Correlation of body mass index and responder status in heart failure patients after cardiac resynchronization therapy: Does the obesity paradox exist?

M. CLEMENS[1]* ■ E. NAGY-BALÓ[1] ■ CS. HERCZKU[1] ■ ZS. KARÁNYI[2] ■ I. ÉDES[1] ■ Z. CSANÁDI[1]

[1]Department of Cardiology, University of Debrecen, Debrecen, Hungary
[2]Department of Internal Medicine, University of Debrecen, Debrecen, Hungary
*Corresponding author: Marcell Clemens M.D., Department of Cardiology, University of Debrecen, Móricz Zs. krt. 22, H-4032 Debrecen, Hungary; Phone: +36-52-411-717; Fax: +36-52-414-928; E-mail: marcellclemens@gmail.com

Abstract: *Aims:* We investigated the influence of body mass index (BMI) on the prevalence of responder status in chronic heart failure patients after cardiac resynchronization therapy (CRT). *Methods:* Data on 169 patients with resynchronization therapy were analyzed. Patients were categorized on the basis of the BMI measured at device implantation according to the WHO classification, as normal (BMI: 18.5–24.9 kg/m^2), overweight (BMI: 25–29.9 kg/m^2) or obese (BMI: ≥ 30 kg/m^2). Patients were considered responders if left ventricular ejection fraction was increased by at least 5% at 6-month follow-up. *Results:* The mean age in the study population was 60.9 ± 10.86 years (females 29%). The BMI subgroups did not exhibit any significant differences in baseline characteristics (age, gender, left ventricular ejection fraction or NYHA class). Elevated BMIs were associated with higher prevalence of responder status (overweight: 71.4%, obese: 63.0%) relative to subjects with a normal BMI (44.7%) ($p = 0.015$). *Conclusions:* In this CRT population, overweight status was associated with a more favorable response to CRT, indicating that the response may possibly be influenced by factors other than those directly related to the heart status or the technical details of the CRT.

Keywords: cardiac resynchronization therapy, body mass index, obesity paradox, dilated cardiomyopathy, responder status

Introduction

Cardiac resynchronization therapy (CRT) has become a well-established treatment modality which leads to better quality of life, improves left ventricular ejection fraction (LV EF) and decreases mortality in a selected group of patients with chronic heart failure. However, a relatively high proportion (20–40%) of such patients do not respond to CRT according to most of the reports, in which mostly functional end-points were used [1, 2]. A number of factors (including the etiology of the cardiomyopathy, the baseline QRS width, the positions of the right and left ventricular leads and multiple echocardiographic parameters) have already been investigated as regards their potential to predict a positive response to CRT. However, the results were either negative or conflicting, therefore an adequate predictor that could be used in routine clinical practice is still lacking [3–9].

Obesity has rapidly become a major public health problem worldwide. The latest WHO statistics disclose that 32.2% of the general population in the United States is obese, with a body mass index (BMI) exceeding 30 kg/m^2 [10]. Elevated BMI is associated with well-known cardiovascular risk factors, such as hypertension, diabetes mellitus and dyslipidemia [11]. Indeed, excess weight itself is an independent risk factor for coronary artery disease, stroke, new-onset heart failure and death [12, 13]. Obesity-related myocardial abnormalities include diastolic dysfunction, LV hypertrophy, increased LV end-diastolic diameter and in rare cases cardiomyopathy [14, 15]. Surprisingly, recent data indicate that elevated BMI favorably alters the course of chronic heart failure, lowering the risk of hospitalization and death in overweight and obese populations as compared with those with normal BMI [16–18]. In acute heart failure, a higher BMI was also associated with lower in-hospital mortality [19]. In a small study involving patients with single or dual chamber implantable cardioverter defibrillators, a higher BMI was likewise associated with better survival [20].

The aim of the present study was to investigate the potential influence of BMI on response to CRT: whether elevated BMI is associated with a higher prevalence of a responder status among patients with chronic heart failure and CRT?

Materials and Methods

Patient population

The data on 229 consecutive patients who underwent CRT (biventricular pacemaker or defibrillator) implantation at our Department of Cardiology between September 2004 and August 2008 were reviewed. The 56 patients were excluded from the study because of missing data or a postimplantation follow-up shorter than 6 months. The 173 patients with complete baseline (including adequate weight and height) and follow-up data were analyzed retrospectively. CRT indications were: impaired LV EF (<35%), LVEDD >55 mm, clinical signs of heart failure (NYHA II–IV) and a sinus rhythm with left bundle branch block (QRS complex duration >120 msec). The underweight (BMI: ≤ 18.4 kg/m^2) patients ($n=4$) in our CRT population were subjects with end-stage heart failure and cardiac cachexia and were therefore excluded from further analysis. All patients received standard heart failure medical therapy with beta-blockers, angiotensin–converter enzyme inhibitors and diuretics, including spironolactone.

BMI categories

Weight was measured daily throughout hospitalization. To avoid the confounding effect of fluid retention in the calculation of the BMI, the discharge weight was used following intravenous diuretic therapy as necessary to compensate the patient. BMI was calculated as the weight in kilograms divided by the square of the height in meters. Patients were categorized on the basis of the BMI according to the WHO classification as normal (BMI: 18.5–24.9 kg/m^2), overweight (BMI: 25–29.9 kg/m^2) or obese (BMI: ≥ 30 kg/m^2).

Definition of response to CRT

Echocardiography was performed prior to device implantation and at every follow-up visit. LV diameters were measured and EFs were calculated by the Quinones method. The responder status was evaluated by echocardiographic measurements at 6-month follow-up: a patient was regarded as a responder if LV EF was improved by at least 5% in absolute terms at 6-month follow-up.

The responder status was also defined by the improvement in clinical status: a patient was considered responder if their NYHA class status has been improved by at least one class at 6-month follow-up compared to baseline.

Statistics

Continuous variables are reported as means ± standard deviation, while categorical variables are presented as percentages. Stochastical correlations between discrete variables were investigated by means of chi^2-test. Kolmogorov-Smirnov test was used for testing whether the distribution is Gaussian or not. Groups of continuous variables were compared by using the unpaired *t*-test and the ANOVA test, as appropriate. P values < 0.05 were considered statistically significant. Statistical calculations were performed by using Prism3 package.

Table I Baseline patient characteristics classified according to BMI

	Normal (BMI 18.5–24.9)	Overweight (BMI 25–29.9)	Obese (BMI ≥ 30)	*p* value
n (%)	45 (26.6%)	70 (41.4%)	54 (32.0%)	
Males (%)	29 (64.4%)	49 (70.0%)	42 (77.8%)	0.34
Age (yrs)	61.1 (± 11.1)	62.5 (± 11.2)	58.3 (± 9.9)	0.10
CAD (%)	15 (33.4%)	22 (31.4%)	19 (35.2%)	0.91
Diabetes (%)	4 (8.9%)	14 (20.0%)	15 (27.8%)	0.06
Hypertension (%)	15 (33.4%)	33 (47.1%)	28 (51.2%)	0.16
NYHA				
II	10 (22.2%)	13 (18.6%)	18 (33.3%)	0.15
III	27 (60%)	46 (65.7%)	29 (53.7%)	0.40
IV	8 (17.8%)	11 (15.7%)	7 (13.0%)	0.80
LV EF (%)	25.8 (± 5.5)	26.5 (± 8.2)	28.0 (± 5.2)	0.25
LVESD (mm)	58.5 (± 8.5)	59.2 (± 11.3)	57.9 (± 8.8)	0.77
LVEDD (mm)	69.6 (± 8.5)	70.6 (± 10.6)	70.0(± 9.1)	0.85
CRT-D (%)	22 (48.9%)	33 (47.1%)	27 (50.0%)	0.95

Abbreviations: CAD – coronary artery disease, LV EF – left ventricular ejection fraction, LVESD – left ventricular end-systolic diameter, LVEDD – left ventricular end-diastolic diameter, CRT-D – biventricular defibrillator
(Statistical tests used for comparing groups of data: Chi2, ANOVA)

Results

Patient characteristics

The baseline characteristics of each BMI subgroups of the 169 patients (females: 49 {29.0%}; mean age 60.9 ± 10.86 years) are presented in Table I. There was an increasing trend in the prevalence of diabetes in the obese population relative to subjects with normal BMI, but the difference did not reach statistical significance. The average LV EF in the overall study population was 27 ± 6.72%. Almost half of the patients received biventricular implantable cardioverter defibrillator (CRT-D) in each BMI subgroups. Only 26.6% of the patients were within the normal BMI range, while 41.4% were overweight and 32% had BMI ≥ 30 (Fig. 1). The mean BMI was 28.7 ± 5.2 for males, and 27.0 ± 4.2 for female patients ($p = 0.049$).

Influence of BMI on responder status

Echocardiographic measurements indicated that the overall proportion of responders to CRT was 61.5% (104/169). Only 44.7% (20/45) of the patients with normal BMI were responders, whereas patients with elevated BMI were more likely to exhibit a positive response to CRT ($p = 0.015$): 71.4% (50/70) of the overweight and 63.0% (34/54) of the obese. The odds ratio of overweight patients displaying a positive response to CRT was 1.6 (CI: 1.12–2.30) relative to patients with normal BMI (Fig. 2).

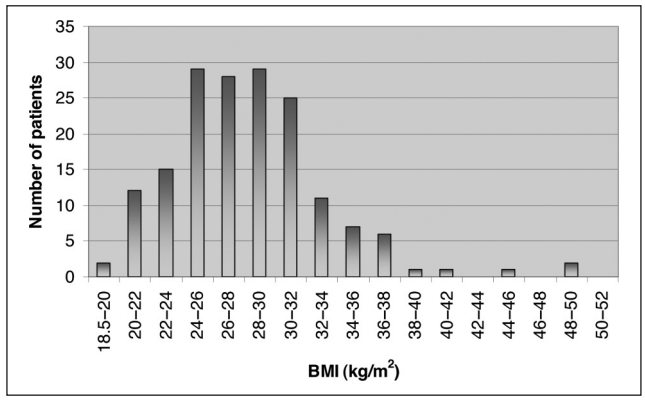

Fig. 1. Distribution of the study population according to BMI

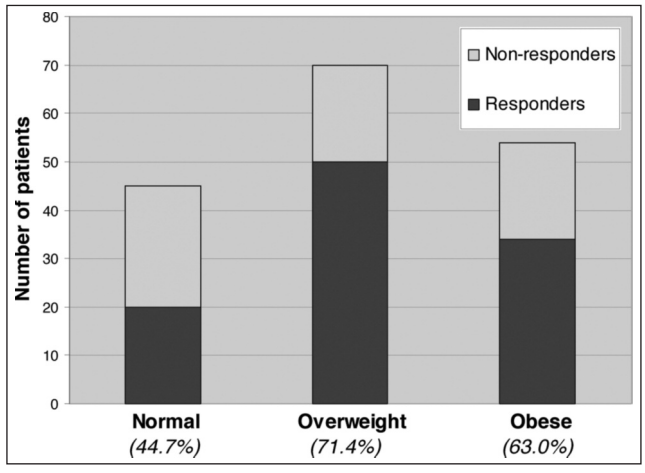

Fig. 2. Prevalence of responder status in the normal, overweight and obese groups evaluated by echocardiography (at least 5% improvement of the left ventricular EF). In the parenthesis: the proportion of the responder patients in each group. (Statistical test used for comparing data: Chi2)

Table II Response to CRT according to gender and BMI category

	Normal	Overweight	Obese
Females ($n = 49$)	8/16 (50.0%)	18/21 (85.7%)	9/12 (75.0%)
Males ($n = 120$)	9/29 (31.0%)	31/49 (63.3%)	25/42 (59.5%)

(Statistical test used for comparing groups of data: Chi2)

The gender differences in response to CRT are presented in Table II. There was a tendency of higher response rate among females in each category. Only 31% of male patients in the normal weight group were responders.

By the improvement in functional status (at least one NYHA class) 59.2% of the patients showed positive response to CRT. Similarly to the echocardiographic results, the highest prevalence of responder status was found in the overweight population (68.6%, 48/70), whereas only 53.3% (24/45) of patients with normal BMI and 51.9% (28/54) of the obese were regarded as a responder, although the difference was not statistically significant ($p = 0.111$) (Fig. 3).

Additional observations

In several patients normalization of the LV EF (≥50%) was observed after CRT. Although statistical analysis was not feasible in these small subgroups (Fig. 4), the trend was corresponding with the main results.

Over a mean follow-up of 23.4 ± 11.1 months (range 6–50 months), a total of 13 deaths occurred in the study population. Deaths during follow-up were more com-

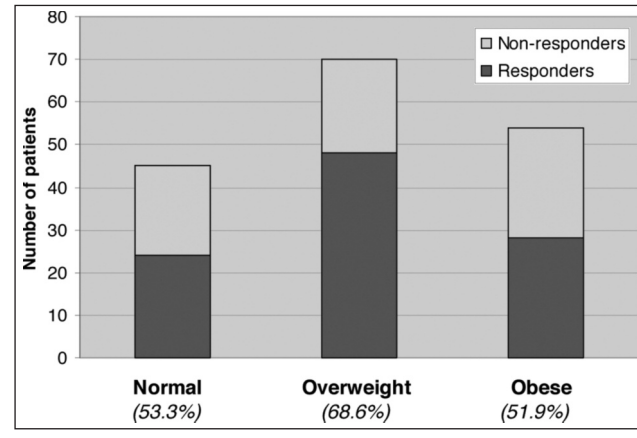

Fig. 3. The prevalence of responder status defined by improvement in functional status (at least one NYHA class) relative to baseline. In the parenthesis: the proportion of the responder patients in each group. (Statistical test used for comparing data: Chi2)

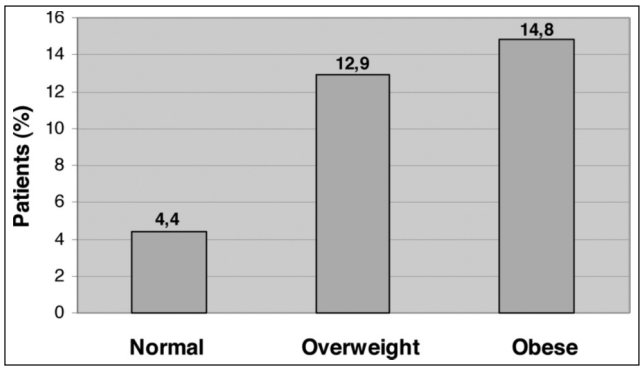

Fig. 4. Proportion of patients with normalized left ventricular ejection fraction (EF ≥ 50%) according to the BMI categories. (Statistical test used for comparing data: Chi2)

mon among non-responders 9/65 (13.4%) than among responders 4/104 (3.8%), $p = 0.0176$. There were 4 deaths (8.9%) in the normal BMI group, 4 (5.7%) in the overweight group and 5 (10.2%) in the obese group.

Discussion

The "non-response" phenomenon in CRT patients has been intensively studied almost since the clinical introduction of this therapy. The clinical variables tested for a possible correlation with the long-term outcome were mostly related to technical aspects of the CRT, such as lead positioning and device programming, functional status of the heart, including the 12-lead ECG appearance and several echocardiographic parameters measured prior to implantation and other well-known prognostic factors in CHF, e.g. the renal function and the serum level of NT-proBNP. The main finding of our current work is that the baseline BMI exhibits a clear correlation with the improvement in echocardiographic parameters 6 months after implantation. The very low (31%) response rate in our male patients with normal weight was especially striking. As far as we are aware, the only previous study of the BMI in patients after CRT was a post-hoc analysis of CARE-HF in a search for potential predictors of long-term outcome among baseline categorical variables and continuous variables measured at baseline and 3 months [21]. In CARE-HF, the BMI did not prove to be a predictor of long-term survival. In view of the relatively low number of deaths among our patients, a potential relationship with mortality could not be statistically tested. In this study responder status was defined 6 months after device implantation by echocardiographic and functional improvement as well. The rationale behind predicting the long-term outcome after CRT by the early response is that it simultaneously tests both the patient substrate and the adequacy of the therapy. Earlier reports suggested that changes in ventricular function, but not in symptoms [22] or changes in the level of natriuretic peptides [23] during the first 3–6 months did indeed predict the long-term response to therapy.

Obesity is a well-known independent risk factor for the development of cardiovascular diseases, but it favorably alters the prognosis in established chronic heart failure, a phenomenon known as the "obesity paradox" [24]. This "reverse epidemiology" has likewise been demonstrated in other chronic, wasting diseases with a significantly reduced life expectancy, where obesity improved the short-term prognosis [25]. The exact mechanism of the obesity paradox is not fully understood. Proposed mechanisms include increased hemodynamic stability in obesity, the protective adipokine profile, the endotoxin-lipoprotein hypothesis, the toxin sequestration of fatty tissue and the antioxidative effect of muscle tissue. The proportion of obese patients in our study population was 32%, while only 27% of the patients had a BMI within the normal range. These statistics are similar to those observed in the general population of the USA and several countries of the European Union, indicating that obesity is a major problem, affecting a significant proportion of the population, including those with chronic heart failure [10]. The phenomenon of the obesity paradox calls attention to the fact that the relevant guidelines and initiatives might need to distinguish between healthy individuals and patients with certain chronic diseases. These latter individuals might require a different nutritional and weight management strategy in order to optimize their life expectancy. Additionally, demonstration of the obesity paradox in relation to CRT outcome underscores the importance of a multidisciplinary approach in a disease with such an extensive potential influence on the neurohumoral status and metabolism.

According to our results the responder rate is the highest in the overweight population, but is lower in patients both with normal and very high (>30, obese) BMI indicating that there is no linearity between BMI and responder status. Although we found a remarkable difference in the prevalence of responder status comparing obese patients to those with a normal BMI (44.7% vs. 63.0%) the difference was not statistically significant at this sample size ($p = 0.07$). Similarly when the responder status was defined by at least one NYHA class improvement in the clinical status the comparable responder rate of obese patients and patients with normal BMI (51.9% vs. 53.3%) might be partially explained by the lower functional improvement of the obese due to their excess weight.

Important limitations to our study must be noted. Patients with NYHA II functional class heart failure were enrolled, though this is not an evidence-based indication and is not included in guidelines at present. However, according to the results of recent studies CRT in NYHA II functional class patients with a poor LV function and a left bundle branch block improves clinical outcome and LV function [26, 27]. The enrollment of these patients did not significantly change the results, as a similar relationship between BMI category and echocardiographic improvement was observed in each functional class. Ad-

ditionaly, the Quinones method was used for echocardiographic calculation of the LV function, which is the general practice of our echocardiographic team.

Conclusions

Higher BMI values were associated with a more favorable response to CRT, indicating that it might be influenced by factors other than those directly related to the heart status or the technical details of the CRT. Appropriate nutritional and weight management strategies need to be developed for these patients.

References

1. Birnie DH, Tang ASL: The problem of non-response to cardiac resynchronization therapy. Curr Opin Cardiol 21, 20–26 (2006)
2. Freemantle N, Tharmanathan P, Calvert MJ, Abraham WT, Ghosh J, Cleland JGF: Cardiac resynchronisation for patients with heart failure due to left ventricular systolic dysfunction — A systematic review and meta-analysis. Eur J Heart Fail 8, 433–440 (2006)
3. Chung ES, Leon AR, Tavazzi L et al.: Results of the predictors of response to CRT (PROSPECT) trial. Circulation 117, 2608–2616 (2008)
4. Mollema SA, Bleeker G, Wall van der E, Schalij M, Bax J: Usefulness of QRS duration to predict response to predict response to cardiac resynchronization therapy in patients with end-stage heart failure. Am J Cardiol 100, 1665–1670 (2007)
5. Gasparini M, Mantica M, Galimberti P et al.: Is the left ventricular lateral wall the best lead implantation site for cardiac resynchronization therapy. Pacing Clin Electrophysiol 26(1 Pt 2), 162–168 (2003)
6. Haghjoo M, Bonakdar HR, Jorat MV et al.: Effect of right ventricular lead location on response to cardiac resynchronization therapy in patients with end-stage heart failure. Europace 11, 356–363 (2009)
7. D'Ivernois C, Lesage J, Blanc P: Resynchronization: What if the left ventricular lead cannot reach the lateral or posterolateral wall? Pacing Clin Electrophysiol 31, 1041–1045 (2008)
8. Achilli A, Peraldo C, Sassara M et al.: Prediction of response to cardiac resynchronization therapy: The selection of candidates for CRT (SCART) study. Pacing Clin Electrophysiol 29 Suppl 2, S11–S19 (2006)
9. Molhoek SG, Bax J, Erven van L et al.: Comparison of benefits from cardiac resynchronization therapy in patients with ischemic cardiomyopathy versus idiopathic dilated cardiomyopathy. Am J Cardiol 93, 860–863 (2004)
10. World Health Organization: Global database of body mass index. Available at: http://www.who.int/bmi/index.jsp. Accessed January 20, 2009
11. Krauss RM, Winston M: Obesity: Impact on cardiovascular disease. Circulation 98, 1472–1476 (1998)
12. Kenchaiah S, Evans JC, Levy D et al.: Obesity and the risk of heart failure. N Engl J Med 347, 305–313 (2002)
13. Poirier P,. Giles TD, Bray GA et al.: Obesity and cardiovascular disease: Pathophysiology, evaluation, and effect of weight loss: an update of the 1997 American Heart Association Scientific Statement on Obesity and Heart Disease from the obesity committee of the Council of Nutrition, Physical Activity, and Metabolism. Circulation 113, 898–918 (2006)
14. Divitiis O, Fazio S, Petitto M et al.: Obesity and cardiac function. Circulation 64, 477–482 (1981)
15. Alpert MA, Terry BE, Mulekar M et al.: Cardiac morphology and left ventricular function in normotensive morbidly obesee patients with and without congestive heart failure, and effect of weight loss. Am J Cardiol 80, 736–740 (1997)
16. Curtis JP, Selter JG, Wang Y et al.: The obesity paradox body mass index and outcomes in patients with heart failure. Arch Intern Med 165, 55–61 (2005)
17. Bozkurt B, Deswal A: Obesity as a prognostic factor in chronic symptomatic heart failure. Am Heart J 150, 1233–1239 (2005)
18. Davos CH, Doehner W, Rauchhaus M et al.: Body mass and survival in patients with chronic heart failure without cachexia: The importance of obesity. J Card Fail 91, 891–894 (2003)
19. Fonarow GC, Srikanthan P, Costanzo MR et al.: An obesity paradox in acute heart failure: analysis of body mass index and inhospital mortality for 108,927 patients in the Acute Decompensated Heart Failure National Registry. Am Heart J 153, 74–81 (2007)
20. Schernthaner C, Pichler M, Strohmer B: Lower body mass index and atrial fibrillation as independent predictors for mortality in patients with implantable cardioverter defibrillator. Croat Med J 48, 59–67 (2007)
21. Cleland J, Freemantle N, Ghio S et al.: Predicting the long-term effects of cardiac resynchronization therapy on mortality from baseline variables and the early response. A report from the CARE-HF (Cardiac Resynchronization in Heart Failure) Trial. J Am Coll Cardiol 52, 438–445 (2008)
22. Yu CM, Bleeker BG, Fung JW-H et al.: Left ventricular reverse remodeling but not clinical improvement predicts long-term survival after cardiac resynchronization therapy. Circulation 112, 1580–1586 (2005)
23. Kubanek M, Málek I, Bytesnik J et al.: Decrease in plasma B-type natriuretic peptide early after initiation of cardiac resynchronization therapy predicts clinical improvement at 12 months. Eur J Heart Fail 8, 832–840 (2006)
24. Horwich TB, Fonarow GC, Hamilton MA et al.: The relationship between obesity and mortality in patients with heart failure. J Am Coll Cardiol 38, 789–795 (2001)
25. Kalantar-Zadeh K, Horwich TB, Oreopoulos A et al.: Risk factor paradox in wasting diseases. Curr Opin Clin Nutr Metab Care 10, 433–442 (2007)
26. Moss AJ, Hall WJ, Cannom DS et al.: Cardiac-resynchronization therapy for the prevention of heart-failure events. N Engl J Med 361, 1329–1338 (2009)
27. Daubert C, Gold MR, Abraham WT et al.: Prevention of disease progression by cardiac resynchronization therapy in patients with asymptomatic or mildly symptomatic left ventricular dysfunction. Insights from the European cohort of the REVERSE (Resynchronization reverses remodeling in systolic left ventricular dysfunction) trial. J Am Coll Cardiol 54, 1837–1846 (2009)