Clin Res Cardiol (2011) 100:159–166
DOI 10.1007/s00392-010-0226-7

ORIGINAL PAPER

Impact of oxygen uptake efficiency slope as a marker of cardiorespiratory reserve on response to cardiac resynchronization therapy

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Received: 25 March 2010 / Accepted: 7 September 2010 / Published online: 23 September 2010

Abstract

Background Cardiac resynchronization therapy (CRT) is limited by the high numbers of nonresponders. This study analyzed the impact of the cardiorespiratory functional reserve to predict the response to CRT.

Methods and results Twenty-eight patients (age 67 ± 9 years, LVEF $< 35\%$, NYHA class III, QRS 158 ± 25 ms) underwent submaximal cardiopulmonary treadmill exercise testing prior and 6 months after implantation of a CRT device. Breath-to-breath gas analysis was used for calculation of the oxygen uptake efficiency slope (OUES = non-effort-dependent index of cardiorespiratory functional reserve) in the responder and nonresponder group. Responders to CRT [defined by a decrease in left ventricular end-systolic volume (LVESV) $> 15\%$] showed a significant lower cardiorespiratory reserve at baseline (prior CRT) as compared to the nonresponders (OUES 1,235 ± 651 vs. 2,480 ± 590; $p < 0.01$). Responders showed an increase in OUES during CRT at the 6 months follow-up (1,879 ± 663; $p < 0.05$) whereas nonresponders showed no significant changes from baseline (2,194 ± 422; ns). Both responders and nonresponders showed an improvement in LVEF at the 6 months follow-up (23 ± 5 vs. 31 ± 9% and 26 ± 7 vs. 32 ± 3%; $p < 0.05$). Responders to CRT showed a decrease in NYHA classification (3.0 vs. 2.6 ± 0.5; $p < 0.05$) and a decrease in LVESV (175 ± 58 vs. 128 ± 40 ml; $p < 0.05$).

Conclusions Nonresponders to CRT showed a more preserved cardiorespiratory functional reserve as compared to responders despite similar NYHA classification. Evaluation of the OUES by submaximal exercise testing improves identification of responders to CRT.

Keywords Cardiac resynchronization therapy · Exercise capacity · Responder

Introduction

Cardiac resynchronization therapy (CRT) has evolved as a cost-effective treatment in patients with severe heart failure refractory to optimized neurohumoral therapy [1]. Large clinical trials showed a significant benefit on mortality and on morbidity in patients with wide QRS complex in NYHA class III and severely reduced left ventricular ejection fraction (LVEF) [2]. Besides the effects on mortality also other beneficial effects of CRT, such as a decrease in mitral regurgitation or even an increase in the conversion rate to sinus rhythm in heart failure patients with persistent atrial fibrillation have been described [3]. However, up to one-third of patients do not respond to CRT although fulfilling all current inclusion criteria for this therapy. Recently, various echocardiographic parameters failed to predict response to CRT (PROSPECT) [4]. Therefore, besides current inclusion criteria such as NYHA class, left ventricular ejection fraction and QRS duration, additional predictors are important to increase the number of responders to CRT.

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Although disease severity and functional limitation are in general excellent markers for risk stratification in CHF, the impact of NYHA classification to predict the response to CRT is poor. Up do date, there are conflicting data about the impact of the NYHA classification, respecting the degree of functional impairment in response to CRT [5, 6]. The REVERSE study showed only a moderate effect of CRT in patients with mild CHF with respect to a reduction in hospitalization [7]. Data from the MADIT-CRT trial showed a benefit in a composite end point (mortality and nonfatal heart failure) [8]; however, the impact of functional exercise capacity on the response to CRT remains yet unclear. In patients with cardiovascular diseases cardiopulmonary exercise testing (CPET) is an important tool for risk stratification [9, 10]. For example, oxygen consumption at peak exercise (peak VO_2) is widely accepted as gold standard for the evaluation of patients prior heart transplantation [11]. However, an accurate estimation of peak VO_2 is difficult to obtain in patients with severe heart failure due to limitations such as peripheral muscle fatigue, motivation or procedural difficulties (selection of an appropriate exercise protocol). Therefore, parameters obtained at submaximal exercise, such as the VE/VCO_2 slope or the ventilatory anaerobic threshold are used to stratify patients with congestive heart failure [12–15]. However, these parameters also show some limitations such as the practicability of measurements (e.g., the ventilatory anaerobic threshold cannot be obtained in about 25% of the patients) [16].

To overcome these difficulties a non-linear measure of ventilatory response to exercise the oxygen uptake efficiency slope (OUES) was proposed by Baba et al. [17]. The OUES reflects the combination of cardiovascular, musculoskeletal and pulmonary influences via a logarithmic transformation during incremental exercise. Due to the linearity throughout exercise, the calculation of OUES does not require maximal effort and is a reliable and reproducible parameter of exercise capacity in patients with cardiac diseases [18–24]. The prognostic value of the OUES in patients with chronic heart failure has been evaluated and appears to be even stronger than peak VO_2, ventilatory anaerobic threshold, and the VE/VCO_2 slope [21].

This study was conducted to evaluate the impact of cardiorespiratory functional reserve, as obtained by OUES, on response to CRT.

Methods

Study subjects

Twenty-eight consecutive patients (6 female, mean age 67 ± 9 years) with severe heart failure (NYHA class III; echocardiographic ejection fraction $< 30\%$) were included into this study prior first time implantation of a CRT device. All patients showed stable sinus rhythm and a left bundle branch block pattern in the standard 12-lead ECG. Each patient exhibited ventricular dyssynchrony with an interventricular mechanical delay ≥ 40 ms as assessed by echocardiography. The left ventricular lead was placed in a posterolateral vein with a position in the LAO 45° projection between 1.30 and 3.30 o'clock in all patients. Venous angioplasty maneuvers for placement of the LV leads were not necessary in our patients [25]. At time of evaluation, the patients were clinically stable without signs of fluid overload and each patient was on optimized neurohumoral therapy (including beta-blocker, ACE inhibitor/AT blocker and diuretics). The study was approved by the local ethics committee and written informed consent was obtained from all patients prior to enrollment.

Data acquisition

Acquisition of echocardiographic and metabolic gas exchange data were carried out 1 day before and 6 months (6 ± 1) after implantation of the CRT device. Immediately after implantation, each CRT device was programmed in a back-up mode (VVI 30) after AV- and VV-delay optimization. Evaluation of hemodynamic response to CRT was performed at the predischarge follow-up during baseline sinus rhythm (VVI 30) as well as during atrioventricular-synchronized biventricular pacing (VDD 30 at a fixed AV-delay) by impedance cardiography. Patients who showed a reduction $>15\%$ in left ventricular end-systolic volume (LVESV) at the 6-month follow-up were considered responders to CRT. Recorded data were analyzed offline in a blinded fashion.

Assessment of hemodynamic response

Noninvasive assessment of hemodynamic parameters was performed using finger plethysmography (continuous blood pressure) and impedance cardiography (cardiac output) using the TaskForceMonitor^{TM} (CNSystems, Graz, Austria). Beat-to-beat values of cardiac output (CO) were automatically calculated as previously described [26–28].

The echocardiographic evaluations were performed in our echocardiography laboratory by independent investigators during routine follow-up before CPET evaluation. Therefore, the echocardiographic investigators were blinded and did not know any results of the CPET. Echocardiographic data were obtained by transthoracic two-dimensional echocardiography using an Accuson Sequoia C256 ultrasound machine (Siemens, Germany). Standard views were used to obtain the left ventricular ejection fraction (LVEF) as well as the LVESV.

Measurement of respiratory response

All patients underwent a submaximal treadmill exercise using the modified Bruce protocol. The patients started with 2.7 km/h at a gradient of 0% followed by 5% respectively 9% incline at the same speed (each level for 3 min). The test was stopped either based on symptoms or after passing all stages. Metabolic gas exchange data were obtained on a breath-by-breath basis using a Jaeger Viasys Oxycon Pro^{TM} system (Viasys$^{®}$ Healthcare Inc., Hoechberg, Germany). Flow meters and gas analyzers were calibrated for accuracy and linearity with a syringe of known volume and precisely analyzed gas mixtures on a daily basis. The oxygen uptake efficiency slope (OUES) was calculated by a single-segment logarithmic curve-fitting model using the following equation $VO_2 = a \times \log \mathrm{VE} + \mathrm{b}$, in which the constant a represents the rate of increase in VO_2 in response to an increase in VE. This constant a is called OUES [17]. A steeper slope, i.e, a higher OUES value, represents a more efficient oxygen uptake. A decreased OUES value represents a higher amount of ventilation required for a given oxygen uptake. Due to the linearity throughout exercise, calculation of OUES does not require maximal effort and is a reliable and reproducible parameter of exercise capacity in patients with cardiac diseases [18–22, 24]. The OUES was calculated using all respiratory data from the beginning until the end of submaximal exercise testing. The VE/VCO_2 slope was calculated by linear regression using the whole exercise period [14, 15]. The ventilatory anaerobic threshold (VAT) was measured using the V-slope method [15]. Peak oxygen uptake (peak VO_2) was defined as the highest average reached during the last 30 s of a symptom limited exercise test which was performed 30 min after submaximal exercise testing in each patient.

Statistical analysis

Results are shown as means (with standard deviations; SD) and are expressed as absolute values or changes from baseline. Statistical analysis of the data was performed with SPSS 17.0 for Windows (SPSS Inc., Chicago, Illinois). Changes in cardiovascular and respiratory parameters during CRT as compared to baseline (no pacing) were examined by two-sided Student's t test for paired data when appropriate. For all reported tests a p value <0.05 was considered statistically significant. Multivariate logistic regression analysis was used to adjust for relevant variables between responders and nonresponders. To assess the cut-off point of OUES for predicting response to CRT a receiver-operating characteristic (ROC) curve was used. The optimal cut-off value was defined as the value with the maximal sum of sensitivity and specificity.

Results

Study population

The patient characteristics are summarized in Table 1. All patients were in NYHA functional class III at time of inclusion. According to current inclusion criteria all patients showed severe left ventricular dysfunction. Left ventricular ejection fraction was 24 ± 5% and QRS duration was 158 ± 25 ms. All patients successfully performed submaximal exercise testing without any adverse event. A total of 19 patients out of 28 patients (68%) were identified as responders to CRT.

Responders versus nonresponders to CRT

There were no differences between the responder ($n = 19$) and the nonresponder group ($n = 9$) according to age (69 ± 9 vs. 63. ± 10 years; ns) and gender (4 vs. 2 females; ns). Systolic and diastolic blood pressure, left ventricular ejection fraction as well as the left ventricular end-systolic volume index showed no significant differences between responders and nonresponders prior initiation of CRT. Interestingly, only responders to CRT showed a significant increase in CO from baseline (13.3 ± 1.7%) after initiation of CRT as compared to the nonresponders (3.6 ± 1.9%; $p < 0.05$). At the 6-month follow-up responders as well as nonresponders to CRT showed an increase in the left ventricular ejection fraction (23 ± 5 vs. 31 ± 9% and 26 ± 7 vs. 32 ± 3%; $p < 0.05$). Responders to CRT demonstrated a decrease in the left ventricular end-systolic volume (175 ± 58 vs. 128 ± 40 ml/m^2; $p < 0.01$), whereas this change was not significant in the

Table 1 Patient characteristics at baseline

	Responders ($n = 19$)	Nonresponders ($n = 9$)	p value
Age (years)	69 ± 9	65 ± 9	ns
Female gender	4	2	ns
NYHA class III	100%	100%	ns
Ischemic heart disease	8	4	ns
ACE inhibitor	74%	67%	ns
Aldosterone antagonist	26%	33%	ns
Beta-adrenergic blocker	94%	100%	ns
Diuretics	100%	89%	ns
BMI (kg/m^2)	26 ± 6	27 ± 4	ns
LVEF (%)	23 ± 5	26 ± 7	ns
QRS duration (ms)	167 ± 29	149 ± 21	ns
Heart rate (bpm) rest	70.1 ± 8	66.9 ± 7	ns

NYHA New York Heart Association, *ACE* angiotensin converting enzyme, *ARB* angiotensin receptor blockers, *BMI* body mass index, *LVEF* left ventricular ejection fraction, *BP* blood pressure

Table 2 Changes from baseline (prior CRT implantation) in New York Heart Association (NYHA) classification, systolic and diastolic blood pressure (BP), left ventricular ejection fraction (LVEF), left ventricular end-systolic volume (LVESV), VE/VCO$_2$ slope and peak VO$_2$ at the 6-month follow-up (CRT)

	Responders ($n = 19$)		Nonresponders ($n = 9$)	
	Baseline	CRT	Baseline	CRT
NYHA class	3.0$^{\#}$	2.6 ± 0.5$^{\#}$	3.0	2.8 ± 0.5
Systolic BP (mmHg)	116 ± 21	120 ± 22	114 ± 15	115 ± 17
Diastolic BP (mmHg)	79 ± 11	78 ± 13	77 ± 10	79 ± 16
LVEF (%)	23 ± 5$^{\#}$	31 ± 9$^{\#}$	26 ± 7$^{\#}$	32 ± 3$^{\#}$
LVESV (ml)	175 ± 58$^{\#\#}$	128 ± 40$^{\#\#}$	153 ± 53	141 ± 69
Cardiac output (%)	100$^{\#}$	113 ± 2$^{\#}$	100	104 ± 2
VE/VCO$_2$ slope	40.2 ± 9	38.0 ± 9	36.4 ± 5	35.7 ± 5
VE (l/min)	43 ± 12	40 ± 14	40 ± 16	39 ± 14
RER	0.92 ± 0.08	0.89 ± 0.07	0.88 ± 0.05	0.87 ± 0.07
HR exercise (bpm)	108 ± 14	105 ± 12	102 ± 17	104 ± 11

Changes in cardiac output (CO) after initiation of CRT are given in percent from baseline (100%)

$^{\#}$ $p < 0.05$ for differences between baseline and CRT; $^{\#\#}$ $p < 0.01$ for differences between baseline and CRT

nonresponder group (153 ± 53 vs. 141 ± 69 ml/m^2; ns). Responders to CRT showed a decrease in NYHA class (3.0 vs. 2.6 ± 0.5, $p < 0.05$) whereas no significant changes were seen in the nonresponder group. Only six patients in the responder group and two patients in the nonresponder group fulfilled the NYHA criteria of response (improvement of ≥1 NYHA class score). At baseline responders to CRT showed lower peak VO$_2$ values as compared to nonresponders [14.3 ± 2 vs. 16.9 ± 2 ml/(kg min), $p < 0.05$] (Table 2). There were no differences in peak oxygen pulse between responders and nonresponders at baseline (9.6 ± 3.4 vs. 10.2 ± 4.1 ml/beat, p = ns) as well as at the 6-month follow-up (9.7 ± 3.7 vs. 10.4 ± 3.6 ml/beat, p = ns). The ventilatory anaerobic threshold (VAT) could only be determined in 11 out of 19 patients of the responder group for both baseline and 6 months follow-up (9.7 ± 2.4 vs. 9.7 ± 2.0 ml/kg/min; p = ns) as well as in 5 out of 9 patients in the nonresponder group [10.5 ± 2.6 vs. 10.8 ± 2.8 ml/(kg min), p = ns].

Impact of the oxygen uptake efficiency slope to the response to CRT

Nonresponders to biventricular pacing showed significant higher baseline OEUS values as compared to the responders (2,480 ± 590 vs. 1,235 ± 651; $p < 0.01$). After 6 months of CRT the OUES increased in the responder group (1,879 ± 663; $p < 0.05$) whereas there was no significant change in OUES in the nonresponder group (2,194 ± 422; ns) as compared to baseline values (Fig. 1). In multivariate analysis the OUES remained statistically significant between responders and nonresponders ($p < 0.05$) (Table 3). ROC analysis revealed an optimal estimated OUES cut-off value of ≥1,720 (100% sensitivity and 84% specificity) for identification of nonresponders to CRT (Fig. 2).

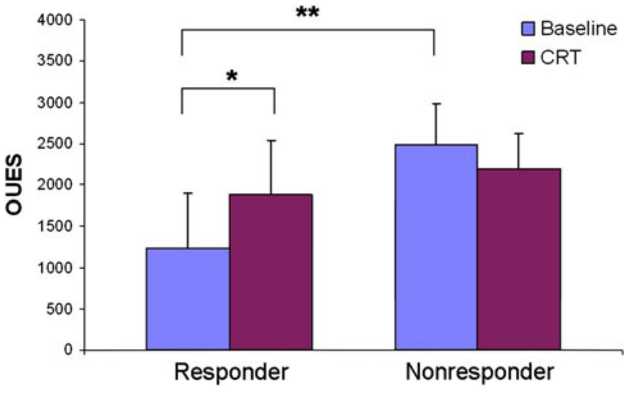

Fig. 1 Differences in the OUES amongst responders and nonresponders to CRT prior pacemaker implantation (baseline) and 6 months after initiation of CRT. *$p < 0.05$; **$p < 0.01$

Discussion

The main finding of this study was that functional exercise capacity, as obtained by OUES, predicted the response to CRT in NYHA class III heart failure patients. Responders to CRT showed a significant impairment of cardiopulmonary reserve, respectively significant lower baseline OUES values, as compared to the nonresponder group despite similar NYHA classification, left ventricular ejection fraction and QRS duration. In the responder group, biventricular pacing

Table 3 Unadjusted and adjusted estimated odds ratios (95% CI) for OUES and responder status

	Odds ratio	Confidence interval	*p* value
Unadjusted model			
OUES	0.997	0.995–0.999	0.01
Adjusted model I*			
OUES	0.997	0.995–1.000	0.02
VE/VCO_2 slope	0.972	0.788–1.198	0.79
VO_2max	0.712	0.408–1.242	0.23
Adjusted model II**			
OUES	0.997	0.994–1.000	0.03
VE/VCO_2 slope	0.961	0.767–1.204	0.73
VO_2max	0.725	0.396–1.325	0.30
LVEF	1.004	0.761–1.325	0.98
LVESVI	1.013	0.962–1.066	0.63

* Adjusted for VE/VCO_2 slope and peak VO_2; ** adjusted for VE/VCO_2 slope, peak VO_2, LVEF, and LVESV

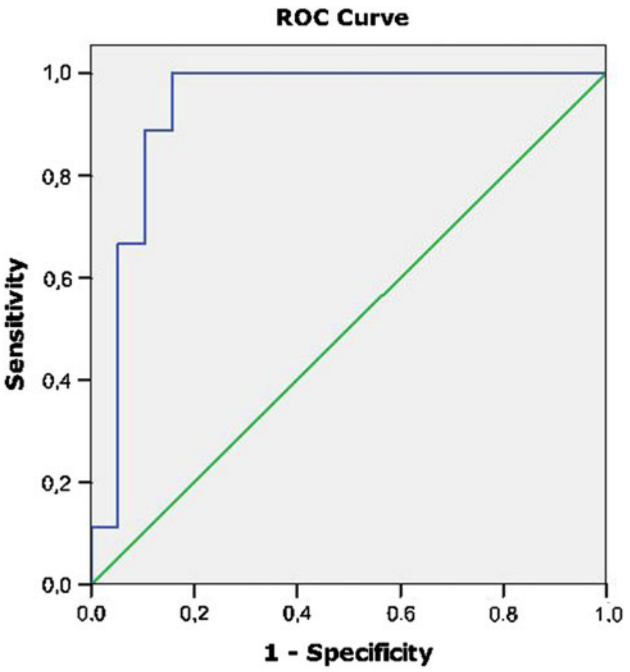

Fig. 2 The optimal estimated OUES cut-off value was ≥1,720 for identification of nonresponders to CRT (100% sensitivity and 84% specificity) with an area under the ROC curve of 0.93

resulted in an immediate improvement of hemodynamic as well as respiratory parameters as previously described [29–31]. Both responders and nonresponders to CRT showed an improvement in left ventricular ejection fraction whereas only responders to CRT showed a significant decrease in left ventricular end-systolic volume and an increase in the OUES at the 6-month follow-up as compared to baseline. In multivariate analysis OUES remained the strongest predictor for response to CRT.

Similar to previous randomized controlled trials, also in this study approximately 30% of patients who received a CRT device were identified as nonresponders although they fulfilled well-established inclusion criteria. It is difficult to predict a beneficial response to biventricular pacing in terms of improvement of heart failure severity and prognosis. There is strong evidence that patients with prolonged QRS duration show worse prognosis [32, 33] but the impact of QRS duration to predict response to CRT is still unclear [34]. Echocardiography, especially estimation of the left ventricular ejection fraction as well as diagnosis of ventricular dyssynchrony, is another important diagnostic tool for CRT evaluation. Nevertheless, many currently used echocardiographic parameters failed to improve responder identification. The PROSPECT trial revealed large interobserver variabilities and lack of reproducibility of echocardiographic measures of dyssynchrony even in echocardiography specialists [4]. Therefore, there is need for better, respectively, more reproducible, parameters for identification of responders to CRT. Besides ECG and echocardiographic parameters, the NYHA classification is another inclusion criteria for CRT. However, estimates of functional capacity such as the NYHA classification and the 6-min walk test strongly depend on patients' motivation and physical condition. The lack of objective criteria for classification of patients' functional status at baseline is a limitation of many CRT studies. Therefore, a direct comparison of the results of these studies remains difficult. More accurate parameters of functional exercise capacity, such as maximal oxygen uptake or the VE/VCO_2 slope, are yet not routinely used for stratification due to difficulties in test availability and performance. For example, the reliability performance of the ventilatory anaerobic threshold measurements as another submaximal parameter of exercise capacity was weak in our cohort. Some previous data already indicated that an impairment in functional exercise capacity may also have influence on response to CRT. Patients with a peak VO_2 >16 ml/(kg min) did not show significant cardiorespiratory improvements during CRT [35, 36]. In contrast, a study by Piepoli et al. [37] showed that patients with a peak VO_2 of ≤7 ml/(kg min) did not benefit from CRT. Obviously, these two studies suggest that functional exercise capacity affects the response to CRT. Besides patients who are too fit, there may be also patients who are too sick to show a benefit from CRT. Some limitations of these two studies may be the disparity of the study populations (NYHA class III and IV patients) and the fact that maximal oxygen uptake at peak exercise was used to assess functional exercise capacity. Also in this study despite similar NYHA classification and left ventricular function, the patients of the nonresponder group showed a higher maximal oxygen uptake at peak exercise [2.6 ml/(kg min) at baseline] which would classify them mainly as Weber B while the responders were mainly Weber class C. As the Weber classification relies on peak VO_2 uptake a maximal exercise test is necessary for evaluation, which is difficult to perform in these patients. A difference of ~ 2 ml/(kg min) in peak VO_2 strongly depends on the motivation of the patients. It is difficult to obtain accurate peak VO_2 measurements in patients with severe heart failure due to limitations such as peripheral muscle fatigue, motivation or selection of an appropriate exercise protocol [38]. Moreover, assumed that the peak VO_2 (which was obtained by treadmill exercise testing in this study) may be $\sim 10\%$ lower during bicycle testing, both groups would then qualify for Weber class C. Multivariate analysis revealed that the OUES was the strongest predictor of response to CRT as compared to peak VO_2 and VE/VCO_2 slope. Therefore, we think estimation of OUES is a more suitable parameter for evaluation of functional exercise capacity in these patients as it helps to overcome these difficulties. OUES can be easily obtained during submaximal exercise as it is marked by linearity throughout exercise [18]. In this study the oxygen uptake efficiency slope, as a non-effort-dependent measure of cardiopulmonary reserve, could be obtained by submaximal exercise testing without any adverse event in each of these compromised patients. This is of special interest as there may be some concerns according maximal effort limited cardiopulmonary exercise testing in “critically” ill patients.

In this study nonresponders to CRT showed significant higher baseline values of OUES (prior CRT) as compared to responders, although all patients were in NYHA classification stage III and showed no differences in baseline left ventricular ejection fraction and QRS duration. Both responders and nonresponders showed an increase in left ventricular ejection fraction, whereas only patients with an immediate hemodynamic response after CRT initiation displayed significant changes in the left ventricular end-systolic volume after 6 months. Accordingly, responders to CRT showed lower baseline OUES values as compared to nonresponders. A low baseline OUES value was the best predictive value for identification of responders to CRT. Some limitations of our findings may be the sample size and the observational nature of the study. Therefore, the predictive value of OUES on CRT response should be tested in additional prospective studies. Another shortcoming of this study is the difficulty to quantify the work rate as patients were tested on a treadmill. Therefore, no statement according the differences in work rate between both groups is possible. Our results suggest an overestimation in NYHA classification in daily routine. Thus, evaluation of cardiorespiratory reserve in addition to current inclusion criteria for CRT may help to overcome this problem and to achieve higher response rates to CRT. Besides screening patients before CRT, submaximal cardiopulmonary exercise testing seems to be an appropriate tool to evaluate the response to CRT. This may be of special interest as there is still no clear consensus definition of response to CRT. Previous studies showed some relevant placebo effects of CRT even in patients with deactivated LV pacing leads [39]. Regardless, despite the compelling benefits of CRT, even in patients with mild heart failure, there is still an unacceptable high percentage of nonresponders [2, 7, 39, 40]. Thus, reproducible (objective) parameters are crucial for a reliable evaluation of the response to a fast growing therapy modality such as CRT (especially with respects to economic reasons).

With respect to the costs and nonresponder rates of about one-third of patients, a more careful selection of patients prior to CRT is crucial. Currently there are only limited parameters available which proved to predict response to CRT. According to our data the OEUS seems a valuable additional parameter to further improve identification of potential responders to CRT. Our data indicate that nonresponders to CRT show a more preserved cardiorespiratory reserve as compared to responders despite similar NYHA classification. In addition to the currently used inclusion criteria, evaluation of functional exercise capacity by estimation of the OUES during submaximal exercise testing can contribute to increase the responder rates to CRT.

Acknowledgments We are particularly indebted to Dr. Reizo Baba from the Tokai University School of Physical Education for his help according the calculation of the OUES. Moreover, we would like to thank Helmut Hoertnagl, Fritz Kuehndl and Herbert Sailer (Institute of Sports Medicine, University Hospital Innsbruck) for their valuable help according exercise testing.

Conflict of interest The manuscript or part of it has not been published elsewhere. The author has no financial or other relations that could lead to a conflict of interest. T.B. has received a fellowship grant from the European Heart Rhythm Association (EHRA).

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