Early and sustained effects of cardiac resynchronization therapy on N-terminal pro-B-type natriuretic peptide in patients with moderate to severe heart failure and cardiac dyssynchrony

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Aims The Cardiac Resynchronization-Heart Failure (CARE-HF) study demonstrated that cardiac resynchronization therapy (CRT) could reduce morbidity and mortality and improve cardiac function in patients with moderate or severe heart failure secondary to left ventricular systolic dysfunction and markers of cardiac dyssynchrony. The purpose of this analysis was to investigate the effect of CRT on plasma concentrations of N-terminal pro-brain natriuretic peptide (NT-pro-BNP), a powerful marker of cardiac dysfunction and prognosis.

Methods and results Blood samples were collected routinely at baseline and 3 and 18 months. Plasma was separated by cool centrifugation and stored at \(-270^\circ\)C until transported to a central laboratory for analysis of NT-pro-BNP using a standard commercial assay. Cardiac function was assessed echocardiographically. At baseline, median plasma concentration of NT-pro-BNP was similar in patients assigned to CRT or medical therapy [1920 pg/mL (inter-quartile range (IQR) 744–4288) and 1809 pg/mL (IQR 719–3949), respectively]. The differences in medians between the CRT and medical therapy groups were highly significant at both 3 months (537 pg/mL; \(P\), 0.0001) and 18 months of follow-up (567 pg/mL; \(P\), 0.0001). These differences could not be accounted for by changes in pharmacological therapy or renal function but were associated with improvement in ventricular volumes and function.

Conclusion CRT exerts an early and sustained reduction in NT-pro-BNP. This appears to reflect improvements in ventricular function. NT-pro-BNP may be a simple method for monitoring the effects of CRT.

KEYWORDS
Heart failure; Cardiac resynchronization therapy; Neurohormones; NT-pro-BNP

Introduction

Despite treatment with angiotensin-converting enzyme (ACE)-inhibitors, beta-blockers, and aldosterone antagonists, morbidity and mortality remains high in patients with chronic heart failure (HF). The prognosis is worse in patients with HF who have prolonged QRS intervals. This may reflect cardiac dyssynchrony and a greater propensity to adverse ventricular remodelling.

The Cardiac Resynchronization-Heart Failure (CARE-HF) study and other trials have shown that cardiac resynchronization therapy (CRT) can improve cardiac function and symptoms, reduce hospitalization, and prolong life in appropriately selected patients. Natriuretic peptides, in particular brain natriuretic peptide (BNP) may have a valuable role as a measure of cardiac dysfunction and as a means of monitoring response to therapy. BNP is produced by and secreted from the cardiomyocyte in its active form (BNP) and an N-terminal fragment (NT-pro-BNP). The purpose of this analysis is to report early and long-term changes in NT-pro-BNP in...
patients assigned to CRT when compared with pharmacological therapy alone in the CARE-HF study.

Methods

The CARE-HF trial

CARE-HF was designed to evaluate the effect of CRT on the morbidity and mortality of patients with moderate to severe HF due to systolic left ventricular (LV) dysfunction with markers of cardiac dyssynchrony already receiving a high standard of pharmacological treatment. Overall, 813 patients were included in the study and randomly assigned to CRT or no CRT. The main primary and secondary outcome measures have already been published, showing that CRT significantly reduces both morbidity and mortality.21

Patients rested in the supine position for at least 15 min before blood sampling. Blood was withdrawn into chilled EDTA tubes, which were then immediately placed into ice-cold water. The tubes were then centrifuged at 4000 r.p.m. at +4 °C for 10 min. Supernatant plasma was then immediately aliquoted into labelled cryo-vials and frozen at −70 °C. Vials were kept at participating centres during the study and transported using a courier service (guaranteeing that samples remained frozen during transport) to the neurohumoral core laboratory (Medical University Graz). They were checked on delivery to ensure that they had remained frozen and were then labelled and frozen at −70 °C until analysis.

Samples were analysed for NT-pro-BNP only after completion of the main CARE-HF study. Thus, investigators were unaware of the NT-pro-BNP values throughout the study. The assays were conducted without knowledge of the assigned treatment. NT-pro-BNP was measured using a commercially available electrochemiluminescence immunoassay based on a polyclonal antibody-based sandwich chemiluminescence assay (Roche Diagnostics, Germany) using an autoanalyser (Elecsys 2010). All kits had the same lot number with an inter-and intra-assay variability of 2.9 and 1.0%, respectively. The normal NT-pro-BNP range of a healthy population is <125 pg/mL, with a lowest detection limit of <5 pg/mL.

Statistics

Baseline characteristics of patients randomized to CRT or medical therapy in the neurohormonal substudy are described in terms of frequencies, percentages, means or medians, and inter-quartile ranges (IQRs). Median NT-pro-BNP values are described at baseline and 3 and 18 months. As NT-pro-BNP is normally distributed on the log scale, analyses were performed on the log-transformed values. Quartiles of NT-pro-BNP were performed on the log-transformed values. Quartiles of NT-pro-BNP at baseline and its changes until 18 months are given for survivors in both groups. Fisher’s exact test was used to compare changes in medication use during the first 3 months are given for survivors in both groups. Fisher’s exact test was used to compare changes in medication use during the first 3 months.

Results

Adequately labelled baseline samples were delivered to the core laboratory for 732 patients (90% of the CARE-HF population) in 81 centres. A sample was not obtained in 81 patients because either the sample was mislaid during storage at investigator sites or inadequately labelled when received in the core laboratory. These patients had similar baseline characteristics to other patients. The characteristics of patients randomized to the CRT and control groups were similar (Table 1). By 3 months, 12 patients assigned to CRT had died compared with 15 in the control, and by 18 months, 52 compared with 75 had died. Of surviving patients, 341 and 308 in the CRT group provided samples at 3 and 18 months compared with 323 and 282 patients assigned to the control group.

Pre-specified variables, log transformed where appropriate, were tested for their ability to predict baseline NT-pro-BNP (Table 2). Increasing age, reduced GFR, low LVEF, and marked mitral regurgitation were independently associated with high NT-pro-BNP at baseline. Model validation indicated no important overfitting and also indicated little potential influence from missing data. Median plasma concentrations of NT-pro-BNP at baseline were 1920 pg/mL (IQR 744–4288) in patients assigned to CRT compared with 1809 pg/mL (IQR 719–3949) in the control group. At 3 months, median plasma concentrations for the CRT and control group were 1112 pg/mL (IQR 482–3053) and 1649 pg/mL (IQR 609–3704), and at 18 months, 765 pg/mL (IQR 237–2271) and 1332 pg/mL (IQR 516–3637), respectively. Some of the apparent fall in NT-pro-BNP over time, especially in the control group, reflected a survivor effect, as patients with high baseline levels were less likely to survive until re-sampling. However, the differences in medians were highly significant both at 3 months (537 pg/mL; P < 0.0001) and at 18 months (567 pg/mL; P < 0.0001) (Figure 1).

Patients who died within 18 months had significantly higher baseline levels of NT-pro-BNP (median 4640 pg/mL, IQR 1451–9922) than those who survived (median 1776 pg/mL, IQR 726–3991; P = 0.0001). There was no interaction between the reduction in mortality with CRT and baseline NT-pro-BNP. The baseline NT-pro-BNP values of those who survived until 18 months were divided into quartiles to assess changes in relationship to initial levels (Figure 2). In the control group, NT-pro-BNP changed little in patients with the highest baseline levels and tended to rise in the middle two quartiles. In patients assigned to CRT, NT-pro-BNP either fell or remained constant in all quartiles. The greatest absolute reduction was observed in patients with the highest baseline NT-pro-BNP. Changes in NT-pro-BNP among patients assigned to CRT relative to the control group were similar in the top three quartiles.

Most surviving patients assigned to CRT (214, 69%) had improved to NYHA class I or II by 18 months, compared with only 136 patients (49%) in the control group. In the control group, plasma concentrations of NT-pro-BNP at 18 months were similar in patients who were reported to be in NYHA class I/II compared with NYHA class III/IV. However, among patients assigned to CRT, plasma concentrations of NT-pro-BNP were substantially lower at 18 months in patients who improved to NYHA I/II when compared both with patients who remained in NYHA class III/IV.
and with patients in the control group, whereas those who remained in NYHA class III/IV had similar plasma concentrations to patients in the control group (Figure 3 and B).

We also investigated the relationship between changes in NT-pro-BNP and LVEF, LV end-systolic volume index (LVESI), mitral regurgitation, and GFR estimated using the modified MDRD equation. Ventricular function changed little in the control group but improved in patients assigned to CRT (Table 3). In a model adjusted for baseline NT-pro-BNP (log transformed), changes in NT-pro-BNP (log transformed) correlated with changes in LVEF, LVESI, mitral regurgitation, and GFR but these variables did not explain all of the effect of CRT on NT-pro-BNP. We could not conduct a formal analysis related to changes in therapy due to the complex variations observed in the study. No differences in the utilization of ACE-inhibitors, angiotensin receptor blockers, beta-blockers, or spironolactone were observed after accounting for the high mortality of patients in the control group who were not taking these treatments. No differences in digoxin use were identified either.

**Discussion**

The CARE-HF study demonstrates for the first time in a randomized controlled trial that CRT exerts a remarkable early and sustained reduction in plasma concentrations of NT-pro-BNP levels when compared with pharmacological therapy alone in patients with moderate to severe chronic heart failure.
HF and markers of ventricular dyssynchrony. These changes were most strongly associated with and most likely due to improvements in LV function and reductions in mitral regurgitation with CRT. However, patients assigned to CRT were more likely to have doses of diuretic reduced and less likely to have them intensified and therefore changes in diuretic therapy seem unlikely to account for the observed changes in NT-pro-BNP. We did not identify any systematic intensification of ACE-inhibitors, angiotensin receptor blockers, beta-blockers, or aldosterone antagonists that might account for short- or long-term changes in NT-pro-BNP.

**Figure 2** Change in median NT-pro-BNP by quartile for CRT and control groups at baseline and NT-pro-BNP. CRT had a positive influence on NT-pro-BNP only in patients with baseline values above the median (Strata 3 and 4). Patients below the median revealed no significant change throughout the study. Strata defined by quartile at baseline. Error bars indicate the upper and lower IQR. MT, medical therapy group.

**Figure 3** Median NT-pro-BNP values in survivors in the (A) CRT and (B) control groups at baseline and 18 months according to the clinical response (improvement in NYHA class). Responders are defined as having improved in NYHA score. Error bars indicate the upper and lower IQR. MT, medical therapy group.

**Table 3** Course of LVEF and LV volumes in CRT and control patients throughout the study period

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<th>Median</th>
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<th>75th percentile</th>
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<tr>
<td>LVEF (%)</td>
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<td>LVEF (%)</td>
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<tr>
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Only CRT patients showed an increase in LVEF and a reduction in ventricular volume.
CRT has a more or less instantaneous effect on cardiac function and mitral valve function.\textsuperscript{13,14} The early reduction in NT-pro-BNP observed in CARE-HF probably reflects the acute haemodynamic improvement. Acute haemodynamic improvement should reduce ventricular filling pressure and improve efficiency and this would be expected to lead to beneficial ventricular remodelling. The significantly greater improvement in LVEF with CRT at 18 months compared with 3 months supports such a hypothesis. Differences in NT-pro-BNP between the control and CRT group appeared early but did not increase over time, suggesting that NT-pro-BNP might be a measure of the stimulus to remodel but not of the remodelling process itself.\textsuperscript{13,25}

Clinical implications

Despite the fact that patients had markedly impaired ventricular function and moderate to severe symptoms, there was a wide spread of baseline NT-pro-BNP. Patients with markedly elevated levels were more likely to die as has been shown in numerous other studies and reported from CARE-HF\textsuperscript{26,27} Indeed, NT-pro-BNP may be the most robust, simple, objective prognostic marker in patients with HF. If natriuretic peptides are a robust guide to prognosis, then it might be expected that change in natriuretic peptide might be a useful guide to the effectiveness of therapy. Plasma concentrations might be used to guide changes in diuretic therapy, the need to increase doses of cardioprotective medication and perhaps to guide when to implement CRT or implantable defibrillators. Preliminary studies suggest that the use of natriuretic peptides to guide treatment may improve morbidity and mortality.\textsuperscript{19,20,28}

If natriuretic peptides are adopted as a therapeutic target in patients with HF, then CRT appears to be a powerful additional intervention to achieve such a target in appropriately selected patients.\textsuperscript{29,30}

Limitations

Several limitations apply to this study. Although every effort was made to include all patients, adequate samples were obtained from only 90\% of the population. This is not surprising for such a large multi-centre study examining the effect of intervention on mortality and major morbidity. However, we have made no attempt to impute missing data nor do we believe that this would be appropriate in this context. Secondly, background medication was not stable throughout the study period, as is always the case with long-term outcome trials. Nevertheless, we did not detect any systematic bias in the use of ACE-inhibitors or beta-blockers that could account for the detected differences. NT-pro-BNP was pre-specified as the principle neuro-endocrine marker of interest for this study and it is possible that these results do not apply to other natriuretic peptides. Although reductions in NT-pro-BNP were observed in patients who improved their investigator-assigned NYHA class with CRT, this was not the case in the control group. This may reflect the rather broad range of symptoms within each NYHA class and it is possible that NYHA class did not adequately reflect modest changes in the control group, but did reflect much larger changes in those assigned to CRT. Further analyses may elucidate this problem further.

Conclusions

CRT results in an early and sustained reduction in NT-pro-BNP. This is associated with early and progressive improvement in echocardiographic LV function. NT-pro-BNP may be a useful way of monitoring the effects of CRT.

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Conflict of interest: J.G.F.C., L.T., and N.F. reported having received research grants, speakers’ bureau/honoraria and having been involved as consultants/advisory boards for Medtronic. F.M.F. reported having received research grants for heart failure studies (incl. Care-HF) and speakers’ bureau/honoraria from Medtronic. L.K. reported having received research grants and having been involved in consultancies/advisory boards for Medtronic. E.E. reported having received speakers’ bureau/honoraria and having been involved in consultancies/advisory board for Medtronic. D.G. reported having been involved in consultancies/advisory boards for Medtronic and Guidant. J.-C.D. reported having received speakers’ bureau/honoraria, ownership interests and having been involved in consultancies/advisory boards for Medtronic and St. Jude Medical. The other authors reported no conflicts.

References

Early and sustained effects of CRT on NT-pro-BNP


