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Melatonin is associated with reverse remodeling after cardiac resynchronization therapy in patients with heart failure and ventricular dyssynchrony

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ABSTRACT

Background: Cardiac resynchronization therapy (CRT) is an effective treatment for left ventricular reverse remodeling (LVRR) in patients with congestive heart failure (HF) and ventricular dyssynchrony. Melatonin is a secretory product of the pineal gland with highly beneficial effects from any tissues including the heart. Herein, we investigated whether the response to CRT is associated with levels of melatonin before CRT implantation in patients with HF and ventricular dyssynchrony.

Methods: Diurnal melatonin levels were performed in serum from 93 patients with HF and ventricular dyssynchrony before CRT implantation. Moreover, we calculated the MADIT-CRT score. Evaluation of patients at 1-year follow-up included an echocardiographic study since the patients were categorized as responders if they presented both a reduction in left ventricular end-systolic volume index >10% and an increase in left ventricular ejection fraction >10%.

Results: At 1-year, 34 patients (36.5%) were considered responders to CRT according to the predefined criteria. The diurnal melatonin levels were significantly lower in the non-responder group (9.9 ± 2.84 vs 14.7 ± 2.32 pg/mL). After adjustment by multivariate analysis, diurnal serum melatonin levels ($P < 0.001$) and diabetes mellitus ($P = 0.03$) were predictors of LVRR. On Cox regression analysis, diurnal serum melatonin levels ($P < 0.001$) and left atrial volume < 40 mL/m^2 ($P = 0.04$) remained independent predictors of the adverse clinical events. The area under of curve for the prediction LVRR of melatonin (0.91, 95%CI 0.85–0.97; $P < 0.001$) was significantly higher compared to MADIT-CRT score (0.69, 95%CI 0.58–0.80; $P = 0.002$).

Conclusion: Diurnal levels of melatonin before CRT implantation are associated with LVRR at 12 month follow-up.

1. Introduction

Cardiac resynchronization therapy (CRT) is an effective treatment for left ventricular reverse remodeling (LVRR) and it enhances systolic function while improving long-term outcome and survival in patients with congestive heart failure (HF) and ventricular dyssynchrony [1]. Although most patients with HF may benefit from CRT, 30% of them do not respond clinically to CRT and up to 45% do not show evidence of LVRR [2,3]. Biomarkers have been useful for the diagnosis of HF and risk stratification and are being evaluated to guide therapy [4]. Additionally, data now suggest that biomarkers may also be useful to predict or monitor LVRR [5–9].

Melatonin (N-acetyl-5-methoxytryptamine) is a secretory product of the vertebrate pineal gland. Among its numerous functions melatonin controls biological rhythms [10], and it has numerous beneficial actions in the heart [11–16] where it plays an important role in the pathophysiology of cardiovascular remodeling [17]. The hypothesis that melatonin may be involved in the pathophysiology of cardiovascular remodeling is supported by the findings that pinealectomy or continuous light exposure, both of which reduce melatonin's production and contributes to fibrosis of the left ventricle [18,19].

We thus have evaluated whether the long-term response to CRT, as assessed in terms of LVRR, is associated with levels of melatonin before CRT implantation in patients with HF and ventricular dyssynchrony. To

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test this relationship, serum melatonin was measured in patients with HF and ventricular dyssynchrony before CRT implantation.

2. Methods

2.1. Patients

A prospective cohort design was used to evaluate patients with HF and ventricular dyssynchrony undergoing CRT implantation, between March 2010 and July 2013. Ninety three patients were included and the criteria applied for CRT implantation were recent New York Heart Association functional class ≥II symptoms despite optimal medical therapy, QRS width ≥120 ms, and left ventricular ejection fraction ≤35%.

Evaluation of patients at the 1-year follow-up included an echocardiographic study. At 1 year, patients were categorized as responders if they exhibited LVRR, defined by a reduction >10% in left ventricular end-systolic volume index [20] and an increment >10% in left ventricular ejection fraction [21], or as non-responders if they did not decrease left ventricular end-systolic volume index or increase left ventricular ejection fraction at the end of the follow-up. If patients were submitted to cardiac transplantation before the 12-month follow-up showing no signs of response in the echochardiographic examination, they were considered as non-responders. A signed informed consent was obtained from each participant before enrollment in the study, in accordance with the principles stated in the Declaration of Helsinki. The protocol was reviewed and approved by the local Ethics Committee.

2.2. Data recording

These patients were evaluated for clinical (cause of HF, cardiovascular risk factors, presence of severe mitral regurgitation, and medication) and electrocardiographic parameters (rhythm and QRS width) at the time of device implantation. The cause of HF was considered ischemic on the basis of their clinical history of myocardial infarction (with electrocardiographic evidence of infarct location) or a history of revascularization.

Although derived in an earlier stage of HF, the Multicenter Automatic Defibrillator Implantation Trial With Cardiac Resynchronization Therapy (MADIT-CRT) score is the only clinical risk score applicable to CRT candidates [22]. We therefore calculated the score by using 7 variables (previous hospitalization of HF, female gender, non-ischemic cause, left bundle branch block, QRS duration, left ventricular end-diastolic volume, and left atrial volume) as described previously [22]. Previous HF admission was assigned a numeric value of 1; female gender, non-ischemic cause, left bundle branch block, QRS ≥150 ms, and left ventricular end-diastolic volume ≥ 125 mL/m^2 were assigned a value of 2; and left atrial volume <40 mL/m^2 was assigned a value of 3.

Moreover, all patients were followed for 12 months to obtain a composite of death from any cause (determined with medical record or the Social Security Death Index), heart transplantation, support with a left ventricular assist device, or HF hospitalization.

2.3. Samples of blood

Blood samples were withdrawn from the left antecubital vein at baseline (pre-implant CRT), during the light period (between 9 and 10 h) and serum obtained was stored at −20 °C until analysis. Melatonin levels in serum samples were measured using an enzyme-immunoassay kit after the samples had been extracted with chloroform (DRG Instruments GmbH, Marburg, Germany). In this ELISA assay, the lowest detection limit of melatonin was 1.67 pg/ml. The coefficients of variation were 7.5% and 11.3% for intra-assay and inter-assay variability, respectively.

2.4. Statistical analysis

Continuous variables are presented as mean ± standard deviation and were compared with independent samples using the Student *t* test. Categorical variables are expressed as

Table 1
Univariate analysis in the prediction of left ventricular reverse remodeling.

Variables	Whole cohort (n = 93)	LVRR (+) (n = 34)	LVRR (−) (n = 59)	*P* value
Age (years)	58.57 ± 10	57.88 ± 11.10	58.97 ± 9.44	0.619
Sex (male)	55 (59.1%)	23 (67.6%)	32 (54.2%)	0.205
CRF				
Hypertension arterial	27 (29%)	3 (8.8%)	24 (40.7%)	0.001
Diabetes mellitus	21 (22.6%)	3 (8.8%)	18 (30.5%)	0.016
Smoking	34 (36.6%)	11 (32.4%)	23 (39%)	0.523
Dyslipidemia	58 (62.4%)	20 (58.8%)	38 (64.4%)	0.592
COPD	13 (14%)	4 (11.8%)	9 (15.3%)	0.64
Non ischemic cause	38 (40.9%)	19 (55.9%)	19 (32.2%)	0.025
MR severe	12 (12.9%)	4 (11.8%)	8 (13.6%)	0.804
BMI	27.1 ± 2.92	26.82 ± 3.92	27.28 ± 2.16	0.463
ECG finding				
Atrial fibrillation	27 (29%)	7 (20.6%)	20 (33.9%)	0.173
LBBB	82 (88.2%)	32 (94.1%)	50 (84.7%)	0.178
QRS > 150 s	90 (96.8%)	34 (100%)	56 (94.9%)	0.181
Conventional Echo				
LVEDV > 125 mL/m^2	59 (63.4%)	26 (76.5%)	33 (55.9%)	0.048
LAV < 40 mL/m^2	12 (12.9%)	10 (29.4%)	2 (3.4%)	0.0001
LVEF, %	26.03 ± 3.73	26.03 ± 3.87	26.03 ± 3.52	0.99
MADIT-CRT score	8.12 ± 2.15	9.06 ± 2.13	7.59 ± 1.94	0.001
Biochemistry				
Melatonin day (pg/mL)	11.66 ± 3.52	14.70 ± 2.32	9.90 ± 2.84	0.0001
BNP (pg/mL)	473 ± 91.97	479.95 ± 83	469.04 ± 91.19	0.585
Medication				
Aldosterone antagonists	59 (63.4%)	18 (52.9%)	41 (69.5%)	0.110
B-blocker	72 (77.4%)	24 (70.6%)	48 (81.4%)	0.232
ACEI	64 (68.8%)	26 (76.5%)	38 (64.4%)	0.226
ARB	29 (31.2%)	8 (23.5%)	21 (35.6%)	0.226
Diuretics	93 (100%)	34 (100%)	59 (100%)	NA
Amiodarone	9 (9.7%)	1 (2.9%)	8 (13.6%)	0.095
Ivabradine	19 (20.4%)	7 (20.6%)	12 (20.3%)	0.977
Digoxin	56 (60.2%)	20 (58.8%)	36 (61%)	0.835
Nitrates	26 (28%)	7 (20.6%)	19 (32.2%)	0.229
Hydralazine	26 (28%)	7 (20.6%)	19 (32.2%)	0.229
Deaths at 1 year	3 (3.2%)	1 (2.9%)	2 (3.4%)	0.917*
HT or LVAD at 1 year	5 (5.4%)	1 (2.9%)	4 (6.8%)	0.436*
HF at 1 year	16 (17.2%)	2 (5.9%)	14 (23.7%)	0.053*
Combined events at 1 year	24 (25.8%)	4 (11.8%)	20 (33.9%)	0.034*

ACE: angiotensin-converting enzyme. ARB: angiotensin receptor blocker. BMI: Body mass index. BNP: brain natriuretic peptide. COPD: Chronic obstructive pulmonary disease. CRF: Cardiovascular risk factors. ECG: electrocardiogram. HF: heart failure. HT: Heart transplant. LAV: Left atrial volume. LBBB: left bundle branch block. LVAD: left ventricular assist device. LVEDV: Left ventricular end-diastolic volume. LVEF: Left ventricular ejection fraction. LVRR: Left ventricular reverse remodeling. MADIT-CRT: Multicenter Automatic Defibrillator Implantation Trial With Cardiac Resynchronization Therapy score. MR: Mitral regurgitation.

* *P* values for clinical events are from log-rank test.