified for ischaemic or non-ischaemic underlying aetiology) to OMT plus CCM ( $n = 215$ ) or OMT alone ( $n = 213$ ). The primary safety endpoint was a test of non-inferiority between groups at 12 months for the composite of all-cause mortality and all-cause hospitalizations (12.5% allowable delta). Efficacy was assessed by changes in exercise tolerance and quality of life at 6 months compared with baseline. Exercise tolerance was indexed by ventilatory anaerobic threshold (VAT; which was the declared primary endpoint) and by peak  $\text{VO}_2$ . The choice of VAT as the primary endpoint was driven by the fact that the study was unblinded and the United States Food and Drug Administration (FDA) required as objective an index of exercise tolerance as possible (i.e. least susceptible to placebo effect). Furthermore, the primary analysis of these endpoints was a 'responders analysis',<sup>27</sup> which was a between-group comparison of the percentage of patients whose VAT increased by  $\geq 20\%$ . Quality of life was assessed by the MLWHFQ.

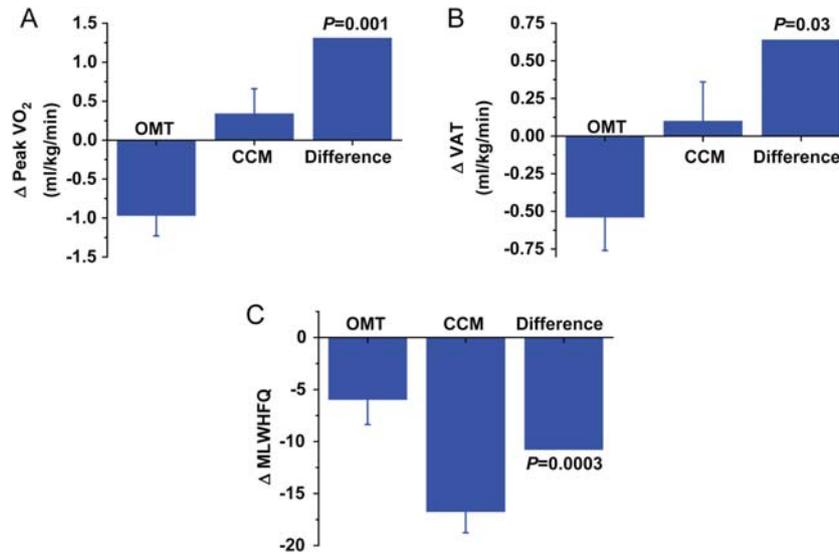
The study groups (OMT vs. CCM) were comparable for age ( $58 \pm 13$  vs.  $59 \pm 12$  years), chronic heart failure aetiology (67%

vs. 65% ischaemic aetiology), QRS duration ( $101 \pm 0.5$  ms vs.  $101 \pm 0.6$  ms), EF ( $26 \pm 7\%$  vs.  $26 \pm 7\%$ ), VAT ( $11.0 \pm 2.2$  mL/kg/min vs.  $11.0 \pm 2.2$  mL/kg/min), peak  $\text{VO}_2$  ( $14.7 \pm 2.9$  mL/kg/min vs.  $14.8 \pm 3.2$  mL/kg/min), MLWHFQ ( $57 \pm 23$  vs.  $60 \pm 23$ ) and other important baseline characteristics. The safety endpoint of the study was met; by the end of 1-year follow-up, 52% of patients in the treatment group and 48% of patients in the control group met a study-specified safety endpoint, which was non-inferior by both a Blackwelder's test of non-inferiority and a log-rank test comparing Kaplan–Meier survival curves. Regarding efficacy, peak  $\text{VO}_2$  was 0.7 mL/kg/min greater ( $P = 0.024$ ) and the MLWHFQ score was 9.7 points better ( $P < 0.0001$ ) in the treatment group than in the control group (Figure 8). However, VAT, the primary endpoint, did not differ between the groups (based neither on a responders analysis nor on a comparison of mean changes between groups) so the study was considered to be a negative study.

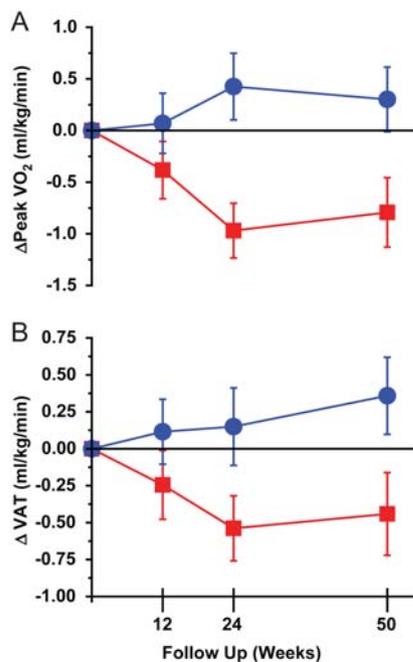
The study protocol indicated that efficacy effects would be explored in specific patient subsets.<sup>28</sup> This analysis showed that particularly large effects on both VAT and peak  $\text{VO}_2$  were observed in patients with a baseline EF  $\geq 25\%$  and NYHA class III symptoms (Figure 9). In this subgroup (which consisted of 97 OMT and 109 CCM group patients, nearly half of the entire study cohort), VAT was 0.64 mL/kg/min greater ( $P = 0.03$ ), peak  $\text{VO}_2$  was 1.31 mL/kg/min greater ( $P = 0.001$ ), and MLWHFQ score was 10.8 points better ( $P = 0.003$ ) in the treatment group than in the control group. Regarding the results of the 'responders analysis', 5.8% of OMT and 20.5% of CCM patients exhibited a  $\geq 20\%$  increase in VAT, a difference of 14.7%, at 6 months



**Figure 8** Key results of the prospective, randomized FIX-HF-5 study showing comparison of changes from baseline in: (A) peak oxygen consumption ( $\text{VO}_2$ ), (B) anaerobic ventilator threshold, and (C) Minnesota Living with Heart Failure Questionnaire (MLWHFQ) score between baseline and 6 months of follow-up in the control group that received only optimal medical therapy (OMT) and in the treatment group that received OMT plus cardiac contractility modulation (CCM) treatment. As shown, although peak  $\text{VO}_2$  and MLWHFQ score were better in the treatment group, there was no difference in anaerobic threshold between groups. Reprinted from reference<sup>40</sup> with permission from Elsevier.



**Figure 9** Key results of a subgroup of patients from the FIX-HF-5 study characterized by New York Heart Association (NYHA) class III symptoms and ejection fraction  $\geq 25\%$ . The graphs show comparisons of the changes from baseline in: (A) peak oxygen consumption ( $VO_2$ ), (B) ventilator anaerobic threshold (VAT), and (C) Minnesota Living with Heart Failure Questionnaire (MLWHFQ) score between baseline and 6 months of follow-up in the control group that received only optimal medical therapy (OMT) and in the treatment group that received OMT plus cardiac contractility modulation (CCM) treatment. As shown, peak  $VO_2$ , VAT, and MLWHFQ score were all better in the CCM treatment group compared with the OMT control group. Reprinted from reference<sup>28</sup> with permission from Elsevier.

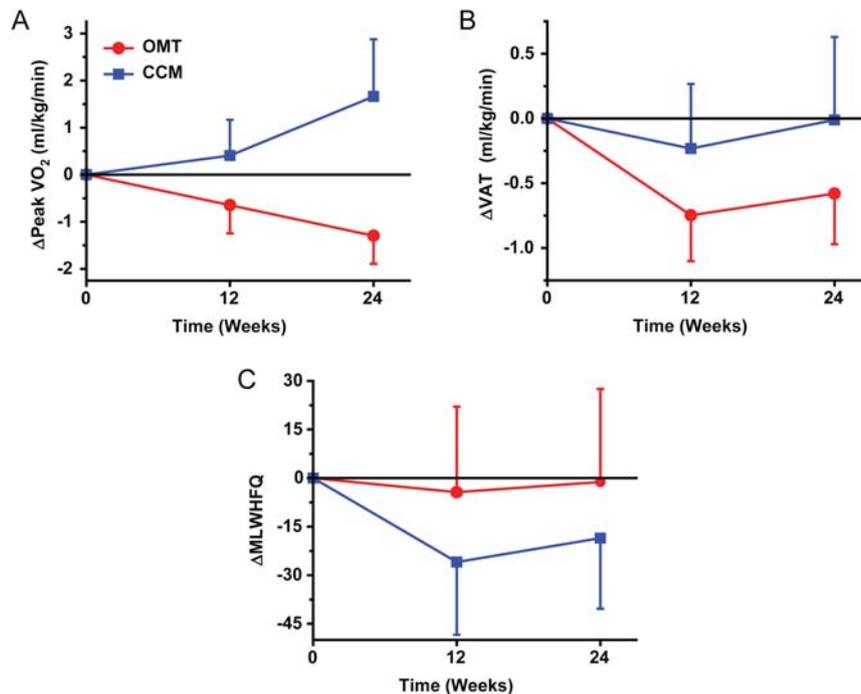


**Figure 10** Results from the same subgroup of patients of the FIX-HF-5 study as described in Figure 9. These results show that the effects on exercise tolerance [quantified by peak oxygen consumption ( $VO_2$ ) and ventilator anaerobic threshold (VAT)] are sustained throughout the entire 12-month follow-up study period. Reprinted from reference<sup>28</sup> with permission from Elsevier.

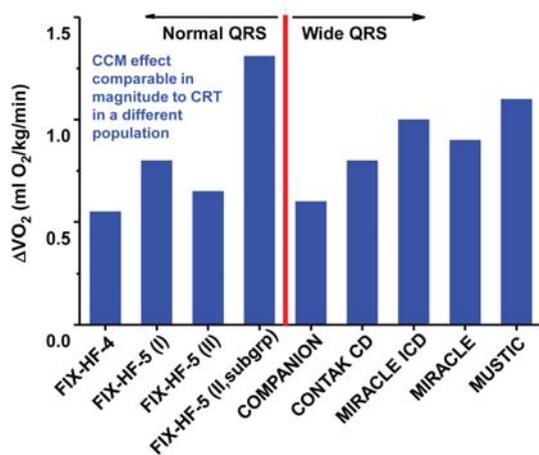
( $P = 0.007$ ). Furthermore, in this subgroup, these effects on exercise tolerance and quality of life were sustained throughout the entire 12-month follow-up period of the study (Figure 10, which shows changes in peak  $VO_2$  and VAT in both study groups). Although pre-specified in the protocol, the results of this analysis were considered retrospective, hypothesis-generating. Accordingly, a new study has been initiated to confirm these findings prospectively (www.clinicaltrials.gov registration number NCT01381172).

An additional subgroup analysis was performed in 38 patients in the FIX-HF-5 study with an EF  $\geq 35\%$ . These patients were admitted to the study because the EF determined at the investigative site was  $<35\%$ ; however, all analyses were based on the core lab EF assessment. Eighteen of the patients were in the treatment group and 20 patients were in the control group. In this subgroup, efficacy parameters were even more greatly improved by CCM: peak  $VO_2$  was 2.96 mL/kg/min greater ( $P = 0.03$ ), VAT was 0.57 mL/kg/min greater ( $P = \text{NS}$ ), and MLWHFQ score was 18 points better ( $P = 0.06$ ) in the CCM group compared with the OMT group (Figure 11). Although not all of these differences were statistically significant in view of the small sample size, the trends suggest greater effects than in the larger subgroup of patients with EF  $\geq 25\%$ . Very interestingly, a similar substudy of the PROSPECT trial suggested that the structural and functional effects of CRT are similar in patients with EF  $>35\%$  to those with EF  $<35\%$ .<sup>29</sup>

To put the current results into clinical perspective, it is interesting to compare results obtained with CCM in patients with a narrow QRS<sup>24–26</sup> with those obtained in several trials with CRT



**Figure 11** An even further refined subgroup of the FIX-HF-5 study characterized by baseline ejection fraction  $\geq 35\%$  (range 35–45%, average of 40%). These findings show that the impact of cardiac contractility modulation (CCM) in these patients on peak oxygen consumption ( $VO_2$ ), ventilator anaerobic threshold (VAT), and Minnesota Living with Heart Failure Questionnaire (MLWHFQ) score are significantly greater than in the entire cohort or even in the subgroup with ejection fraction  $\geq 25\%$ . Printed from reference<sup>34</sup> with permission from Springer. CCM, cardiac contractility modulation; OMT, optimal medical therapy.



**Figure 12** Comparison of the effects of cardiac contractility modulation (CCM)<sup>24–26</sup> and cardiac resynchronization therapy (CRT)<sup>1,30–33</sup> on peak oxygen consumption ( $VO_2$ ) obtained from different clinical trials.<sup>34</sup> Although studied in different populations, one with wide QRS and the other with narrow QRS, as detailed in the original papers, most of the other baseline features are very similar between the groups. With this as a caveat, the impact of CCM on peak  $VO_2$  is comparable with the impact of CRT. Reproduced from reference<sup>34</sup> with permission from Springer.

in patients with a wide QRS duration<sup>1,30–33</sup> (Figure 12).<sup>34</sup> Although QRS durations of the groups are different, examination of the other baseline features of patients enrolled in CRT trials are remarkably similar to those of patients enrolled in CCM trials with regard to NYHA class (predominantly class III), chronic heart failure aetiology (predominantly ischaemic), EF ( $\sim 25\%$ ), peak  $VO_2$  ( $\sim 14.5$  mL/kg/min), and other important baseline factors. With the caveat that patients with CRT have a longer QRS duration, the result of this comparison suggests that the impact of CCM on exercise tolerance as indexed by peak  $VO_2$  is comparable with that of CRT. Early acceptance of CRT was based on demonstration of improved exercise tolerance and quality of life. However, CRT is now more widely accepted because of recent studies showing benefits on survival and heart failure exacerbations.<sup>35,36</sup> Such data are not yet available for CCM but are the focus of a new study that has been initiated in Europe.

## Combining cardiac contractility modulation with cardiac resynchronization therapy

Cardiac contractility modulation signals applied in the acute setting to heart failure patients simultaneously receiving CRT provide additive effects on LV contractility indexed by  $dP/dt_{max}$ .<sup>11</sup> In view

of the fact that symptoms persist in more than ~30% of patients with prolonged QRS duration receiving CRT, it has been postulated that addition of CCM treatment may provide an option for these patients. It should be recognized that the group of patients characterized as 'CRT non-responders' represents a therapeutic challenge, known to have a high rate of hospitalization and mortality. After an initial report of combining CCM in a CRT non-responder demonstrated that the implantation procedure is technically feasible, that the OPTIMIZER and CRT-D devices can co-exist without interference, and that acute haemodynamic and clinical improvements can be observed,<sup>37</sup> a small feasibility study was conducted in 16 CRT non-responders.<sup>38</sup> These patients had a mean EF of  $27.3 \pm 7.4\%$  and NYHA class III ( $n = 9$ ) or IV ( $n = 7$ ) symptoms despite CRT plus OMT. Acute application of CCM signals in these patients increased LV  $dp/dt_{max}$  by an average of 14%. During an average of 5 months follow-up, NYHA class improved from 3.4 to 2.8 ( $P < 0.01$ ) and EF increased from  $27.3 \pm 5$  to  $31.1 \pm 6$  ( $P < 0.01$ ). There were three deaths, which occurred at Days 81, 104, and 318 of treatment. The authors concluded that it is feasible to deliver CCM signals to CRT non-responders when no other options are available. An additional study (the FIX-HF-12 study) is currently underway to collect additional information on this challenging group of patients.

## Summary and conclusions

Cardiac contractility modulation signal delivery enhances contractile strength without acutely increasing myocardial oxygen consumption and, over longer periods, induces reverse ventricular remodelling. The mechanisms of action appear to involve effects on myocardial gene expression (including a reversal of several aspects of the fetal gene programme expressed in heart failure) and protein phosphorylation. CCM does not yet appear in treatment guidelines for heart failure<sup>39</sup> because the long-term effects on mortality and hospitalizations have not been determined. At the present time, the use of CCM is based on evidence showing that exercise tolerance and quality of life are improved. Ongoing studies will define the impact on long-term mortality and heart failure hospitalizations.

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