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Subclinical hypothyroidism and its relationship with therapy failure in patients underwent cardiac resynchronization therapy

M. BALLI[1], F. KÖKSAL[1], N. SÖYLEMEZ[1], E. ERTÜRK[2], B. AYDINLI[3], B. ÖZKAN[4], V.K. VURGUN[5]

[1]Department of Cardiology, [2]Department of Cardiovascular Surgery, Mersin City Education and Research Hospital, Mersin, Turkey
[4]Department of Cardiology, Mersin University Medical School, Mersin, Turkey
[5]Department of Cardiology, Ankara Liv Hospital, Ankara, Turkey

Abstract. – OBJECTIVE: Cardiac resynchronization therapy (CRT) is used in patients with heart failure (HF), an important problem in cardiology practice, with reduced left ventricular systolic dysfunctions and left ventricular dyssynchrony to improve morbidity and mortality. Thyroid diseases have undeniable effects on cardiac functions. So, we aimed to evaluate the effect of subclinical hypothyroidism on CRT response in HF patients in this study.

PATIENTS AND METHODS: After the exclusion, 386 consecutive patients who received first-time CRT-defibrillator (CRT-D) or CRT-pacemaker (CRT-P) were retrospectively included. Known overt hypothyroidism or hyperthyroidism patients were excluded. The response of CRT was defined as a relative increase (≥15%) or absolute increase (≥10%) in left ventricular ejection fraction (LVEF) from implantation to one-year after follow-up.

RESULTS: Diabetes mellitus, atrial fibrillation and coronary artery disease ratios were similar between responder vs. non-responder groups. Thyroid stimulating hormone (TSH) levels were higher (p <0.005) in non-responder group. Responder group had higher baseline LVEF (p <0.001), and follow-up LVEF (p <0.001) and longer baseline QRS interval (p =0.004), but similar post-implant QRS interval duration (p >0.005) with non-responder group. Baseline QRS interval (p =0.002), baseline LVEF (p <0.001) and the presence of subclinical hypothyroidism (SCH) (p =0.001) were independent predictors of CRT response. Adding SCH as a risk factor to our baseline risk modelling has an independent prognostic impact to predict non-responder patients (p =0.01).

CONCLUSIONS: Presence of the SCH may be an important predictor of non-response in patients undergoing CRT. Evaluating the risk factors associated with non-response to CRT may be logical in identifying patients who obtain maximum benefit from CRT treatment.

Key Words:
Subclinical hypothyroidism, Cardiac resynchronization therapy, Response, Non-response, Heart failure.

Introduction

Heart failure (HF) is a challenging cardiovascular problem in daily practice, and significant proportion of HF patients have conduction abnormalities such as delayed ventricular activation[1]. As a consequence of these abnormalities, some patients may have atrioventricular, interventricular and intraventricular mechanical dyssynchrony[2]. Cardiac resynchronization therapy (CRT) is the modulation of impaired left ventricular (LV) function due to atrioventricular, interventricular and/or intraventricular conduction delay by using electrical stimulation.

In addition to optimal medical therapy (beta-blockers, renin angiotensin system blockers, etc.), CRT option is also used in patients with HF with reduced left ventricular systolic dysfunctions and left ventricular dyssynchrony to improve symptoms, and to decrease morbidity and mortality[3]. Current data shows that CRT therapy is not used adequately in patients who need it. Because of the many clinical conditions and pathophysiological mechanisms underlying HF, approximately 1/3 of patients with an implanted CRT device do not benefit from this treatment. Failure of CRT therapy, known as non-responders, is dependent on definitional criteria and also related to many pre- and post-procedure factors[4].

As common endocrine diseases, thyroid diseases have undeniable effects on cardiac

Corresponding Author: Mehmet Balli, MD; e-mail: dr_mehmetballi@hotmail.com

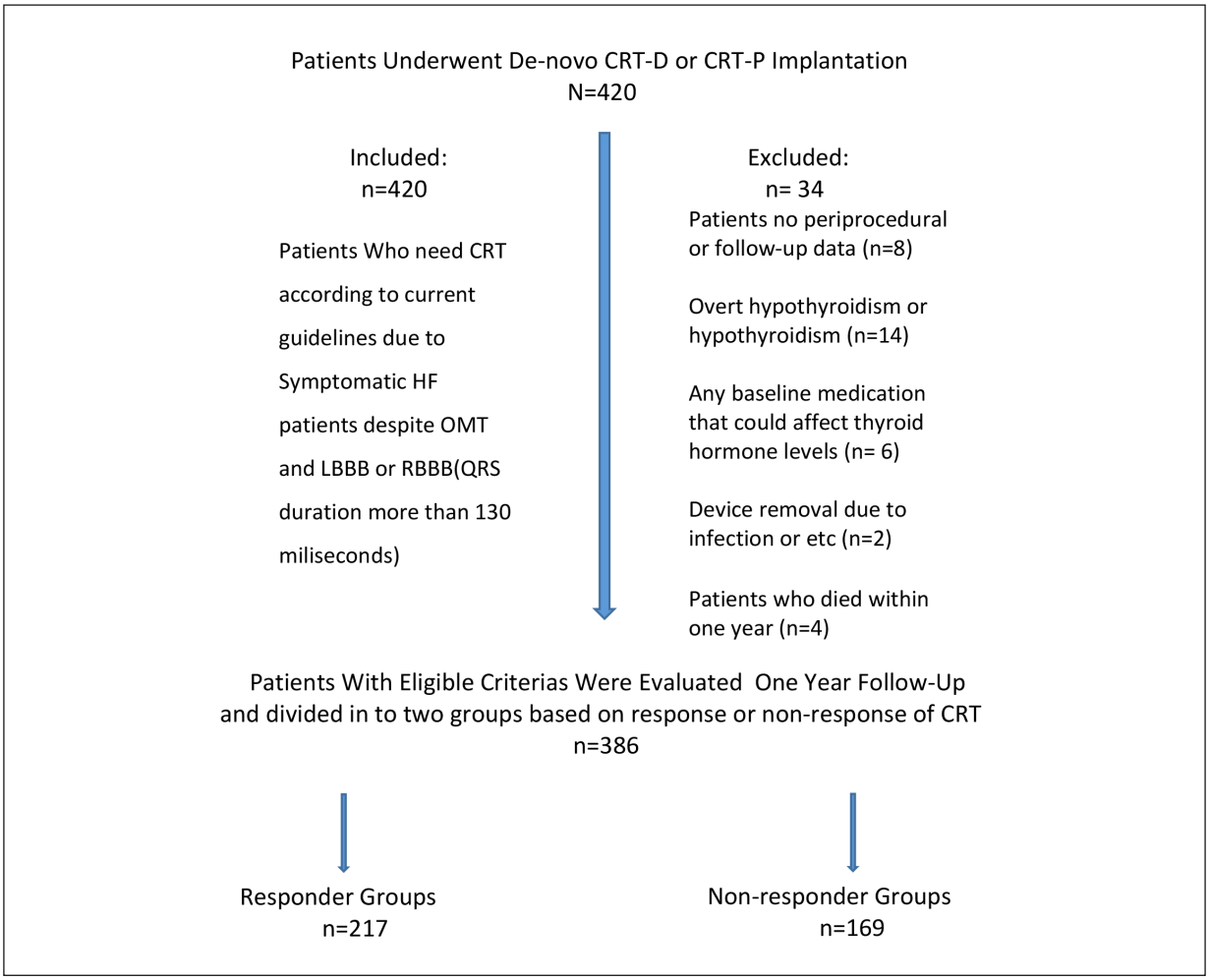

Figure 1. Study flow chart.

functions[5]. Hypothyroidism is associated with increased vascular resistance, decreased cardiac systolic-diastolic function and ventricular filling, and may also be related to atherosclerosis and coronary artery disease[6,7]. Previous studies[8,9] have shown that thyroid stimulating hormone (TSH) acts on vascular smooth muscle cells, adversely affect endothelial functions and impairs vascular smooth muscle cells migration even if patients are subclinical. Moreover, subclinical hypothyroidism (SCH) is also associated with atherosclerosis, increased carotid intima-media thickness, carotid plaques and progression of cardiovascular disease[10,11]. Although many clinical or technical factors affecting treatment response have been evaluated in patients treated with CRT, there are no clear data about the effects of SCH on treatment response.

Patients and Methods

Study Population

Between March 2021 and December 2016, 420 consecutive patients who received first time CRT-defibrillator (CRT-D) or CRT-pacemaker (CRT-P) were retrospectively included in this cohort study. CRT was applied to patients with symptomatic HF despite having guideline-directed optimal medical treatment for at least 3 months and QRS duration of 130 milliseconds or greater according to current guidelines[12]. Patients with a life expectancy of less than one year and who had a pacemaker or underwent CRT upgrade procedure were excluded. Known overt hypothyroidism or hyperthyroidism patients, acute or sub-acute thyroiditis patients, patients with renal replacement therapy, who did not permit the use of their records for research,

and patients who did not have peri-procedural and follow-up data in hospital records, were also excluded from the study. Patients who used any medication that could affect thyroid hormone levels, such as levothyroxine sodium, propylthiouracil, amiodarone, estrogens, lithium, or corticosteroids were also excluded[13-15]. Patients who underwent technically suboptimal implantation procedure such as placement of a left ventricular lead in a location other than the posterolateral or lateral cardiac veins, were excluded to avoid confusing results. Details are shown in Figure 1. Our study was approved by the Clinical Research Ethics Committee of Mersin University based on strict maintenance of participant anonymity (App. No.: 2018/272 and E-78017789-600-2011405). Informed consent was also obtained from all subjects.

Blood Sampling and Laboratory Assays

In addition to routine biochemical and hematological parameters, serum TSH, free triiodothyronine (FT3), and free thyroxin (FT4) levels were also measured routinely prior to CRT implantation procedures. Blood samples were obtained from a peripheral vein after 8 hours of fasting. Hematological parameters were measured using an XT-2000i analyzer (Sismex America Inc., Mundelein, IL, USA). Serum urea, creatinine, triglyceride, total cholesterol, high-density lipoprotein, low-density lipoprotein, and glucose levels were measured using routine laboratory techniques. FT3, FT4, and TSH levels were evaluated by chemiluminescence immunoassay method using E170 (Elecsys module) immunoassay analyzers (Roche Diagnostics, Mannheim, Germany). The reference intervals for FT3, FT4, and TSH were 1.71-3.71 pg/dL, 0.70-1.48 ng/dL, and 0.35-4.94 IU/mL, respectively.

Definitions

Hypertension (HT), hyperlipidemia (HL), HF and diabetes mellitus (DM) were identified and treated during the follow-up period according to current guidelines[4,16]. All echocardiographic evaluations were performed while patients were at rest using the modified Simpsons' method (Vivid S6 N GE Vingmed Ultrasound, Horten, Norway) by a different cardiologist who was blinded to the study design. QRS duration (baseline or paced) was calculated from the beginning of the Q wave to the end of the S wave by precordial V1-6 derivation, and the average of these values was accepted as the QRS duration. All patients' serum TSH, FT3 and FT4 levels were obtained before CRT implementation. Patients with normal FT3 and FT4 levels and TSH levels that were higher than reference interval were accepted as SCH according to previous reports[13]. The response of CRT was defined as a relative increase (≥15%) or absolute increase (≥10%) in LVEF from implantation to one-year after follow-up[17,18].

Device Implantation and Follow-Up Procedure

In our pacemaker clinic, we implanted commercially available Medtronic Compia®, Protecta® CRT-Ds or Medtronic Solara® CRT-Ps systems for patients who needed CRT. The bipolar steroid eluting active atrial lead was implanted into the right atrial appendage, the active right ventricular lead was implanted into the right ventricular apical area and the left ventricular lead was inserted into the coronary sinus posterolateral (primary target vein) or lateral vein. All lead implantations were performed using axillary vein puncture. The pacing generator was implanted in the right or left subpectoral area according to the patient's preference and anatomical considerations. At the end of the optimal lead and battery generator implantation, the patients were routinely monitored overnight at the hospital. In our pacemaker clinic we checked the pacemaker pocket before discharge and pacing parameters were also controlled and optimized by experienced cardiologists using 12 derivations surface electrocardiogram and/or transthoracic echocardiography. All patients' medical conditions were revised, and medical treatments were conducted according to current HF guidelines[4]. After discharging, device was evaluated and programmed routinely after one month and every six months in case of necessity at our outpatient pacemaker clinic.

Statistical Analysis

Statistical analysis was performed with SPSS 22.0 software (IBM Corp., Armonk, NY, USA). The clinical characteristics are presented as mean ± standard deviation for quantitative variables and as percentages for categorical variables. Distribution of the data was tested with Shapiro-Wilk test. Student's *t*-tests or Mann-Whitney U tests were performed to compare the continuous variables. Chi-square (x^2) tests were run to compare proportions. Multivariable logistic regression models were created to evaluate the relationship between CRT response and SCH. As potential risk factors, baseline QRS duration, age, gender, base-

Table 1. Baseline clinical and laboratory characteristics of study groups according to the CRT response.

Variables	Responders N=217	Non-responders N=169	*p*-value
Age, Years	62.9 ± 10.9	62.3 ± 12.4	0.615
Gender, Female, n (%)	56 (25.8)	50 (29.6)	0.410
BMI	27.6 ± 3.1	27.4 ± 3.1	0.573
Diabetes mellitus, n (%)	117 (53.9)	94 (55.6)	0.739
Hypertension, n (%)	125 (57.6)	103 (60.9)	0.509
Hyperlipidemia, n (%)	117 (53.9)	78 (46.2)	0.131
Smoking, n (%)	47 (21.7)	39, (23.1)	0.741
History of obstructive CAD, n (%)	140 (64.5)	118 (69.8)	0.273
COPD, (%)	4 (1.8)	6 (3.6)	0.296
Urea, mg/dL	52.1 ± 25.9	53.6 ± 47.8	0.682
Creatinine, mg/dL	1.06 ± 0.63	1.06 ± 0.52	0.996
Albumine, d/dL	4.0 ± 0.5	4.0 ± 0.5	0.532
Wight Blood Cells, counts/uL	7,933.1 ± 2,627.0	8,748.9 ± 6,722.0	0.103
Platellet counts, x1000/μL	236.6 ± 65.3	255.7 ± 166.7	0.124
Haemoglobine, g/dL	13.0 ± 1.8	12.8 ± 1.8	0.285
Na, mmol/L	138.3 ± 3.0	137.7 ± 3.6	0.098
K, mmol/L	4.4 ± 0.5	4.5 ± 0.5	0.054
TSH, IU/mL	2.2 ± 1.7	3.4 ± 2.6	**<0.001**
Ft3, pg/dL	2.7 ± 0.5	2.6 ± 0.5	0.067
Ft4, ng/dL	1.2 ± 0.2	1.2 ± 0.3	0.657
Baseline LVEF,(%)	29.5 ± 4.2	27.0± 4.9	**<0.001**
Follow-up LVEF,(%)	38.8 ± 5.0	27.3 ± 4.9	**<0.001**
Δ LVEF, (%)	9.2 ± 3.1	0.3 ± 0.6	**<0.001**
Baseline QRS interval, msec	147.1 ± 13.2	143.3 ± 12.0	**0.004**
Postimplantation QRS interval, msec	124.6 ± 6.7	123.9 ± 6.1	0.335
LBBB, n (%)	179 (82.5)	145 (85.8)	0.381
Medications:			
ACEI-ARB, n (%)	192 (88.5)	156 (92.3)	0.211
CCB, n (%)	72 (33.2)	63 (37.3)	0.404
BB, n (%)	203 (93.5)	152 (89.9)	0.197
Digoxine, n (%)	7 (3.2)	2 (1.2)	0.188
Ivabradine, n (%)	79 (36.4)	51 (30.2)	0.200
Spiranolactone, n (%)	163 (73.1)	126 (74.6)	0.900
Furosemid, n (%)	200 (92.2)	148 (87.6)	0.134
ARNI, n (%)	2 (0.9)	2 (1.2)	0.802
SGLT-2 inhibitors, n (%)	1 (0.5)	1 (0.6)	0.859
Insuline, n (%)	37 (17.1)	24 (14.2)	0.436
OAD(all groups), n (%)	83 (38.2)	65 (38.5)	0.994
Lead Meassurements:			
RA Thresolds at baseline	0.6 ± 0.1	0.6 ± 0.2	0.907
RV Thresholds at baseline	0.7 ± 0.4	0.6 ± 0.2	0.054
LV thresholds at baseline	0.9 ± 0.5	0.8 ± 0.3	0.511
SCH, n (%)	12 (5.5)	27 (16.0)	**0.001**
CRP, mg/dl	1.05 ± 1.4	0.90 ± 1.1	0.288
AF,n (%)	13 (6.0)	4 (2.4)	0.086

BMI, body mass index[weight(Kilograms)/Height(meters)^2]; CAD, coronary artery disease; COPD, chronic obstructive pulmonary diseasse; TSH, thyroid stimulating hormone; FT3, free triiodothyronine; FT4, free thyroxin; LVEF, left ventricular ejection fractions, Δ LVEF, changes of left ventricular ejection fractions; LBBB, left bundle branch block; ACEI, Angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blockers; BB, beta blockers; CCB, dihydropyridine calcium channel blockers; ARNI, angiotensin receptor neprylisin inhibitor; SGLT-2, sodium-glucose cotransporter-2; OAD, oral antidiabetics; RA, right atrium; RV, right ventricule; LV, left ventricule; SCH, subclinical hypothyroidism; CRP, C reactive protein; AF, atrial fibrillation.

Table II. Predictors of CRT response after one year follow-up.

Variables	OR	95% CI	*p*-value
Baseline QRS interval, msec	**1.033**	**1.012 – 1.055**	**0.002**
Age, years	1.004	0.986 – 1.023	0.652
Gender, (female)	1.127	0.693 – 1.834	0.630
Baseline LVEF, (%)	**1.135**	**1.081 – 1.192**	**<0.001**
Postimplant QRS, msec	0.991	0.954 – 1.029	0.635
Hypertension,n (%)	0.972	0.610 – 1.550	0.905
CAD, n (%)	1.246	0.774 – 2.005	0.365
SCH, n (%)	**0.279**	**0.129 – 0.604**	**0.001**
LBBB, n (%)	1.443	0.785 – 2.655	0.238
BMI	1.005	0.938 – 1.078	0.878
Diabetes mellitus, n (%)	0.930	0.591 – 1.462	0.752

CAD, coronary artery disease; SCH, subclinical hypothyroidism; LBBB, left bundle branch block; BMI, body mass index[-weight(Kilograms)/Height(meters)^2].

line LVEF, post-implantation QRS duration, the presence of coronary artery disease (CAD), HT, left bundle branch block (LBBB) and DM and body mass index were included in the base model. Then the final model was created by adding SCH to the variables in the base model. To demonstrate the independent prognostic effect of SCH, the performance measures of the base and final models were compared using -2 log-likelihood, R^2, the Akaike's information criterion (AIC) and the receiver operating characteristic-area under the curve (ROC-AUC) (c-statistics). The relationship between SCH and the CRT response was quantified using the adjusted odds ratio (OR) and 95% clinical index (CI). We also performed multivariate regression analysis using potential risk factors such as presence of DM, LBBB, SCH, baseline QRS duration, baseline LVEF and postimplant QRS duration to identify independent predictors of CRT non-responsiveness. For all statistical analyses, *p*-values of less than 0.05 were considered statistically significant.

Results

A total of 386 patients, with available data who meet the inclusion criteria from implantation to the one-year follow-up visit, were included in this retrospective cohort study. After one year follow up, patients were divided into two groups based on their CRT response (responders 56.3% *vs.* non-responders 43.7%). When the demographic data were evaluated, age, gender and the presence of DM, atrial fibrillation and CAD were similar between responder *vs.* non-responder groups. Although there was no statistical significance in terms of the presence of LBBB, or biochemical and hematological values, TSH levels were higher (p <0.005) in non-responder group.

We also evaluated postimplant medications [such as angiotensin-converting enzyme inhibitor and angiotensin receptor blocker (ACEI-ARB), beta blockers, angiontensin receptor neprilysin inhibitor (ARNI) and sodium-glucose cotransporter-2 (SGLT-2) inhibitor usage] and lead diagnostics, and found insignificant differences between the two groups (p >0.005). According to the study results, the responder group had higher baseline LVEF (p <0.001), higher follow-up LVEF (p <0.001) and longer baseline QRS interval (p =0.004), but similar post-implant QRS interval duration (p >0.005). Other demographic and clinical data are presented in Table I.

We performed logistic regression analyses to determine the risk factors to contribute to CRT

Table III. Comparison of base model without SCH patients and final model with including SCH patients.

Models	2 LL	R2	AIC	AUC
Base model	-486	0.136	509	0.680
Final model	-476	0.171	500	0.700

LL, log likelihood; AIC, Akaike's information criterion; AUC, area under curve.

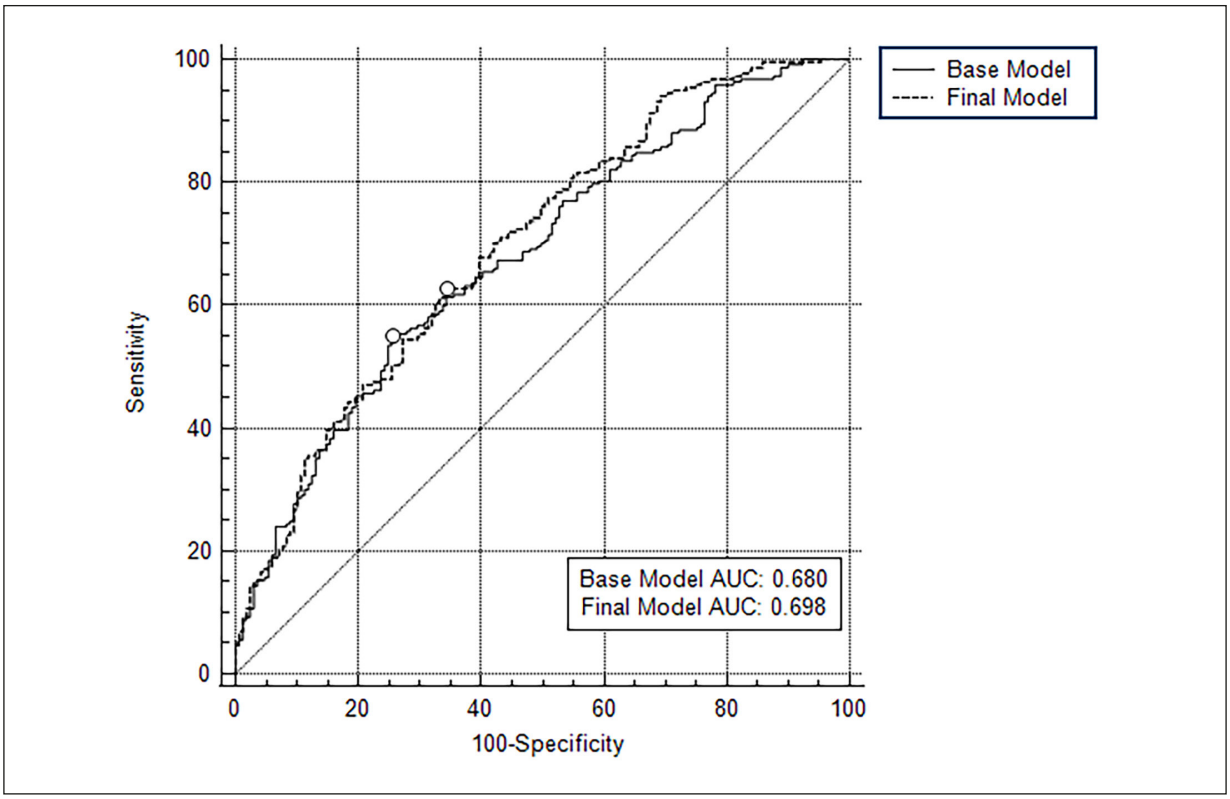

Figure 2. Comparison of the ROC curve of base model without SCH patients and final model with including SCH patients.

non-response including the presence of DM, CAD and HT, the baseline LVEF, SCH, LBBB, the baseline QRS duration, postprocedural QRS duration, age, gender, and body mass index (BMI). We found that the baseline QRS interval [B, 0.033; OR, 1.033; 95% CI, 1.012-1.055; p =0.002], the baseline LVEF [B; 0.127; OR, 1.135; 95% CI, 1.081-1.192; p <0.001] and the presence of SCH [B; -1.278; OR, 0.279; 95% CI, 0.129-0.604; p =0.001] were independent predictors of CRT response (Table II). Then, we performed logistic regression analysis alternatively by including the serum FT3 levels instead of the presence of SCH, with the other risk factors being the same. We found that the baseline QRS interval [B, 0.033; (OR, 1.034; 95% CI, 1.013-1.054; p =0.002], baseline LVEF [B; 0.127; OR, 1.135; 95% CI, 1.081-1.192; p <0.001] and serum FT3 level [B; 0.472; OR, 1.604; 95% CI, 1.072-2.339; p =0.021] also predicted therapy response.

We also created base model (without the presence of SCH) and a final model (including SCH) to demonstrate the independent prognostic effect of SCH and found to be $ROC\text{-}AUC_{Base\ model}$; 0.680, (95% CI 0.630-0.730) *vs.* $ROC\text{-}AUC_{Final\ model}$; 0.700, (95% CI 0.650-0.750). Details are shown in Table III and Figure 2.

Discussion

Our study has important results and is the first to focus on the relationship between presence of SCH and treatment response in patients who underwent CRT. Mainly, we showed that the presence of SCH before resynchronization therapy was associated with increased CRT non-responsiveness and related worse LVEF recovery. In addition, shorter preprocedural QRS duration and lower baseline LVEF were also independent predictors of CRT non-responsiveness.

The rate of non-response to CRT varies according to the definition criteria and characteristics of the patients in the previous studies and reaches up to 40%[4]. In our study, we found the non-responder rate to be 43.7%, which may be considered slightly higher than in the current literature. As an objective method, we used LVEF change as an easy and reproducible parameter to determine responsiveness before and after the CRT procedure. Although in one study, Yang et al[19] defined CRT responsiveness using a 5% change in LVEF, we defined CRT response using relative increase

(≥15%) or absolute increase (≥10%) in LVEF after 1 year which was similar to previous studies[8,9]. The fact that we used relatively higher echocardiographic criteria to evaluate the CRT response and that the majority of our patient group had ischemic etiology (64.5% responders *vs*. 69.8% non-responders) may explain our slightly higher rate of non-responders.

It is well known that overt hypothyroidism is related to impaired cardiac output, cardiac systolic dysfunction and heart failure[19]. SCH is another spectrum of thyroid deficiency and also associated with adverse effects on cardiovascular system, even subclinical[5-7]. The present study is the first to focus on the relationship between the presence of SCH and CRT response and showed that SCH independently predicted CRT non-responsiveness at one year follow up and adding the presence of the SCH to the known risk factors may be a rational approach for identifying non-responders.

Several pathophysiological mechanisms may explain the association between SCH and CRT unresponsiveness. First, cardiac contractile functions may be adversely affected due to vascular smooth cell apoptosis, cardiac sarcomere lengthening and chamber dilatation in patients with insufficient thyroid function[20-22]. Second, it is well known that the endothelial system plays a key role in cardiovascular endpoints and experimental studies have shown that injecting TSH impairs endothelial vasodilatation[9]. In addition, SCH patients have increased peripheral vascular resistance[23], and these factors may be also related to CRT non-responsiveness in this patient groups.

In our study we also found that the higher serum TSH and lower FT3 levels predicted CRT non-responsiveness. Because of FT4 cannot be transported by myocytes, heart muscle is basically FT3 dependent and exerts its effects through genomic and nongenomic pathways[24,25]. Chen et al[26] showed that low-normal FT3 levels were associated with poor prognosis CRT patients. However, they did not evaluate SCH patients in their study. In contrast to our study, one study[19] found no relation between presence of SCH and CRT non-responsiveness. However, their study data did not include FT3 and FT4 levels so, a lack of these data may cause inaccuracy in the diagnosis of SCH and these conflicting results.

Study Limitations

Despite the clear relationship between presence of SCH and CRT non-responsiveness in this present study, we did not evaluate the effect on thyroid replacement therapy (TTR) and CRT patients due to the study design. This issue may be one of the limitations of our study. In one randomized study, Gencer et al[27] found no benefit of TTR on cardiac systolic and diastolic functions in patients with SCH. However, too many heart failure patients were excluded in their study and there was a significant difference between the study group and the control group in terms of LVEF, unlike our study. To date whether TTR has some beneficial effect or not in patients SCH and underwent CRT remains unclear. Second, we used the LVEF changes to evaluate the CRT response at one year follow up. In addition to the LVEF changes, functional capacity assessment and evaluation of some biomarkers such as brain natriuretic peptide (BNP) or N-terminal pro b-type natriuretic peptide (NT-proBNP) could make additional contributions to our study. However, the retrospective cohort design, the relatively large number of CRT patients and the relatively high LVEF cut-off value used to evaluate CRT non-response, may be considered as an advantage of our work.

Conclusions

The present study is the first to focus on the relationship between the presence of SCH and the treatment response in patients who underwent CRT. According to our results, the presence of the SCH is one of the independent predictors of therapy failure and non-response in HF patients undergoing CRT. Considering the presence of SCH, when evaluating the risk factors associated with CRT, unresponsiveness may be an important approach to identify patients who obtain maximum benefit from CRT treatment. In addition, the detection and elimination of risk factors, that may be associated with treatment unresponsiveness, is a rational approach in patients undergoing CRT.

Conflict of Interest

The authors declare no conflict of interest.

Ethics Committee

Our study was approved by the Clinical Research Ethics Committee of Mersin University based on strict maintenance of participant anonymity (App. No.: 2018/272 and revised E-78017789-600-2011405).

Informed Consent

Informed consent was also obtained from all subjects.

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