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Do we need to monitor the percentage of biventricular pacing day by day?☆

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ABSTRACT

Background: Incidence and clinical significance of transient, daily fluctuations of biventricular pacing percentage (CRT%) remain unknown. We assessed the value of daily remote monitoring in identifying prognostically critical burden of low CRT%.

Methods and results: Prospective, single-centre registry encompassed 304 consecutive heart failure patients with cardiac resynchronization therapy defibrillators (CRT-D). Patients with 24-h episodes of CRT% loss < 95% were assigned to quartiles depending on cumulative time spent in low CRT%: quartile 1 (1–8 days), 2 (9–20 days), 3 (21–60 days) and quartile 4 (>60 days). During median follow-up of 35 months 51,826 transmissions were analysed, including 15,029 in 208 (68.4%) patients with episodes of low CRT%. Overall, mean CRT% ≥ 95% vs. <95% resulted in a 4-fold lower mortality (17.3 vs. 68.2%; $p < 0.001$). Fifty-four percent of patients experienced episodes of CRT% loss, despite 85.6% having mean CRT% ≥ 95%. Mortality was lowest in quartile 1 (7.7%), while longer periods of CRT% loss resulted in significantly higher death rates (25.0 vs. 34.6 vs. 57.7%; quartiles 2–4 respectively, $p < 0.001$), despite mean CRT% still being ≥95% in quartiles 1–3. Cumulative low CRT% burden was the independent risk factor for death (HR 1.013; 95% CI 1.006–1.021; $p < 0.001$). Mortality rose by 1.3 and 49% with every additional day and quartile of CRT% loss, respectively.

Conclusions: Daily remote monitoring allows one to detect 24-h episodes of CRT% loss < 95% in over two-thirds of CRT-D recipients during median observation of 3 years. Cumulative low CRT% burden (in days) independently predicts mortality before mean CRT% drop.

1. Introduction

Cardiac resynchronization therapy (CRT) is a proven and well established method that reduces mortality and morbidity in patients with symptomatic heart failure, reduced left ventricle ejection fraction (LVEF) and broadened QRS complex [1–5]. However, up to 1/3 of patients who were implanted with CRT devices do not respond adequately to this therapy [6]. One of the reasons for CRT non-response is a transient loss of biventricular pacing. A direct correlation between CRT response and maintenance of high percentage of biventricular pacing (CRT%) has been well proven [7]. Moreover, CRT% loss usually precedes heart failure worsening [7]. More than 50% of patients with CRT devices do experience episodes of low CRT% and the major reasons for that are atrial fibrillation/atrial tachycardia, premature ventricular contractions and ventricular sensing episodes [7,8]. Different cutoff values for CRT% (from 92 to 98%) have been postulated to be optimal for the greatest clinical benefit in CRT recipients [7,9]. Current European Society of Cardiology (ESC) and European Heart Rhythm Association (EHRA) guidelines recommend CRT% of 100% [10,11]. However, CRT% is a continuous parameter and values obtained at certain points in time, i.e. during device interrogation do not reflect its periodic fluctuations (i.e. short episodes of biventricular pacing loss). Moreover, mean CRT% gives only retrospective information about inadequate biventricular pacing with no possibility to intervene at the time of the event. Therefore, a constant, everyday monitoring of CRT% variations, rather than obtaining its mean values, might be better in both detecting CRT% loss with minimal delay in time (24 h) and taking urgent action to regain optimal biventricular pacing. In contrast to the mean values of CRT%, the incidence and impact of 24-h fluctuations of CRT% on mortality have

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never been studied. We aimed to assess the value of day by day remote monitoring in identifying prognostically critical burden of cumulative low CRT pacing percentage.

2. Methods

2.1. Study population

Prospective, single-centre registry encompassed 305 consecutive, symptomatic heart failure patients, who were implanted with cardiac resynchronization therapy defibrillators (CRT-D) between February 2009 and November 2012 at the tertiary-care, university hospital — Department of Cardiology, Congenital Heart Diseases and Electrotherapy, Medical University of Silesia, Silesian Centre for Heart Diseases, Zabrze, Poland. In line with the ESC guidelines, every patient qualified for CRT-D implantation was in New York Heart Association (NYHA) class III or IV with QRS broadening ≥ 120 ms or NYHA class II and ORS width ≥ 150 ms, despite optimal medical therapy for at least three months before device implantation. LVEF was ≤35% in all subjects. The study complied with the Declaration of Helsinki.

2.2. Data collection and follow-up

Every patient on the day of implantation and after signing an informed, written consent, received a portable, wireless transmitter for remote monitoring of CRT-D. All patients were instructed in detail how the system works. In short, the transmitter interrogates the implanted devices, routinely over the night, and subsequently transmits data via telephone network to the central server. Data are then available online to medical staff with access code only. The Biotronik *Home Monitoring* (71.0%) and Medtronic *CareLink* (29.0%) remote monitoring systems were used.

All patients were followed in an outpatient setting 1 week and 1 month after CRT-D implantation, and every 6 months thereafter. These visits included clinical assessment as well as device interrogation and check-up. Apart from routine, monthly scheduled remote transmissions, in every case, in which a pre-defined alert was fulfilled and the patient was in the neighbourhood of the transmitter, an immediate, additional wireless transmission was initiated. All remote monitoring data have been gathered daily and subsequently combined with patients' clinical data and outcomes to create an electronic database for analysis. The last day of the study was 31 December 2014.

Study end-point was all-cause mortality. Heart failure hospitalizations were also reported. Data on study outcomes were collected prospectively during planned and unscheduled visits from patients, relatives, witnesses, attending physicians, hospital records, outpatient notes, letters, death certificates, device memory and all other available sources.

2.3. Device type and CRT pacing percentage monitoring

Biotronik Lumax 340 HF-T (Berlin, Germany) and Medtronic Consulta™ CRT-D, Maximo™ II CRT-D, Protecta™ CRT-D, InSyncSentry™7298 Inc. (Minneapolis, MN, USA) CRT-D devices with remote monitoring function (Biotronik *Home Monitoring*, Medtronic *CareLink*) were used in the study. The percentage of biventricular pacing was routinely monitored in all patients on a daily basis via remote monitoring. The pre-specified alert notification for low CRT% was set at <95%, as the remote monitoring technology allows one to transmit an everyday alert of a 24-h CRT% loss < 95% in *Home Monitoring* system as well as an everyday report including the mean CRT% of the preceding 24-h in case of the *CareLink* system.

Day by day monitoring of the of CRT% was initiated in all patients on the third day of the study and after the second remote monitoring transmission. From that day onwards, the cumulative number of days spent in low CRT% has been calculated for all patients. As it has been assumed that the duration of CRT% loss (in days) may affect clinical outcomes, all subjects with at least one, 24-h episode of CRT% drop < 95%, regardless of mean CRT% values, were assigned to quartiles depending on the cumulative number of days spent in low CRT% [Fig. 1]. The design of the study was to prospectively collect device and clinical data to allow a subsequent comparative analysis across all study quartiles, but always in relation to a reference (Group 1, which consisted of patients with 0 days of CRT% loss < 95% during the whole follow-up).

One of the patients has withdrawn the consent for everyday monitoring during the follow-up period and was excluded from the study. Ultimately, 304 consecutive CRT-D patients were included for final data analysis.

2.4. Response to low biventricular pacing and to other alerts of remote monitoring system

Every remote monitoring transmission was assessed by on site electrophysiology nurse and a cardiologist with experience in cardiac implantable devices. Every episode of 24-h CRT% drop < 95% was considered individually, but an intervention protocol was created and implemented to assure homogeneous reactions to various alerts. Interventions depended directly on the type of transmission [Table 1] and consisted of:

1. No reaction (i.e. routine, periodic intracardiac electrogram (IEGM), etc.)
2. Specific interventions (telephone contact with patient/patient's family/general practitioner (GP)/physician on call in case of acute hospital admission)

- calling an ambulance
- calling a patient for an urgent outpatient visit (next working day) — always when direct clinical assessment, physical examination, device reprogramming and referring for further diagnostic and therapeutic procedures, i.e. ventricular extrasystoles (VES)/ventricular tachycardia (VT), atrial fibrillation (AF), atrio-ventricular node (a-v node) or SVT (supra-ventricular tachycardia) ablation were necessary
- medication introduction/change/dose up-titration
- informing the patient about transmission content

2.5. Statistical analysis

The continuous parameters were expressed as median (range), whereas categorical variables as numbers and percentages. To compare study groups the Chi-square, Kruskal-Wallis or Mann–Whitney U tests were performed, as appropriate. Predictive values of low CRT pacing percentage and cumulative low CRT pacing burden were calculated with uni- and multivariate Cox regression models. Results were expressed as hazard ratio (HR) with 95% confidence intervals (CI). Receiver-operating characteristics were assessed to establish cut-point with the most balanced sensitivity and specificity of independent predictor. Statistical significance was set if the p value was less than 0.05.

To assess if number of days with low CRT% influences mortality independently of commonly accepted risk-predictors, but also regardless of overall CRT% (mean CRT% within whole follow-up period), three Cox-regression models were constructed. Apart from commonly used confoundings (age, gender, NYHA class, LVEF, ischaemic aetiology of heart failure, renal function, left bundle branch block and atrial fibrillation burden), duration of low CRT% period was incorporated into the first model, overall mean CRT% into the second, and both parameters simultaneously into the third model.

All statistical analyses were performed using the software package Statistica (version 6.0, StatSoft Inc., Tulsa, OK, USA and version 10.0).