Transient repolarization instability following the initiation of cardiac resynchronization therapy

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Aims
Cardiac resynchronization therapy (CRT) may cause changes in ventricular repolarization (VR), particularly in the initial phase of treatment. This study investigated the effect of CRT cessation and re-initiation on parameters of VR duration and heterogeneity at different paced heart rates.

Methods
Cardiac resynchronization therapy was inactivated for 2 weeks in 16 treatment responders to CRT. QT and JT intervals were measured on the surface electrocardiogram at 60, 70, and 80 bpm (randomized order) and vectorcardiography (VCG) was performed with CRT ‘on’ (day 0), ‘off’ (day 0, 1, 7, and 14) and after CRT re-initiation (day 14, 15, 16, and 21). On day 0 (‘on’) and 14 (‘off’) echocardiography, the 6 min walking distance and brain natriuretic peptide were assessed.

Results
The QT interval at baseline (CRT ‘on’), measured at 60, 70, and 80 bpm, was 482 ± 31, 468 ± 37, and 457 ± 39 ms, respectively, and decreased by 5, 5, and 6% during the first week following CRT cessation (all P < 0.05). Immediately after re-initiation on day 14, it increased again by 20 ± 18 (4%; P < 0.05), 34 ± 39 (8%; P < 0.01), and 16 ± 38 ms (4%, ns) followed by a gradual decrease towards previous ‘off’ levels. Similar changes were observed for the JT interval. Ventricular repolarization duration was significantly shortened by increasing the paced heart rate from 60 to 70 and 80 bpm. Vectorcardiography parameters reflecting VR gradients (ST-vector magnitude, Tarea, and Tavplan) increased significantly (by 31, 45, and 71%) after CRT cessation. A similar but non-significant pattern was observed after CRT re-initiation.

Conclusion
The increase in repolarization duration and gradients observed after CRT cessation suggests a transient state of VR instability that can be attenuated by programming of higher paced heart rates during the initial phase of treatment.

Keywords
Cardiac resynchronization therapy • Repolarization • Vectorcardiology • Heart rate • Pro-arrhythmia

Introduction
Cardiac resynchronization therapy (CRT), with and without the additional capabilities of an implantable cardiac defibrillator (ICD), has been firmly established to reduce morbidity and mortality in patients with drug-refractory heart failure and ventricular electromechanical dyssynchrony. The beneficial long-term effects of CRT are linked to progressive left ventricular (LV) reverse remodelling 1,2 that has been associated with an overall reduction in ventricular arrhythmic events.3,4 However, the true impact of CRT on the risk of ventricular arrhythmia remains a matter of controversy.5 While, data from extended follow-up in the Cardiac Resynchronization–Heart Failure (CARE-HF) trial suggested that CRT (without ICD) reduces not only mortality related to refractory heart failure but also sudden cardiac death,6 other studies failed to confirm a reduced ventricular arrhythmia incidence during CRT.7–9

In fact, concerns have been raised that CRT might promote the development of ventricular arrhythmia in certain susceptible patients, especially at the onset of therapy.10–14 Possible pro-arrhythmic mechanisms include increased dispersion of global ventricular repolarization (VR) due to a non-physiological activation sequence with simultaneous stimulation from two ventricular sites with different transmural activation times.13,15,16 Accordingly, studies in humans and animals demonstrated that

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biventricular or left-ventricular-epicardial pacing can induce a prolongation of the QT and JT interval as well as increased VR dispersion.\textsuperscript{12,13} Furthermore, case reports highlighted possible pro-arrhythmic effects of CRT resulting in both polymorphic and monomorphic ventricular tachycardia during the initial phase of treatment.\textsuperscript{13,17–19} These observations suggest similarities with the transient pro-arrhythmic state following atrioventricular junction ablation and initiation of right ventricular (RV) pacing in atrial fibrillation (AF) patients, which is prevented by temporary adjustments of the basic pacing rate.\textsuperscript{20}

Therefore, the aim of this study was to assess VR changes following the discontinuation and re-initiation of CRT. We hypothesized that pacing at an increased heart rate might exert a protective effect during the initial phase of treatment.

Methods

This study was performed in a subset of 16 CRT patients with a slow spontaneous heart rate ($\leq$60 bpm at last regular follow-up before inclusion) participating in an ‘on’-‘off’ protocol.\textsuperscript{21} They had been treated with CRT for $\geq$6 months and were considered treatment responders due to an improvement in New York Heart Association (NYHA) functional class and/or an increase in 6 month walking distance by $\geq$10%. The CRT indication was NYHA class III–IV drug-refractory heart failure with an LV ejection fraction (LVEF) $\leq$35% and a QRS duration of $\geq$150 ms. Patients with chronic AF and a slow ventricular response rate could be included. During the month before inclusion, patients had to be clinically stable, and no change in drug treatment was allowed during this period and throughout the study, except for adjustments in diuretics, if necessary. Right ventricular leads had been implanted in apical position and LV leads in a postero-lateral or lateral branch of the coronary sinus tributary. The study was approved by the local ethics committee and all patients provided written informed consent.

Protocol

Patients were studied during three conditions: CRT ‘on-off-on’ (Figure 1) CRT was stopped for 14 days, and the pacemaker was programmed to atrial inhibited mode (AAL, $n=14$), or, in two patients with AF, to the ventricular inhibited mode (VVI) with stimulation from the RV apex only. The basic heart rate and rate-response function had been programmed at the discretion of the treating physician and remained unchanged throughout the study. Electrocardiogram (ECG) and vectorcardiography (VCG) were performed on nine occasions during supine rest. In addition, at day 0, with active CRT (‘on’), and at day 14, after CRT had been switched off for 2 weeks (‘off’) patients were assessed regarding NYHA class, the 6 min walking test, quality of life (QoL) using the Minnesota Living with Heart Failure Questionnaire, plasma levels of brain natriuretic peptide (BNP) and Doppler echocardiography.

Transthoracic Doppler echocardiography (Vingmed System V, Vingmed A/S, Horten, Norway) was performed with a 2.5 MHz transducer. Chamber dimensions were determined from the para-sternal long-axis view and LV ejection fraction (LVEF) was calculated using Simpson’s method. The inter-ventricular mechanical delay (IVMD) and the difference between the time to peak tissue velocities of the septum and the lateral wall ($T_s$ lat-sep) were calculated according to Bax et al.\textsuperscript{22} Analysis was performed off-line as the average of three consecutive beats.

Brain natriuretic peptide samples were obtained in EDTA glass tubes, immediately chilled, and centrifuged at +4°C. The plasma was stored at −70°C until analysis by a specific immuno-radiometric assay (Shionogi, Osaka, Japan).

Electrocardiogram-recording and analysis

Electrocardiograms were recorded at 60, 70, and 80 bpm with a paper speed of 50 mm/s and calibration 1 mV = 10 mm using a 6-channel ink-recorder (Minograph 7, Siemens-Elema AB, Solna, Sweden). Prior to each ECG recording at least 5 min of rest was allowed for heart rate adaptation of VR. The order of heart rates was randomized for each day of the study. Electrocardiograms were analysed by the agreement of two investigators (H.P. and L.B.) who marked the QRS onset and end and the T-end on the ECG paper (‘measure points’). In order to apply consistent criteria for intra-individual analysis, a complete ECG-set (day 0–21) was analysed for each patient. Investigators were unaware of patient identity and the date of examination, but complete blinding was not possible due to the presence of ventricular pacing spikes, indicating whether the patient was in the ‘on’ or ‘off’ mode. Next, the intervals between the ‘measure

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Figure 1 The study protocol. BNP, brain natriuretic peptide; CRT, cardiac resynchronization therapy; 6MWT, 6 min walk test; QoL, assessment of quality of life with the Minnesota Living with Heart Failure Questionnaire (a lower score indicates better QoL). Electriccardiogram and vectorcardiography were recorded each study day.
points' were calculated electronically using a cross-head connected to a digitizer table (Calcomp 2000, Digitizer Product Division, Anaheim, CA, USA) working in point mode (10 lines/mm, accuracy ± 0.635 mm). Three consecutive intervals (or 5 for RR) in each lead were averaged providing a patient mean. The QRS onset was defined by the pacing spike ('on') or the beginning of Q or R ('off'). The T end was defined as the point at which the down sloping limb of the T wave returned to the isoelectric baseline. If U waves were clearly separated from the T waves, T end was defined as at the nadir of the curve between the T and U waves. Otherwise, T end was defined as where a tangent to the steepest down-sloping limb crossed the isoelectric line.\(^{23}\) Leads where the T wave could not be identified were excluded from analysis. The JT interval was calculated as the difference between QT and QRS interval.

**Vectorcardiography**

Vectorcardiography (MIDA 1000 system, Orthivus AB, Danderyd, Sweden) was recorded from eight electrodes positioned according to the Frank orthogonal lead system (X, Y, and Z). Briefly, for each 1 min period an averaged 3-dimensional QRST complex and T vector loop were created, and from the latter the direction of the maximum QRS and T vectors were determined. Analysis of the ST vector magnitude (ST-VM), the T vector and T loop morphology was performed off-line by one operator (A.R.) as detailed elsewhere.\(^{24,25}\) ST-vector magnitude expresses the VM of the ST loop, which is normally oriented in one individual preferential plane, was characterized by Tavplan, and Teigenvalue. Tavplan expresses the bulginess of the T loop defined as its mean distance from the preferential plane. Teigenvalue reflects the symmetry of the T loop being the quotient between the two highest eigenvalues (approximately the largest perpendicular diameters in the preferential plane) of the matrix of inertia \(\delta \frac{d^2}{d^2}\). A perfect circle has Teigenvalue = 1 (abnormal); the more elliptical ('healthier'), the higher the Teigenvalue. For illustrations see Sahlen et al.\(^{25}\) In addition, Tarea was calculated as the '3-dimensional' area under the curve from the J point to T end in X, Y, and Z leads, \((T_x^2 + T_y^2 + T_z^2)^\frac{1}{2}\).

**Statistical methods**

Mean and standard deviations (SD) or median (with 25th and 75th percentiles) were used for descriptive statistics. QT and JT intervals are displayed together with their 95% confidence intervals (CI). The data distribution was tested by Shapiro–Wilk's W test. For comparison of the data between two different pacing modes (CI). The data distribution was tested by Shapiro–Wilk’s W test. Repeated measures analysis of variance (ANOVA) with Greenhouse–Geisser epsilon correction, or the Friedman two-way ANOVA by ranks were used to test the effects of CRT inactivation (between day 0 ‘on’ and day 14 ‘off’) and CRT re-initiation (between day 14 ‘off’ and day 21 ‘on’). A P value <0.05 was considered statistically significant. All analyses were performed using the program Statistica for Windows, version 6.0 (StatSoft, Tulsa, OK, USA).

**Results**

Patient characteristics are presented in Table 1 and changes from ‘on’ to ‘off’ in Table 2. During the ‘off’ period, four patients reported symptoms consistent with deterioration by one NYHA class. However, there were no signs of overt cardiac decompensation and body weight remained stable. Baseline BNP was elevated in all subjects, (range 38–285 nmol/L; normal <22 nmol/L) and increased significantly by 42% during ‘off’. Quality of life and walking distance decreased after 14 days in the ‘off’-state. The left atrial end-systolic diameter, left ventricular end-diastolic

<table>
<thead>
<tr>
<th>Table 1 Patient characteristics</th>
</tr>
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<tbody>
<tr>
<td>Number</td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td>Age (years)</td>
</tr>
<tr>
<td>Ischaemic/dilated cardiomyopathy</td>
</tr>
<tr>
<td>CRT duration (month)</td>
</tr>
<tr>
<td>Rhythm (sinus/atrial fibrillation)</td>
</tr>
<tr>
<td>Medication</td>
</tr>
<tr>
<td>ACE inhibitor/ARB</td>
</tr>
<tr>
<td>Betablocker</td>
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<tr>
<td>Spironolactone</td>
</tr>
<tr>
<td>Digoxin</td>
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<tr>
<td>Furosemide</td>
</tr>
<tr>
<td>Warfarin</td>
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<tr>
<td>Amiodarone</td>
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</tbody>
</table>

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker.

<table>
<thead>
<tr>
<th>Table 2 Clinical results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 0 (on)</td>
</tr>
<tr>
<td>NYHA class</td>
</tr>
<tr>
<td>Quality of life (score)*</td>
</tr>
<tr>
<td>6 min walk test (m)</td>
</tr>
<tr>
<td>Body weight (kg)</td>
</tr>
<tr>
<td>BNP (ng/L)</td>
</tr>
<tr>
<td>LVEDD (mm)</td>
</tr>
<tr>
<td>LVESD (mm)</td>
</tr>
<tr>
<td>LVEF (%)</td>
</tr>
<tr>
<td>IVMD (ms)</td>
</tr>
<tr>
<td>TS (lat-sep) (ms)</td>
</tr>
</tbody>
</table>

BNP, brain natriuretic peptide; LVEDD and LVESD, left ventricular end-diastolic and -systolic diameter; LVEF, left ventricular ejection fraction; IVMD, inter-ventricular mechanical delay; TS (lat-sep). Difference between time to maximum systolic tissue velocity measured in the septum and lateral left ventricular wall.

* A higher score means worse quality of life.
diameter, and left ventricular end-systolic diameter increased significantly from ‘on’ to ‘off’ while LVEF remained unchanged. No complex ventricular arrhythmia was observed clinically, during ECG recording or by interrogation of the pacemaker memory.

Electrocardiogram analysis

Left bundle branch block, left anterior fascicular block and other conduction abnormalities were present in 10, 3, and 3 patients, respectively, and the mean QRS duration with vs. without CRT was 174 ± 18 and 162 ± 34 ms (ns). The average QT interval, measured at 60 bpm with CRT ‘on’ (day 0), was 482 ± 31 ms (range 423–526) and 463 ± 43 ms (range 385–525) with CRT ‘off’ (day 14; \( P < 0.05 \)).

Figure 2 shows the mean QT intervals at different pacing rates together with the 95% CI. The QT interval decreased significantly after cessation of CRT (day 0 vs. day 7) without further decrease beyond day 7. After CRT re-initiation at day 14, the QT interval showed an immediate increase from 463 ± 43 ms (range 385–525) to 482 ± 48 ms (range 429–538) at 60 bpm, from 443 ± 43 ms (range 344–505) to 478 ± 36 ms (range 418–541) at 70 bpm, and from 439 ± 46 ms (range 335–497) to 455 ± 29 ms (range 403–498) at 80 bpm. The corresponding percentage increase of
this instant VR prolongation upon CRT re-initiation was 4, 8, and 4%, respectively, and statistically significant at 60 and 70 bpm. It was followed by a plateau at 60 bpm and a gradual decline up to day 21 at 70 and 80 bpm. Repeated measures ANOVA during the period of CRT re-initiation between day 14 'off' and day 21 confirmed statistically significant changes of the QT interval at 60 and 70 bpm. The pattern of QT changes at 80 bpm was similar to 70 bpm albeit attenuated (ns).

Similarly, the JT interval (Figure 3) decreased during the first week off CRT with the largest fall occurring between day 1 and day 7 (significant at 60 and 70 bpm). On day 14, the initiation of CRT was associated with an immediate increase of the JT interval from 301 ± 33 (range 244–348) to 320 ± 33 ms (range 258–360) at 60 bpm, from 285 ± 34 (range 210–336) to 304 ± 33 ms (range 258–325) at 80 bpm. The corresponding percentage increase was 6, 7, and 5%. This immediate prolongation was statistically significant at 60 and 70 bpm and was followed by a gradual shortening during the first week of treatment. Again, this marked JT increase after re-initiation was followed by a gradual decline up to day 21 with significant changes in the repeated measures ANOVA at 60 and 70 bpm but with an attenuated trend at 80 bpm.

As expected, increasing the pacing rate from 60 to 70 bpm or from 70 to 80 bpm was associated with a highly significant decrease in the QT and JT intervals (both P < 0.0001 repeated measures ANOVA covering the entire study period).

All the above observations were confirmed when the analysis was rerun without the two patients with permanent AF and chronic RV pacing. In particular, the described acute and intermediate changes of the QT and JT interval after CRT re-initiation remained statistically significant at 60 and 70 bpm.

**Vectorcardiography**

On day 0 the switch from CRT ‘on’ to ‘off’ created significant increases in ST-vector magnitude, Tarea, and Tavplan by 31, 45, and 71%, respectively, reflecting increased VR gradients. In contrast, the abnormal T vector angles and the QRS-T angle remained unchanged (Table 3, Figures 4 and 5). These VR changes returned almost completely to baseline (day 0) levels within one week.

### Table 3 Results from vectorcardiography analysis

<table>
<thead>
<tr>
<th>Parameter</th>
<th>0 on</th>
<th>0 off</th>
<th>1 off</th>
<th>7 off</th>
<th>14 off</th>
<th>14 on</th>
<th>15 on</th>
<th>16 on</th>
<th>21 on</th>
</tr>
</thead>
<tbody>
<tr>
<td>ST-VM (µV)</td>
<td>233</td>
<td>306</td>
<td>291</td>
<td>246</td>
<td>247</td>
<td>239</td>
<td>222</td>
<td>213</td>
<td>219</td>
</tr>
<tr>
<td>T elevation (°)</td>
<td>84</td>
<td>80</td>
<td>81</td>
<td>84</td>
<td>94</td>
<td>93</td>
<td>96</td>
<td>92</td>
<td>82</td>
</tr>
<tr>
<td>Tazimuth (°)</td>
<td>93</td>
<td>72</td>
<td>71</td>
<td>75</td>
<td>71</td>
<td>38</td>
<td>25</td>
<td>67</td>
<td>90</td>
</tr>
<tr>
<td>QRS-T angle (°)</td>
<td>146</td>
<td>157</td>
<td>152</td>
<td>155</td>
<td>154</td>
<td>142</td>
<td>147</td>
<td>144</td>
<td>129</td>
</tr>
<tr>
<td>Tarea (µV)</td>
<td>78</td>
<td>113</td>
<td>97</td>
<td>81</td>
<td>79</td>
<td>92</td>
<td>86</td>
<td>81</td>
<td>73</td>
</tr>
<tr>
<td>Tavplan (µV)</td>
<td>0.7</td>
<td>1.2</td>
<td>1.0</td>
<td>0.6</td>
<td>0.7</td>
<td>0.9</td>
<td>0.8</td>
<td>0.7</td>
<td>0.5</td>
</tr>
<tr>
<td>Tmean (unitless)</td>
<td>11</td>
<td>8</td>
<td>10</td>
<td>5</td>
<td>11</td>
<td>15</td>
<td>8</td>
<td>12</td>
<td>10</td>
</tr>
</tbody>
</table>

Values are: mean ± SD or median [25th and 75th percentile].

Significant difference compared with the day 0 ‘on’: **P < 0.05. ***P < 0.01. ****P < 0.001.

Significant difference compared with the day 14 ‘off’: *P < 0.05. **P < 0.01. ***P < 0.001.
Discussion

The main findings of this study suggest that (re-)initiation as well as the abrupt cessation of CRT is associated with significant VR alterations. First, VR duration described by the QT and JT intervals, increased when switching CRT on (Figures 2 and 3). Secondly, VR changes were transient in nature, most prominent during the first day and levelled out after 1 week. Thirdly, increasing the paced heart rate alleviated the CRT-induced transient VR prolongation. Finally, VR heterogeneity measured by VCG increased in particular when switching CRT off (Figures 4 and 5).

Heart failure patients are generally at increased risk for ventricular arrhythmias based on both re-entrant and focal mechanisms due to the presence of arrhythmia substrates related to the underlying structural disease, increased wall stress, neurohumoral activation, and other factors. This risk may further increase in the presence of additional triggers. Our results suggest that CRT initiation potentially induces a mild pro-arrhythmic effect. The VR prolongation in this study was ≈7% (JT interval at 70 bpm, day 14 ‘off’ to ‘on’), which is in accordance with previous reports in CRT patients and after ablate and pace (20) but probably not enough to be clinically relevant in most patients. However, it is conceivable that this effect may be more pronounced and become clinically important in certain individuals with a reduced repolarization reserve.

Patients entering the study protocol were treatment responders to CRT, clinically stable and had probably developed some degree of reverse remodelling after CRT implantation, performed on average 16 months before. Presumably, this contributed to decrease the degree of observed VR instability that may be larger in the clinical scenario of de novo device implantation and CRT initiation in patients with less controlled heart failure. In fact, experimental observations as recently summarized by Kass, suggest that CRT not only improves mechanical function but also reduces the arrhythmogenic state. In animal studies it has been shown that the altered regional expression and function of ionic currents and calcium transients is partially restored by CRT especially in the lateral wall of the left ventricle thus reducing the regional action potential duration gradient and the frequency of potentially arrhythmogenic early depolarizations.

Focusing on the VR response and its rate dependence during CRT on-off-on, our study was neither designed nor powered to document the incidence of ventricular arrhythmia potentially resulting from the induced VR instability. However, the findings corroborate previous reports indicating that CRT-associated VR abnormalities may cause malignant arrhythmia in some patients, especially in the initial phase of treatment. Our results are also consistent with observations following changes in the ventricular activation pattern after ‘ablate and pace’ in AF patients, and seem to reflect a general VR instability during ~1 week after a maintained change in ventricular activation. This has also been observed during RV pacing-induced cardiac memory in sick sinus syndrome patients and after ablation in patients with Wolff–Parkinson–White syndrome.

Detailed VCG analysis revealed significant changes in ST-vector magnitude, Tarea and Tavplan in particular following the cessation of CRT. Increased Tarea and Tavplan have been associated with VR heterogeneity according to computer simulations and studies on acute ischaemia in humans. Moreover, increased Tavplan has been related to the occurrence of ventricular fibrillation in pigs. In the present patients with a severely diseased intraventricular conduction, T vector angles and the QRS-T angle were abnormal at baseline and minimally affected by switching CRT from ‘on’ to ‘off’ which is in contrast to observations from cardiac memory development in sick sinus syndrome patients with structural normal hearts. Recently, Padeletti et al. described changes in Tmagnitude by CRT that were similar to our findings on Tarea while the CRT effect on Tazimuth and Televariation differs between the studies. Possible explanations for this disparity include differences in study design, individual variations of the 3-dimensional repolarization pattern due to differences in the type and severity of intra-ventricular conduction disturbances and the occurrence of functional block, the localization and size of myocardial scars and the implantation site of pacing leads.

While the clinical impact of VCG abnormalities remains to be established, QT prolongation is linked to an increased propensity for polymorphic arrhythmias of the torsades de pointes type. Previous studies have described CRT-induced VR changes also by means of QT dispersion or transmural dispersion of repolarization (T-top-end). However, QT dispersion mainly reflects variations in T-loop morphology which we directly assessed by VCG. Importantly, measurements of QT dispersion are significantly less reliable than those of the QT interval and this may be particularly true in patients with severe heart failure. In fact, similar to the experience of other authors, reliable analysis of T-top-end was not feasible owing to the frequent occurrence of flat, bifasic or bifurcated T-waves during biventricular stimulation. Previous observations support that changes in Tpeak-end correspond to those in Tamplitude or Tarea, which is provided in this study.

Importantly, our study shows that the potential pro-arrhythmic phase seems to be transient and present during the first days of treatment. However, in the rare event of an LV lead failure or extraction, a similar unstable situation might arise upon abrupt cessation of CRT. Moreover, our study confirms that pacing at higher heart rates after altered ventricular activation has beneficial effects with regard to VR abnormalities also during CRT therapy. Therefore, it may be considered to programme a high heart rate (80 bpm) during the initial phase of CRT in order to minimize the pro-arrhythmia risk. Even if the actual risk for CRT induced malignant arrhythmia is low (just as after ‘ablate and pace’), a temporary heart rate increase could be a simple measure to further improve treatment safety. However, while acute programming of increased heart rates may improve haemodynamics in CRT patients, the longer-term effect of elevated paced heart rate settings warrants further study. A significant number of CRT patients, in particular among the elderly, is implanted with CRT-alone devices and, thus, not protected against life-threatening arrhythmia by an ICD. Furthermore, in patients with a CRT-ICD device the reduction of unnecessary ICD-shocks is an important therapy goal.

In this group of intentionally selected responders to CRT, treatment cessation was associated with marked changes in clinical, mechanical, and neurohormonal parameters. After 2 weeks with CRT ‘off’, walking distance and QoL had deteriorated and atrial
and ventricular diameters increased. This was associated with a significant increase in BNP, a marker of volume load, and wall stretch. Although not evaluated in our protocol, it is likely that these alterations were reversed upon re-initiation of CRT. Thus, it is conceivable that CRT-mediated positive effects on mechanical function in responders contribute to attenuate the negative consequences of CRT-induced VR instability observed during the first days of treatment.

Our study is limited by the small sample size. However, it was sufficient to show significant changes in VR parameters that occurred in a largely uniform pattern among the individual study patients. The presence of myocardial scar may significantly contribute to VR inhomogeneities but our study lacks power for subgroup analysis of ischaemic vs. non-ischaemic patients.

Analysis of the QT interval might have been affected by the determination of the first measure point at either the pacing spike or the onset of QRS during CRT ‘on’ and ‘off’, respectively. However, we obtained similar findings for the JT interval indicating that the definition of QRS onset had no major impact on the results.

**Conclusion**

Cardiac resynchronization therapy initiation is associated with a transient state of VR instability as suggested by an increase in VR duration and heterogeneity. This finding corresponds well to previous reports of polymorphic ventricular tachycardia after initiation of CRT treatment. The adverse effect of CRT on the QT and JT interval was attenuated by increasing the paced heart rate that may be considered during the first few days post-implantation to reduce the risk of pro-arrhythmia.

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