

The quest for improvement of cardiac resynchronization therapy

Ph.D thesis

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Introduction

Since two decades of the clinical application, cardiac resynchronization therapy (CRT) has revolutionized the care of patients with heart failure and dyssynchrony. It also strengthened the cooperation among different field of cardiology, including electrophysiology, heart failure and cardiac imaging.

Today, CRT is a well-established therapeutic strategy for patients with advanced congestive heart failure (HF) and prolonged QRS complex. It has been shown to improve cardiac pump function, HF symptoms and quality of life. CRT significantly reduces mortality and morbidity in this population, but despite its proven clinical value, a minority of patients do not derive benefit from CRT; termed “non-responders.” The ratio of non-responders ranges from 30-50%.

Reasons for non-response are likely multifactorial. Part of the explanation may be the absence of significant dyssynchrony prior to treatment, ineffective resynchronization due to suboptimal device programming or lead placement. Furthermore, implantation of biventricular devices and multiple leads mean considerable costs to the health-care system, therefore the best possible application and patient selection is essential from the human and financial point of view.

Successful CRT can be fostered by the following factors: improved patient selection, optimal lead positioning, therapy optimization, and multidisciplinary postoperative care.

Our intention was to investigate the complex process from patient selection to post-operative care and contribute to improved care with the following projects:

Atrioventricular dyssynchrony resulting impaired left ventricular filling is common in patients with wide QRS complex on ECG, and especially in the setting of concomitant prolonged PR interval with AV block I. Mechanically, correction of the prolonged PR interval by CRT pacing should have a positive effect

on ventricular filling in diastole “on top of“ the resynchronization of ventricular contraction during systole. On the other hand, a prolonged PR interval can also be a marker of more advanced heart disease and therefore associated with a poor prognosis. There is conflicting evidence regarding the clinical outcomes in CRT for patients with prolonged PR interval.

QRS duration and morphology reflect the electrical timing and activation sequence of the ventricles, hence it is plausible to evaluate the effect of CRT using pacing-induced changes in ECG findings, since reversal of the electrical pathology indicates a potentially good effect of the treatment. Moreover, an easy to use ECG-based algorithm for optimization of pacemaker lead placement and immediate prediction of response and clinical outcome could be a valuable tool.

We hypothesized that the T-wave may provide additional information, since it is reflective of the plateau and repolarization phases of the myocardial action potential. For more comprehensive analysis of the T-wave, ECG signals were converted into vectorcardiograms (VCG), that contains three-dimensional information of the electrical forces within the heart and might provide more valuable information than the one-dimensional ECG.

Hyponatremia and hypothyroidism are common abnormalities, seen in patients with HF and has been particularly demonstrated to be of prognostic factors in HF population. However, there are limited data looking at how serum sodium and TSH levels impact patients who receive CRT.

For effective clinical management of heart failure patients living with CRT, early risk-stratification to identify potential non-response, and also finding simple and reliable method to evaluate the functional status is important. Although 6-minute walk test (6MWD) and cardiopulmonary exercise testing (CPX) have been shown to provide prognostic information for all-cause hospitalization and mortality in HF population, they have significant limitations both logistically and in their reproducibility. The activity information can be acquired on a daily basis over

prolonged periods of time, with most contemporary devices. There are limited data examining the relationship of device-based physical activity measures and clinical response to CRT.

Despite of the continuous technical developments in the last few years, implantation of a CRT system may be challenging. The success rate of coronary sinus (CS) lead positioning is 88-96%. During follow-up, 5-10 % of patients require re-operation because of CS lead dysfunction.

Stent implantation, which anchors the CS electrode to the wall of the coronary sinus side branch, may increase the stability of the lead.

Objectives

- To assess the relationship between PR interval duration and outcomes in patients undergoing CRT;
- To search for novel predictors based on 12-lead ECG, registered before and after biventricular pacing. Our aim was to establish a simple score for early risk stratification and therapy optimization;
- To compare the different depolarization and repolarization parameters to the established ECG predictor of QRS duration, based on vectorcardiographic analyses, and investigate the potential predictive values of these repolarization parameters within different QRS morphologies, in terms of therapy response and long-term clinical outcome;
- To examine the effect of pre- and postoperative hyponatremia on HF patients receiving CRT, and the influence of CRT on this electrolyte abnormality and consequently clinical outcomes;
- To determine how hypothyroidism in patients with HF impacted response to CRT;
- To investigate the prognostic value of device-measured physical activity data as compared to a one-time 6MWT in predicting clinical response to CRT;
- To observe the effectiveness, safety and long-term outcome of stent implantation to anchor the lead to the wall of the CS side branch.

Methods

Study population

The CRT patient register of the Massachusetts General Hospital (MGH) consisted of 569 consecutive cases, who underwent CRT implantation, between 2004 and 2010. The patients were prospectively followed according to a standardized protocol in a multidisciplinary clinic, including evaluation by electrophysiologists, heart failure specialists and echocardiography imaging specialists. Clinical events including heart failure hospitalizations, heart transplantation, left ventricular assist devices (LVAD) and mortality were recorded and crosschecked with the social security death index. Transthoracic echocardiography was performed in a standardized manner. For assessment of left ventricular ejection fraction Simpson's biplane method of disks was applied. CRT response was defined as at least 10% improvement of LVEF at the six-month follow-up, compared to baseline (echo-responders). Novel predictors of CRT were investigated on this patient population.

ECG registration: Before CRT implantation and during follow-up visits, supine 12-lead ECGs were recorded and stored digitally as PDF files.

The PR intervals were measured automatically by the ECG machine and subsequently verified manually. Based on the intrinsic PR interval measurements, patients were divided into two cohorts: <200 ms and ≥ 200 ms, in accordance with previous studies.

The measurements on the ECGs were made with CardioCaliper 3.3. The predetermined ECG score was based on the standard 12-lead ECG, and included three parameters, on which one point was assigned

- for a reduction of QRS width of at least 20ms compared from baseline ECG to post-implant ECG;

- for a reduction of at least 50% in the summed amplitude of R+S in lead V1 from baseline ECG to post-implant ECG;
- if the intrinsicoid deflection (ID) point was identified within the first 40ms from QRS onset at the follow-up ECG in the V1 lead.

VCG analysis: The digital ECG signals were semi-automatically analysed using a custom-made computer program written in MATLAB. The **QRS and T area** were the 'three-dimensional' area between the curve and the baseline from the beginning to end of the wave.

Laboratory values for **serum sodium** were collected at baseline which was defined as 72 hours prior to device implantation and at follow-up during their at 3-6 month visit. Hyponatremia was defined as sodium level <135 mEq/litre.

Hypothyroidism was defined by clinical history obtained by reviewing electronic medical record, treatment with thyroid hormone repletion and serum TSH around the time of device implantation. Reference range for TSH was 0.40-5.00 $\mu\text{U/mL}$.

Device-based physical activity data was obtained through device interrogations during follow-up visits. Diagnostic data from devices of 2 different companies (Medtronic & St. Jude Medical) were used for this analysis, which implanted devices measure activity by an accelerometer.

Coronary sinus stenting has been performed since 2004 in Heart and Vascular Center, Semmelweis University, in selected patients. Stent fixation of the CS lead was indicated in cases of (1) postoperative dislocation, (2) when intraoperative macroscopic or microscopic dislocation occurred and (3) there was no other suitable vein accessible or when phrenic nerve stimulation (PNS) was observed in a stable anatomical position in the distal part of the side-branch necessitating the lead to be fixed in a more proximal part of the target vein, where instability was present.

Statistical analysis was performed with IBM SPSS statistics software version 21. Continuous and discrete variables are presented as mean±standard deviation (SD) and counts (percentages), respectively. Comparison between different patient groups was performed using either one-way ANOVA (continuous variables) or the χ^2 test (discrete variables). The classification performance of the examined parameters in identifying CRT response was evaluated by odds ratios (OR) calculated using logistic regression models. The Kaplan-Meier estimator of survival function was used to evaluate the associations between variables and reaching the primary or secondary endpoints. The log-rank test was used to determine probability values. The predictive performance of parameters in predicting CRT response was evaluated by the Cox proportional hazard regression analyses and tested using the Wald-test. The Cox regression models were fitted for covariates ($p < 0.10$), where a backward stepwise selection approach was used. A two-sided p-value < 0.05 was considered statistically significant.

Results

PR interval

Patients with normal PR interval ($< 200\text{ms}$) were more likely to experience an improvement in symptoms (improvement of ≥ 1 NYHA class) at the 6-month follow-up visit, compared to patients with PR interval ≥ 200 ms (104 [70.2%] vs. 86 [51.2%], respectively, $p=0.007$). There were no significant differences in cardiac dimensions and LVEF between the groups prior to CRT implant. However, patients with prolonged PR interval had a smaller average improvement in LVEF, and were less likely to be echo-responders of LVEF (64% vs. 77%, OR 0.6 CI 0.3-1.0, $p=0.06$). Kaplan-Meier analysis showed worse clinical outcomes in the group with prolonged PR interval (log rank test $p=0.040$). In univariate analysis prolonged PR interval (dichotomized) (hazard ratio, HR 1.49; 95% confidence interval, CI 1.02-2.17; $p=0.041$), female gender (HR 0.69; 95% CI 0.49-0.96; $p=0.041$), ischaemic cardiomyopathy, and right bundle branch block (RBBB) on ECG were associated with the primary endpoint. However, in multivariate analysis only ischaemic cardiomyopathy remained as a statistically significant predictor of poor prognosis (HR 1.64; 95% CI 1.07-2.53; $p=0.024$).

ECG score

At least 20 msec narrowing was observed in 163 (37%) cases. The patients with at least 20 msec reduction in QRS duration had a lower risk of experiencing the composite endpoint; HR 0.66 ([0.48-0.90] $p=0.009$), and they were more likely to have significant reverse remodeling on echo; odds ratio (OR) 2.90 [1.8-4.7], $p<0.001$). The summed amplitude in V1 lead decreased in 309 cases (71%) and the magnitude was less than 50% of the baseline value in 194 cases (45%). The patients in this group were more likely to have left bundle branch block (LBBB) morphology (56%

vs. 43%, $p=0.007$), but no other significant differences were noted between the two groups. Decrease in summed amplitude in V1 was associated with a hazard ratio (HR) of 0.67 ([0.49-0.90], $p=0.09$) for reaching the primary endpoint, and an OR of 1.3 ([0.85-2.1], $p=0.21$) for LV remodeling on echocardiography. In 167 (34%) patients the time to ID onset was ≤ 40 msec, and this was associated with a HR of 0.62 ([0.46-0.86] $p=0.004$) for reaching the primary endpoint. The corresponding odds ratio for significant LV remodeling was 1.6 ([1.03-2.5] $p=0.04$). In survival analysis increasing total score was associated with a reduced risk for the combined primary endpoint (*Figure 1*).

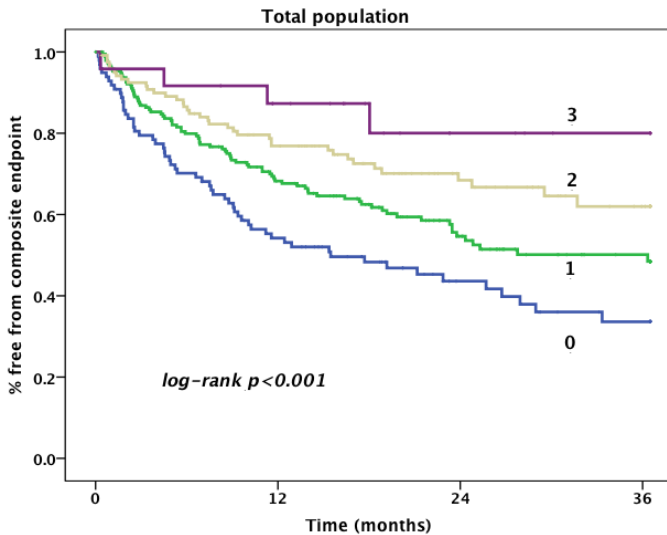


Figure 1. Kaplan-Meier curves of event free survival regarding composite endpoint, according to ECG score subgroups.

The three individual components were to varying degrees associated with LBBB-morphology on ECG, and as a post hoc test the score was therefore applied to this ECG-homogenous, specific group of patients, as well as the remaining group of patient with non-LBBB. The adjusted hazard ratio for the combined score for

prediction of the primary endpoint in the LBBB group was 0.62 ([0.46-0.84] p=0.002).

T-wave area

Logistic regression models indicated VCG-derived repolarization variables as good predictors of CRT response. An increase in T-vector amplitude or T-wave area was associated with a greater probability of $\geq 10\%$ points increase in LVEF. Prediction of LVEF increase by the T-vector amplitude and T-wave area (1.127 [1.062-1.207] p<0.001) was even stronger than by the QRS-vector amplitude (1.068 [1.015-1.124] p=0.011) or QRS area (1.094 [1.030-1.149] p= 0.003).

As expected, non-LBBB patients were more frequently non-responders than responders. Non-LBBB patients also had fairly small T-wave area and QRS area. In the LBBB group most patients were responders and T-wave area and QRS area were larger than in the non-LBBB group (Figure 2.).

In order to investigate whether T-wave area had a predictive value complementary to LBBB, the LBBB and non-LBBB patient groups were subdivided in subgroups with a baseline T-wave area $<$ or \geq the median.

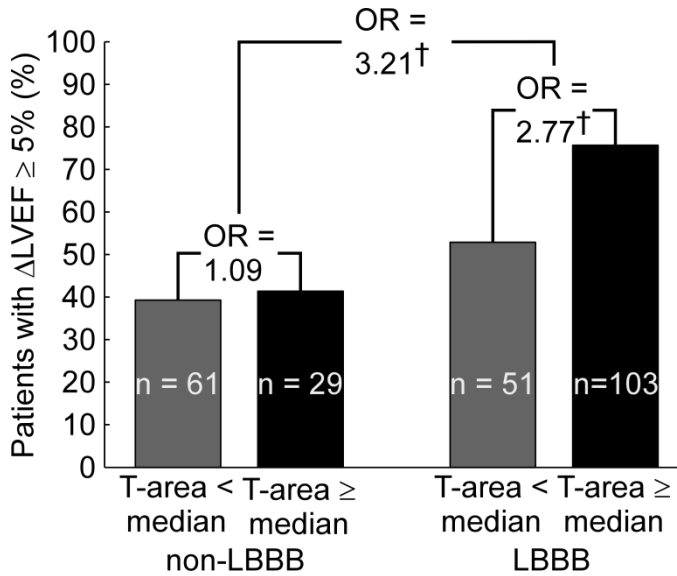


Figure 2. The percentage of echocardiographic responders in LBBB and non-LBBB QRS morphology. The ORs between the two QRS morphologies and between small and large T-wave areas are indicated. [†]p<0.01.

Patients with QRS-, T-, and sum QRST areas \geq than their median values all reached the long-term hard clinical endpoint significantly less frequently than patients with areas < the median values.

The subgroup of patients with LBBB and a large T-wave area had a significantly lower incidence of reaching the composite (HF hospitalization, cardiac transplantation, LVAD implantation, death, HTLD) endpoint (36%) compared to the LBBB patients with a small T-wave area (48%, p=0.01) as well as the non-LBBB patient groups (p<0.01). T-wave area did not significantly affect HTLD in the non-LBBB patients (57% for a small T-wave area vs. 51% for a larger T-wave area, p=0.65). The multivariate model indicated that patients with a large T-wave area had a 44% lower risk of reaching HTLD compared to those with a small T-wave area. Additionally, within LBBB patients the hazard ratio for HTLD between a T-

wave area \geq or $<$ the median value was 0.54, a ratio that remained significant after adjustment for significant covariates (HR=0.48, p=0.01)

Hyponatremia

Of 569 patients, a total of 402 patients with available serum sodium levels within the defined time period were included, out of them 88 had hyponatremia at baseline.

Hyponatremic patients were significantly younger than normonatremic patients. They also were more likely to have history of diabetes mellitus and had significant difference in baseline serum creatinine.

In univariate Cox proportional hazard model for predictors of primary end-point, hyponatremia, creatinine and diuretics were associated with clinical outcome. In a multivariate model, creatinine [HR 1.40 95% CI (1.238-1.595), $p < 0.001$] and diuretics [HR 3.916 95%CI (1.791-8.694, $p = 0.001$) continued to remain significantly associated with composite endpoint.

We also analyzed the data in regard to follow-up serum sodium levels after CRT implantation. Out of 88 patients with baseline hyponatremia, serum sodium level normalized in 37 cases. Kaplan-Meier curve (*Figure 3*) in regards to event free survival showed that patients who were initially hyponatremic but had normalized serum sodium levels (2) post-device implantation also had better long-term outcome. Interestingly, patients who had normal serum sodium levels before device but developed low serum sodium levels later (4) performed as poorly as patients who consistently remained hyponatremic.

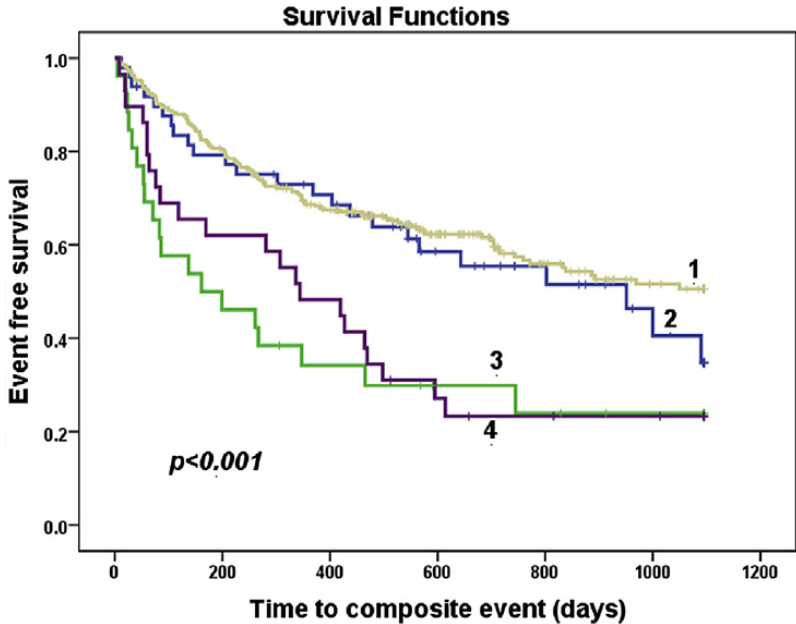


Figure 3. Kaplan-Meier curve showing occurrence of adverse events in different patient groups.

Hypothyroidism

Of 511 patients who met study criteria, 84 had a history of hypothyroidism prior to CRT placement.

Univariate predictors of the composite outcome with $p < 0.10$ (female gender, hypothyroidism, creatinine, diabetes mellitus, digoxin and angiotensin converting enzyme inhibitors use) were considered for multivariate analysis which demonstrated that creatinine, female gender and hypothyroidism were significantly associated with the composite outcome. Kaplan-Meier curve for event free survival showed that patients with history of hypothyroidism had a significantly higher incidence of the composite endpoint as compared to euthyroid patients ($p=0.019$).

Device measured physical activity

Significant differences in device measured activity levels were seen for the summarized data between visits. Specifically, there was increase in median activity at 3- (168 (96-237) min/day, $p=0.001$) & 6-months (162 (87-237) min/day ($p=0.011$)) when compared to 1 month (135 (72-210) min/day) in the entire cohort. Significant correlation between 6MWT and device based physical activity data was observed at each visits. The correlation between summarized device diagnostic activity data and 6MWT was observed at 1 month ($R=0.407$, $p<0.01$), at 3 months ($R=0.358$, $p<0.01$), and at 6 months visit ($R=0.392$, $p<0.01$).

To assess the predictive value of the device based physical activity and 6MWT data we substratified the patients into tertiles. Patients with higher levels of device-based activity had a better event free survival with respect to time to first HF hospitalization compared to the lowest tertile ($p=0.004$) by log-rank test, similarly to composite outcome ($p<0.001$). In adjusted multivariate Cox-proportional hazard modeling, device-based physical activity at 1- and 3- months remained a significant predictor of HF hospitalization. In a model predicting composite outcome, physical activity was a predictor, regardless of baseline creatinine level.

Echo response was lower in lowest tertile vs. the highest tertile of device based physical activity at 1 month (20 % vs. 45%, $p=0.005$), respectively. An additional hour of higher activity at 1 month translated to 1.38 times (95% CI: 1.075-1.753, $p=0.011$) higher likelihood of improved echocardiographic response.

The coronary sinus side branch stenting

Coronary sinus side branch stenting was successfully performed in 312 of 317 patients (98.4%). No implantation related death occurred in our patient group. Mechanical injury caused by CS stenting was not experienced. During implantation coronary sinus dissection with pericardial tamponade was detected in one patient. Compared with the values measured after the implantation, the LV

pacing threshold did not change significantly either after 6 months (1.0 [0.6-1.6] V vs. 0.8 [0.6-1.3] V, $p=0.052$) or after 24 months follow-up (0.8 [0.6-1.6] V vs. 0.8 [0.6-1.5] V, $p=0.419$). A clinically remarkable rise in pacing threshold was observed in two cases (0.6%). Macroscopic dislocation was not detected on X-ray in these four patients. Phrenic nerve stimulation was observed in 18 patients (5.7%). In 11 cases reprogramming of pacing parameters was successful to terminate PNS. In 7 cases (2.2%) repositioning of the lead was necessary. The stented LV leads were retracted with an ablation catheter introduced via the femoral vein in all patients 1-28 months after implantation. In 5 cases suitable pacing threshold was reached, while in one patient the threshold increased to 5.0 V@1 ms. In another patient the CS lead dislocated into the right atrium, it was explanted and a new lead was implanted. PNS was not detected after repositioning.

Explantation of the stented LV lead was needed in three patients because of pocket infection ($n=2$) and endocarditis ($n=1$) after 3, 49 and 18 months. Leads were extracted without any complication while the stent remained in the CS side branch.

Conclusions

Cardiac resynchronization therapy is a highly effective treatment of heart failure patients with conduction abnormalities. In the quest for improvement of CRT, I have been devoted to observe and analyse the complex process of pre- and postoperative care of this patient group.

Our results has shown, that patients with LBBB morphology of the QRS complex, a larger baseline T-wave area is an important independent predictor of LVEF increase following CRT.

A vectorcardiographically derived T-wave area assessed before the start of CRT was able to strengthen the prediction of long-term clinical outcome in a CRT patient cohort, especially in patients with LBBB morphology on the ECG. The combined analysis of QRS morphology and T-wave provides an easy and widely applicable approach to improve **selection of CRT candidates**.

Prolongation of the pre-implant PR interval in CRT recipients is associated with a higher risk of heart failure hospitalization or death, even in the presence of individual echo-guided AV optimization post-implant. The a priori increased risk for patients with prolonged PR interval, is not compensated by the positive effect of CRT on restoring AV synchrony, and the clinical prognosis remains worse than for patients with normal PR interval. These findings should be taken into account when addressing risk stratification in patients with heart failure scheduled for CRT, especially for those with non-LBBB morphology on ECG.

Ready-at-hand data from a simple 12-lead ECG can predict the remodeling effect and long-term clinical prognosis after CRT-treatment. The proposed ECG score may be a valuable added tool in the early evaluation and risk assessment during and after CRT implant, but will need further validation in prospective trials. It also can contribute to **personalized lead positioning**.

Coronary sinus side branch stenting to **stabilize CS lead position** seems to be an effective and safe procedure. Using this technique,

the electrode can be fixed in an anatomically unstable but electrically appropriate position, such that the frequency of lead dislocations, phrenic nerve stimulation, and reoperations may be decreased. In our practice stented CS leads were transvenously explantable in all patients when necessary. We endorse CS stent implantation in cases of postoperative or intraoperative lead dislocation or if the electrode position is not stable enough and an alternative side branch is not available at the chosen location.

In an era with an explosion of novel biomarkers to aid diagnosis, guide therapy and HF management, simple conventional chemistry including serum sodium level could hold added value. Serum sodium level is a dynamic marker and its changes are seen soon after CRT device implantation. Post- CRT device implantation, hyponatremia holds negative prognostic influence and may aid further risk stratification and lead to consideration of alternative interventional strategies (i.e. LV assist device implantation and heart transplant evaluation) of this patient cohort.

Our study shows that a history of hypothyroidism is associated with a poor clinical outcome, even after CRT device implantation. Those results draw attention to **multidisciplinary postoperative patient care**, where heart failure specialist can adjust medical therapy according to comorbidities and status of the patient, beside the electrophysiologist.

Device-derived measures of physical activity can help predict clinical outcome and ventricular remodeling in patients receiving cardiac resynchronization therapy. This study shows that device diagnostic measures of averaged physical activity correlates with the 6-minute walk tests and further, can serve as a surrogate in the prediction of functional response and long-term clinical outcome and survival after CRT. It can serve as an easy to approach **"status report", during follow-up**.

I hope the these minor observations of retrospective analyses can contribute to the improved care of this special patient group.

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