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Original Article

The prognostic significance of serum sodium in a population undergoing cardiac resynchronisation therapy

Kaushik Guha[a,b,*], Jens Spießhöfer[a,b,c], Adam Hartley[d], Simon Pearse[a,b], Philip Y. Xiu[a,b], Rakesh Sharma[a,b]

[a] Dept of Cardiology, Royal Brompton Hospital, London, United Kingdom
[b] National Heart and Lung Institute, Imperial College London, London, United Kingdom
[c] Dept of Respiratory Medicine, Hannover Medical School, Hannover, Germany
[d] Dept of Cardiology, Harefield Hospital, London, United Kingdom

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ABSTRACT

Purpose: To determine the prognostic implications of changes towards hyponatremia at varying time-points in the treatment of patients undergoing cardiac resynchronisation therapy (CRT).
Methods: A retrospective series of 249 patients was studied from 2002 to 2013. The population was categorized on the basis of serum sodium profile at baseline, at 1 month and at 6 month follow up visits following successful CRT implantation. The composite endpoint was all-cause mortality and heart failure hospitalisation (defined by the need for intravenous diuretic therapy) following CRT implantation.
Results: A total of 249 patients (67.8 ± 12.5 years; NYHA class III/IV 75; LVEF 27.2 ± 8.8%) were followed up for a median of 5.5 years. Hyponatremia at baseline, 1 month or 6 months follow up did not predict the composite endpoint. 26% of patients showed hyponatremia at baseline prior to CRT implantation, while it was present in 19.9% of patients 1 month ($p = 0.003$) and in 16% ($p < 0.001$) 6 months after CRT implantation. There was a significantly worse outcome for those patients who developed hyponatremia 6 months after CRT implantation. In multivariate analysis, the intake of loop diuretics (HR 1.76 [1.04–2.95], $p = 0.03$) and renal impairment (urea > 7.0 mmol/l) (HR 1.61 [1.05–2.46], $p = 0.03$) at baseline were associated with an increased risk of unplanned heart failure hospitalisation and all-cause mortality after CRT implantation.
Conclusions: A change towards hyponatremia when observed 6 months after CRT implantation may predict a worse clinical outcome. Additionally, renal impairment and higher diuretic doses are associated with an increased risk of mortality in the population analysed.

1. Introduction

Hyponatremia (defined as serum sodium <135 mmol/l) has previously been described to be an adverse prognosticator in populations with heart failure.[1–3] Hyponatremia and changes towards hyponatremia have been suggested to be associated with adverse outcomes in patients undergoing CRT implantation.[4,5]

This study aimed to determine whether hyponatremia is an adverse prognosticator in patients undergoing CRT implantation by investigating (1) whether the time-point of the hyponatremia influences its prognostic value (i.e. before CRT implantation, 1 month and 6 months after); (2) examining whether change in serum sodium may have independent prognostic significance and (3) whether further prognosticators of adverse outcomes after CRT implantation could be identified.

2. Methods

A series of 285 patients undergoing CRT implantation from a single tertiary university centre was studied. The trial period was between 2002 and 2013.

Abbreviations: 1MFU, 1 month follow up; 6MFU, 6 months follow up; BL, baseline; BP, blood pressure; CRT, cardiac resynchronisation therapy; CRT-D, cardiac resynchronisation therapy (with an ICD); CRT-P, cardiac resynchronisation therapy (without an ICD); ESC HFA, European Society of Cardiology guidelines for the diagnosis and treatment of acute and chronic heart failure 2012; HF, heart failure; ICD, implantable cardioverter defibrillator; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association class.

* Corresponding author at: Dept of Cardiology, Queen Alexandra Hospital, Southwick Hill Road, Portsmouth, PO6 3LY, United Kingdom.
E-mail address: kguha@doctors.org.uk (K. Guha).

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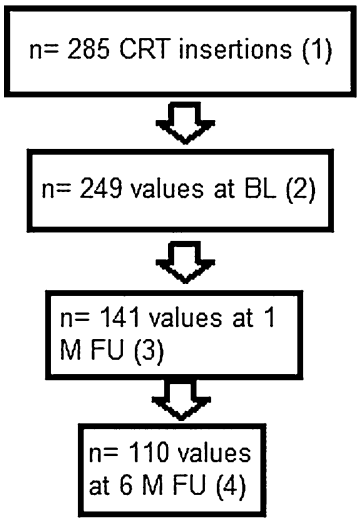

Fig. 1. Flow chart of patients being inserted a CRT device (1), with available data on sodium at baseline (2), at a 1 month follow up visit (3), at a 6 months follow up visit (4).

All implants were performed as per contemporary guidelines.[7–9] Prior to implantation clinical, biochemical and cardiac imaging data was recorded. This included NYHA status, documenting clinical variables including systolic blood pressure and using transthoracic echocardiography to derive a Biplane Simpson's measure of left ventricular ejection fraction, a measure of the 12 lead electrocardiogram QRS duration was also documented.

The patient then received CRT as per the contemporary guidance and had CRT implanted via standard transvenous techniques. A conventional range of generators and leads was used. All individuals were then systematically reviewed in the dedicated heart failure pacing clinic at 1 month whereby the serum sodium was again measured and within the heart failure service at 6 months. Baseline measurement was up to 48 h prior to CRT implantation.

Hyponatremia was defined as per the current guidance from the European Society of Cardiology-2012 as a serum sodium level <135 mmol/l.[9]

The endpoint was defined as a composite of emergency unplanned hospitalisation for heart failure which required the use of intravenous diuretics and all-cause mortality. The analysis was time to first event driven.

Statistical analyses were performed using Sigma Plot software (Version 11.0, Systat Software Ltd.), while Kaplan Meier Curves were created using GraphPad Prism (Version 5.00 GraphPad Software).

Data are depicted as mean value ± standard deviation (SD) for continuous variables, for which differences between groups were compared by a *t*-test. A paired *t*-test was used to detect changes in individual patients with time. The Mann–Whitney Rank Sum test was used for non-normally distributed data. Categorical data are summarized as frequencies and percentages and the Chi-square test was used to compare differences between groups.

Kaplan–Meier curves were constructed to compare event rates in hyponatremic and normonatremic groups with respect to the composite end point after CRT insertion.

This was done separately for those patients with available sodium values at baseline, at 1 month and at 6 months follows up and for different patient groups based on their changes in sodium from baseline to 1 month follow up and from baseline to 6 months follow up.

The difference between survival curves was assessed by the log-rank (Mantel–Cox) test.

To assess baseline predictors of the composite endpoint, univariate Cox proportional hazards were calculated, which required a categorisation of continuous variables if they failed to

Table 1
Baseline characteristics (frequency or mean ± standard deviation) for the entire cohort and hyponatremic and normonatremic patients.

Characteristic	Whole cohort $n=249$	Hyponatremia $n=50$	Normonatremia $n=199$	*p*-Value
Age (years)	67.8 ± 12.6	66.7 ± 11.9	68.1 ± 12.7	0.444
Female	54 (21%)	12 (24%)	42 (21%)	0.173
Creatinine (μmol/l)	120 ± 53	121 ± 56	121 ± 52	0.899
Urea (mmol/l)	10 ± 6	11 ± 6	10 ± 6	0.221
Sodium at baseline (mmol/l)	137 ± 3	132 ± 2	138 ± 2	<0.001
Hemoglobin (mg/dl)	13.0 ± 1.6	12.9 ± 1.6	13.1 ± 1.6	0.450
Systolic BP (mmHg)	116.8 ± 21.2	112.1 ± 23.4	118.0 ± 20.5	0.021
Diastolic BP (mmHg)	69.7 ± 13.8	69.1 ± 12.8	69.9 ± 14.1	0.549
NYHA class III/IV (%)	187 (75%)	42 (84%)	145 (73%)	0.407
LVEF (%) [missing]	27. 2 ± 8.7 [46]	25.3 ± 8.7 [10]	27.6 ± 8.6 [36]	0.130
LVIDd (mm) [missing]	6.6 ± 1.0 [46]	6.7 ± 1.0 [10]	6.6 ± 1.0 [36]	0.408
LVIDs (mm) [missing]	5.6 ± 1.1 [46]	5.6 ± 1.1 [10]	5.6 ± 1.1 [36]	0.800
QRS duration (ms)	161.4 ± 28.2	165.6 ± 33.3	160.3 ± 26.8	0.195
Ischaemic HF	125 (50%)	18 (36%)	107 (54%)	0.399
Non Ischeamic HF	124 (50%)	32 (64%)	92 (46%)	0.399
Atrial fibrillation	57 (23%)	9 (18%)	48 (24%)	0.214
Diabetes mellitus	58 (23%)	12 (24%)	46 (23%)	0.304
Hypertension	62 (25%)	12 (24%)	50 (25%)	0.686
Medications				
Angiotensin converting enzyme inhibitor	157 (63%)	34 (68%)	123 (62%)	0.514
Angiotensin receptor blocker	67 (27%)	12 (24%)	55 (28%)	0.379
Aldosterone antagonist	(54%)	(66%)	(51%)	0.232
Total daily dose of aldosterone antagonist	13.7 ± 13.4	16.8 ± 13.5	12.8 ± 13.3	0.071
Beta-blockers	165 (66%)	30 (60%)	135 (68%)	0.479
Digoxin	45 (18%)	10 (20%)	35 (18%)	1.000
Diuretics	203 (82%)	44 (88%)	159 (80%)	1.000
Total daily dose of Lasix[a] (mg)	53.4 ± 49.2	60.0 ± 51.0	51.7 ± 48.8	0.246

Hypertension = blood pressure ≥ 140/90 mmHg.
[a] Total daily dose of Lasix or Lasix equivalent (1 mg bumetanide = 40 mg frusemide).

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