

# openheart Does recovery from submaximal exercise predict response to cardiac resynchronisation therapy?

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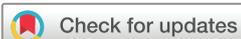
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## ABSTRACT

**Background** Exercise parameters are not routinely incorporated in decision making for cardiac resynchronisation therapy (CRT). Submaximal exercise parameters better reflect daily functional capacity of heart failure patients than parameters measured at maximal exertion, and may therefore better predict response to CRT. We compared various exercise parameters, and sought to establish which best predict CRT response.

**Methods** In 31 patients with chronic heart failure (61% male; age 68±7 years), submaximal and maximal cycling testing was performed before and 3 months after CRT. Submaximal oxygen onset ( $\tau\text{VO}_2$  onset) and recovery kinetics ( $\tau\text{VO}_2$  recovery), peak oxygen uptake ( $\text{VO}_2$  peak) and oxygen uptake efficiency slope (OUES) were measured. Response was defined as ≥15% relative reduction in end-systolic volume.

**Results** After controlling for age, New York Heart Association and  $\text{VO}_2$  peak, fast submaximal  $\text{VO}_2$  kinetics were significantly associated with response to CRT, measured either during onset or recovery of submaximal exercise (area under the curve, AUC=0.719 for both;  $p<0.05$ ). By contrast,  $\text{VO}_2$  peak (AUC=0.632;  $p=0.199$ ) and OUES (AUC=0.577;  $p=0.469$ ) were not associated with response. Among patients with fast onset and recovery kinetics, below 60 s, a significantly higher percentage of responders was observed (91% and 92% vs 43% and 40%, respectively).

**Conclusions** Impaired  $\text{VO}_2$  kinetics may serve as an objective marker of submaximal exercise capacity that is age-independently associated with non-response following CRT, whereas maximal exercise parameters are not. Assessment of  $\text{VO}_2$  kinetics is feasible and easy to perform, but larger studies should confirm their clinical utility.

## INTRODUCTION

Cardiac resynchronisation therapy (CRT) is an effective treatment for patients with chronic heart failure (HF) and a reduced left ventricular (LV) ejection fraction (EF). Although patient eligibility is currently primarily based on the presence of left bundle branch block (LBBB) on the ECG, approximately 30%–40% of patients are non-responders.<sup>1,2</sup> Research has focused on

## WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Novel ECG and imaging markers are widely investigated to improve patient selection criteria for cardiac resynchronisation therapy. Exercise parameters may add to prediction models, but whether maximal or submaximal parameters are better remain unclear.

## WHAT THIS STUDY ADDS

⇒ Not maximal exercise parameters, but impaired submaximal  $\text{VO}_2$  kinetics are associated with non-response, independently of age, New York Heart Association or  $\text{VO}_2$  peak.

## HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Incorporation of  $\text{VO}_2$  kinetics in clinical practice omits the need for strenuous exertion, while assessment is easy and better reflects daily functional capacity.

deriving new and more advanced markers from the ECG or echocardiogram to better predict response after CRT.<sup>3</sup> However, sensitivity and specificity should be further improved in order to truly affect clinical decision making.<sup>4,5</sup>

Incorporation of exercise parameters may further improve patient selection, but these are not yet part of routine clinical decision making for CRT.<sup>5</sup> However, several studies showed a positive relationship between pre-implantation maximal exercise capacity (peak oxygen uptake;  $\text{VO}_2$  peak) and CRT response,<sup>6,7</sup> suggesting that more severely impaired HF patients are less likely to achieve an echocardiographic response. This may be because their exercise capacity is more severely limited by peripheral derangements. Yet, studies investigating the influence of baseline ‘exercise’ characteristics on echocardiographic response are relatively scarce, as opposed to trials investigating electrical and mechanical substrates.<sup>3,5</sup>

A barrier for the widespread implementation of assessment of maximal exercise capacity is that symptom limiting exercise testing is burdensome, and often not truly achievable for patients with severe HF.<sup>5,8</sup> Therefore, 'submaximal' exercise testing could be a valuable alternative. One of the submaximal exercise parameters that reflect exercise capacity are oxygen kinetics.<sup>9–12</sup> Oxygen kinetics describe the rate of increase of oxygen uptake during a short constant-load submaximal exercise bout ( $\text{VO}_2$  onset kinetics) and the rate of decline during recovery ( $\text{VO}_2$  recovery kinetics). Assessment of  $\text{VO}_2$  kinetics is safe, feasible and not physically burdensome for severely impaired patients, as it only requires an exercise effort of several minutes below the anaerobic threshold. In HF patients, oxygen kinetics were shown to be reproducible and well correlated with exercise capacity and prognosis.<sup>12–15</sup> In addition,  $\text{VO}_2$  recovery kinetics were shown to be useful as a predictor of the effect of an exercise training programme.<sup>16</sup>

The main goal of this study was to investigate whether submaximal exercise testing, and in particular oxygen uptake kinetics, can be used to predict the response to CRT. In addition, use of submaximal exercise parameters was compared with conventional parameters that require maximal exertion.

## METHODS

### Patient population and study protocol

We performed a prospective multicentre trial in an open cohort of patients. A total of 34 patients with HF eligible for CRT were enrolled. Inclusion criteria were based on ESC guidelines implemented at the time of inclusion: (1) New York Heart Association (NYHA) II or III HF despite optimal medical treatment; (2) EF  $\leq$ 35% and (3) QRS-duration  $\geq$ 120 ms. Participation in an exercise training programme in the last year and during the study were excluded.

Resting echocardiography and two cardiopulmonary exercise tests (CPET) were performed at baseline and 3 months after CRT implantation. After echocardiography, patients performed a submaximal constant load CPET, followed by a symptom limited maximal CPET, both with respiratory gas analysis. In order to familiarise the patient with the test procedure, and to determine the workload for the constant load CPET, an additional symptom limited CPET was performed at baseline. Implantation of CRT devices was performed according to standard techniques and local protocols in the Catharina Hospital, Eindhoven and University Medical Center, Utrecht, the Netherlands. Algorithms based on the intracardiac electrogram were used for device optimisation.

Echocardiographic response was used as a well-accepted surrogate marker of long-term prognosis after CRT, and was defined as a decline in end-systolic volume (ESV)  $\geq$ 15%, 3 months after implantation.<sup>17</sup> A clinical response was defined as an increase in  $\text{VO}_2$  peak  $\geq$ 1 mL/kg/min.<sup>18,19</sup>

### Echocardiography

Standard two-dimensional, colour and spectral Doppler measurements were performed using a Phillips Epic 7C echo machine and an X5-1 transducer. LV dimensions were measured in the parasternal long axis view. EF was determined using the Simpson's rule algorithm by tracing the LV 2D-area in both standard apical two-chamber and four-chamber view at end-systole and end-diastole. Images were analysed independently by two physicians.

### Exercise testing

All exercise tests were performed in an upright seated position on an electromagnetically braked cycle ergometer (Lode Corival; Lode BV, Groningen, The Netherlands). A 12-lead ECG was registered continuously. During the test, ventilatory parameters were measured breath-by-breath (ZAN 680 USB; ZAN Messgeräte, Oberthulba, Germany) and were averaged over 10 s intervals after the removal of outliers (values  $>$ 3 SD from the local mean). Volume and gas analysers were calibrated before each test.

Maximal CPET consisted of a symptom-limited test using an individualised ramp protocol for a total test duration of 8–12 min. The test was preceded by 4 min of unloaded pedalling and ended when the patient was unable to maintain the required pedalling frequency. The results of this baseline test were used in order to determine the workload for the submaximal CPET. Exercise performance was determined as the maximally achieved resistance at the end of the exercise.  $\text{VO}_2$  peak was defined as the final 20 s averaged value of the maximal CPET. Ventilatory aerobic threshold (VAT) was assessed by the V-slope method, using the mean of the value calculated by two blinded physicians. The efficiency of  $\text{CO}_2$  exchange was measured by assessing the required minute ventilation for  $\text{CO}_2$  elimination (ie,  $\text{VE}/\text{VCO}_2$ ). Finally, the oxygen uptake efficiency slope (OUES) was measured, as it is a reliable and reproducible measure of effort-independent cardiopulmonary reserve. The OUES was derived from the logarithmic relation between  $\text{VO}_2$  and VE during incremental exercise.<sup>20</sup>

Submaximal constant load exercise testing commenced with a 2 min resting period, followed by a 6 min bout at 80% of the workload corresponding to the VAT achieved during the preceding maximal exercise test. Patients were instructed to maintain a pedalling frequency of 70 rotations per minute. After the load phase, there was a 5 min recovery phase with no movement of the leg in order to assess  $\text{VO}_2$  kinetics.

### Analysis of oxygen uptake kinetics

Analysis of  $\text{VO}_2$  kinetics during onset and recovery of the constant load tests was reported previously.<sup>11</sup> All data were resampled into 10 s intervals and the first 20 s of the  $\text{VO}_2$  data (eg, exercise onset) were omitted. This was done because during this period (cardiodynamic phase), increases in  $\text{VO}_2$  merely reflect an increase in pulmonary blood flow, rather than actual changes in

tissue gas exchange. A non-linear least squares regression procedure (Matlab V.8.6 R2015b, MathWorks, USA) was applied to the onset phase in order to calculate the time constant of  $VO_2$  onset (formula 1).

**Formula 1.**  $VO_2$  kinetics for onset phase.

$$VO_{2\text{ onset}}(t) = Y_{\text{baseline}} + A \cdot \left(1 - e^{-(t-Td)/\tau}\right)$$

where A=amplitude during exercise onset; Td=time delay (seconds) and  $\tau$ =time constant (seconds). Recovery kinetics of  $VO_2$  were calculated as well (formula 2);  $Y = VO_2$ .

**Formula 2.**  $VO_2$  kinetics for recovery phase.

$$VO_{2\text{ recovery}}(t) = Y_{\text{steady state}} - A \cdot \left(1 - e^{-(t-Td)/\tau}\right)$$

where A=amplitude during recovery from steady state; Td=time delay (seconds) and  $\tau$ =time constant (seconds);  $Y = VO_2$

### Statistical analysis

Data were analysed using SPSS statistics (V.25.0, SPSS). Continuous variables were tested for normality using a Shapiro-Wilk test and were expressed as the mean $\pm$ SD. Data with a normal distribution were evaluated using the paired samples t-test for within group differences and by independent samples t-test concerning between-group differences. Categorical data were presented as absolute count and were compared with a Fisher's exact test.

Receiver operator characteristic curves were created for exercise-related predictors of CRT outcome. Optimal cut-off values were based on the level that resulted in the highest (sensitivity – [1 – specificity]), and subsequently an integer within this numeric range was selected in order to prevent unjustified overfitting of data. The relationship between these predictors and echocardiographic response was established using analysis of covariance with

age, NYHA class and peak  $VO_2$  as covariates. Agreement between exercise kinetics and NYHA class was assessed using Cohen's kappa coefficient. All statistical tests performed were two tailed and a  $p < 0.05$  was considered statistically significant.

### RESULTS

A total of 34 patients were included. One patient did not complete the CPET on the visit after CRT implantation due to dizziness when sitting on the bike, two other patients did not show up for the examinations post-CRT without giving reason. A total of 31 patients completed all tests; all patients underwent CRT implantation, without complications. Paired respiratory gas analysis data during (sub)maximal exercise testing could be successfully retrieved. The majority of the population were male (61%) with non-ischaemic cardiomyopathy (58%) and a mean age of  $68 \pm 7$  years (table 1). An overview of changes in echocardiographic and exercise parameters before and after CRT of the total study population is presented in online supplemental table 1.

### Echocardiographic responders versus non-responders

Relative changes in exercise-related variables between the group of echocardiographic non-responders versus responders are presented in table 2. No significant between-group differences in exercise capacity were observed at baseline. Yet, in contrast with non-responders, only responders showed a significant improvement in peak power output (P peak),  $VO_2$  peak, OUES and  $VE/VCO_2$  slope following CRT. Although  $\tau VO_2$  recovery was significantly reduced after CRT on group level ( $77 \pm 39$  vs  $61 \pm 18$ ;  $p = 0.030$ ), no significant changes were seen when stratified

**Table 1** Characteristics at baseline of study population

Characteristic	Total (n=31)	Non-responder (n=11)	Responder (n=20)	P value
Age (years)	68.4 $\pm$ 7.1	72.2 $\pm$ 4.0	66.3 $\pm$ 7.6	0.026
Male (%)	19 (61)	10 (91)	9 (45)	0.020
Ischaemic aetiology—n (%)	13 (42)	7 (64)	6 (30)	0.128
NYHA III—n (%)	21 (69)	10 (91)	11 (55)	0.055
HF duration (months)	16 (6–66)	39 (14–66)	13 (6–60)	0.215
Sinus rhythm—n (%)	23 (82)	8 (73)	18 (90)	0.224
LBBB—n (%)	26 (84)	8 (80)	18 (95)	0.267
QRS width (ms)	154 $\pm$ 17	157 $\pm$ 21	153 $\pm$ 15	0.556
LVEF (%)	26.6 $\pm$ 8.1	24.5 $\pm$ 8.6	27.7 $\pm$ 7.7	0.298
ACE/ARB—n (%)	31 (100)	11 (100)	20 (100)	1.000
Beta blocker—n (%)	28 (90)	10 (91)	18 (90)	1.000
$VO_2$ peak (mL/kg/min)	16.4 $\pm$ 5.4	14.8 $\pm$ 3.9	17.3 $\pm$ 6.1	0.215

Values are presented as mean $\pm$ SD, median with IQR, number or percentage.

ARB, angiotensin II receptor blocker; LBBB, left bundle branch block; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association;  $VO_2$  peak, peak oxygen uptake capacity.

**Table 2** Relative changes in echocardiographic and exercise-related variables in patients with or without echocardiographic response, before and 3 months after CRT implantation

Variable	Non-responder (n=11)		Responder (n=20)	
	Baseline	3 months	Baseline	3 months
	Rest			
EF (%)	24.5±8.6	24.7±8.0	27.7±7.7	40.5±8.8*
EDV (mL)	289±105	287±101	221±72	171±52*
ESV (mL)	223±102	218±92	161±59†	106±45*
	Maximal			
P peak (W)	97±35	102±39	107±47	118±47*
VO <sub>2</sub> peak (mL/kg/min)	14.8±3.9	16.0±3.2	17.3±6.1	19.7±6.6*
OUES	1445±479	1610±520	1610±521	1943±586*
VE/VCO <sub>2</sub> slope	38.9±9.9	37±6.1	34.9±8.4	31.7±7.0*
	Submaximal			
τVO <sub>2</sub> on (s)	87.2±39.1	90.1±48.8	58.6±34.2	55.4±32.2
τVO <sub>2</sub> rec (s)	79.5±21.4	67.0±19.4	75.0±47.3	57.6±17.3

Values presented as mean±SD.  
 \*p<0.05 for within-group difference.  
 †p<0.05 for between group difference at baseline.  
 CRT, cardiac resynchronisation therapy; EDV, end-diastolic volume; EF, ejection fraction; ESV, end-systolic volume; OUES, oxygen uptake efficiency slope; P, performance; VE/VCO<sub>2</sub> slope, minute ventilation for CO<sub>2</sub> elimination; τVO<sub>2</sub>, time constant of oxygen uptake.

according to response groups. In both responders and non-responders, the extent of LVESV-reduction and clinical improvement ( $\Delta$ VO<sub>2</sub> peak) after CRT were not correlated significantly ( $R=0.284$ ;  $p=0.135$ ).

### Exercise-related predictors for echocardiographic response

The optimal cut-off values of various exercise parameters, measured at baseline, to predict echocardiographic response are shown in table 3. For τVO<sub>2</sub> onset and τVO<sub>2</sub> recovery, the highest area under the curve (AUC) was found at a cut-off of 60 s (AUC 0.719;  $p<0.05$  for both). τVO<sub>2</sub> onset  $\leq 60$  s predicted echocardiographic response with a specificity of 90% and a sensitivity of 61%, whereas τVO<sub>2</sub> recovery predicted

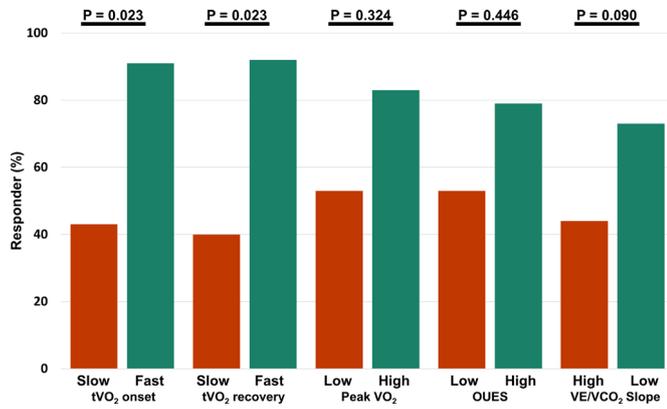
echocardiographic response with a specificity of 90% and a sensitivity of 67%. Maximal exercise parameters (VO<sub>2</sub> peak, VE/VCO<sub>2</sub> slope, OUES) showed lower AUC's (0.632, 0.600, 0.577, respectively), which were all not significant (online supplemental table 2). None of the exercise parameters were significantly associated with a clinical response ( $p>0.05$  for all).

Only among patients with fast onset and recovery kinetics (τVO<sub>2</sub> onset and τVO<sub>2</sub> recovery  $\leq 60$  s) at baseline, a significantly higher percentage of responders were observed (92% and 92% vs 44% and 40%, respectively). By contrast, maximal parameters (VO<sub>2</sub> peak, OUES, VE/VCO<sub>2</sub> slope) could not differentiate

**Table 3** Baseline test characteristics of exercise-related predictors for echocardiographic response 3 months after CRT implantation

Predictor	AUC	P value	Cut-off value	Met?	Total	Sens (%)	Spec (%)
τVO <sub>2</sub> onset	0.719	0.029	$\leq 60$ s	Yes	11	61	90
				No	16		
τVO <sub>2</sub> recovery	0.719	0.025	$\leq 60$ s	Yes	12	67	90
				No	15		
VO <sub>2</sub> peak	0.632	0.199	$\geq 18$ mL/kg/min	Yes	12	50	82
				No	18		
VE/VCO <sub>2</sub> slope	0.600	0.371	$\leq 40$	Yes	22	80	45
				No	8		
OUES	0.577	0.469	$\geq 1500$	Yes	14	55	73
				No			

AUC, area under the curve; CRT, cardiac resynchronisation therapy; OUES, oxygen uptake efficiency slope; sens, sensitivity; spec, specificity; VE/VCO<sub>2</sub> slope, minute ventilation for CO<sub>2</sub> elimination; τVO<sub>2</sub>, time constant of oxygen uptake.



**Figure 1** Difference in echocardiographic response based on various exercise-related parameters at baseline, with significance corrected for age, NYHA and VO<sub>2</sub> peak. Patients with poor (red) and good (green) testing results during (sub) maximal exercise. NYHA, New York Heart Association; OUES, oxygen uptake efficiency slope; VE/VCO<sub>2</sub>, minute ventilation for carbon dioxide elimination; VO<sub>2</sub>, oxygen uptake.

response after CRT. Controlling for age, NYHA class and VO<sub>2</sub> peak as covariates did not significantly influence these results (figure 1). Patients with fast  $\tau$ VO<sub>2</sub> recovery demonstrated significantly more ESV-reduction than patients with delayed  $\tau$ VO<sub>2</sub> recovery (32±14 vs 17±21; p=0.033), and had a twofold larger increase in LVEF (online supplemental table 3). A scatterplot with individual values of submaximal VO<sub>2</sub> kinetics at baseline and their association with reverse remodelling is shown in figure 2.

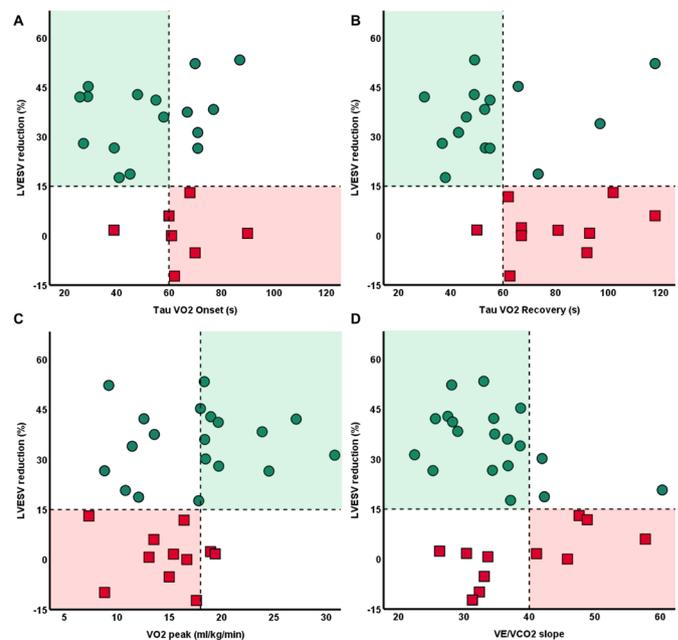
Baseline onset and recovery VO<sub>2</sub> kinetics were not correlated to each other (R=0.092; p=0.640), which suggests their interaction with echocardiographic response is due to independent mechanisms. Patients that demonstrated an echocardiographic response despite poor VO<sub>2</sub> recovery kinetics were more frequently female (p=0.002) and tended to have a smaller LVESV and LVEDV (p<0.01, for both). For tVO<sub>2</sub> onset, these patients had a higher LVEF (p=0.008).

### Comparison with NYHA functional class

Baseline NYHA functional class was not significantly associated with response (AUC=0.680; p=0.103). When comparing NYHA II and NYHA III, similar reductions in ESV were observed (28±15 vs 20±21; p=0.289). In patients classified as NYHA III functional impairment, fast  $\tau$ VO<sub>2</sub> onset and recovery kinetics <60 s were seen in 35% of patients regardless. There was no agreement between NYHA class and VO<sub>2</sub> kinetics dichotomised at 60 s (Cohen's kappa=0.000), or NYHA class and VO<sub>2</sub> peak dichotomised at 18 mL/kg/min (Cohen's kappa=0.000).

### Factors associated with oxygen kinetics

Patients were stratified according to fast and slow baseline  $\tau$ VO<sub>2</sub> recovery, that is, below or above 60 s,



**Figure 2** Distribution of patients with (green dots) and without (red squares) echocardiographic response relative to their exercise performance at baseline. Responders, defined as ≥15% decrease in LVESV, are characterised by faster baseline oxygen VO<sub>2</sub> during onset (A) and recovery (B) of exercise. By contrast, no significant association was observed when evaluating VO<sub>2</sub> peak (C) or VE/VCO<sub>2</sub> slope (D). LVESV, left ventricular end-systolic-volume; VE/VCO<sub>2</sub>, minute ventilation for carbon dioxide elimination; VO<sub>2</sub>, oxygen uptake.

respectively. Age was significantly higher in patients with prolonged VO<sub>2</sub> recovery, as compared with fast recovery time (72±4 vs 64±8; p=0.001). Importantly, in addition to peak VO<sub>2</sub>, no other associations were found with other well-known patient characteristics associated with response, including sex, aetiology, NYHA, LBBB morphology or QRS duration (online supplemental table 4). Age correlated with  $\tau$ VO<sub>2</sub> recovery (R=0.453; p=0.016), but not with  $\tau$ VO<sub>2</sub> onset (R=0.164; p=0.403). Lastly, no significant differences were found when comparing patients with fast and slow oxygen kinetics during 'onset' of submaximal exercise.

### DISCUSSION

This study suggests that oxygen uptake kinetics during onset and recovery from submaximal exercise may add to the prediction of the effect of CRT. An association with volumetric response was seen independently of age, VO<sub>2</sub> peak and NYHA class. Conversely, more conventional exercise parameters such as VO<sub>2</sub> peak, OUES and VE/VCO<sub>2</sub> slope, measured during peak exercise intensity, were not significantly associated with CRT response. Moreover, both submaximal VO<sub>2</sub> kinetics and VO<sub>2</sub> peak were not significantly associated with NYHA functional class, suggesting limited clinical representability of this assessment.

### Exercise-related predictors of response to CRT

To our knowledge, this is one of the first studies that show that submaximal exercise parameters can help in predicting outcome of CRT. Previously, Berger *et al* showed that the OUES at baseline was related to the CRT response.<sup>21</sup> However, we were unable to reproduce the high sensitivity and specificity of OUES that was reported.  $\text{VO}_2$  peak and  $\text{VE}/\text{VCO}_2$  slope were shown to be related to CRT response in other studies, possibly because of their higher sample size.<sup>6,7</sup> Regardless, our results point towards a superior predictive value of  $\text{VO}_2$  kinetics, also when directly compared with maximal exercise parameters. In addition, our findings were consistent, both during onset and recovery of submaximal exercise. Moreover, determining a valid OUES in patients with severe HF requires exercise testing above anaerobic threshold,<sup>22</sup> whereas this is not required for determining  $\text{VO}_2$  kinetics.

Lastly, although very easy to use and therefore widely adopted into clinical practice, assessment of NYHA functional class is subjective and non-specific. Indeed, interobserver agreement for NYHA is only 54%,<sup>23</sup> and NYHA poorly reflects exercise capacity.<sup>24</sup> This in line with our results, which showed no agreement with objective assessments of (sub)maximal exercise capacity, and no significant association with response to CRT.

### Pathophysiology of impaired submaximal exercise performance

The association between low  $\text{VO}_2$  peak at baseline and better CRT-induced improvements in  $\text{VO}_2$  peak has been established previously.<sup>25</sup> It should, however, be noted that increasingly worse  $\text{VO}_2$  peak may be associated with improved clinical response of the same parameter. As such, and in line with our findings, actual prognostic benefit from CRT has been linked to higher levels of  $\text{VO}_2$  peak at baseline in 181 CRT recipients before.<sup>26</sup> Conversely,  $\tau\text{VO}_2$  recovery kinetics can be used to objectively quantify one's (in)ability to physiologically recover from submaximal exercise. Hence, opposed to  $\text{VO}_2$  peak and NYHA, submaximal testing may be more representative of the functional capacity of patients with HF during ordinary daily activity.

A possible explanation for the finding that patients with slow  $\text{VO}_2$  kinetics are less likely to respond to CRT lies in the pathophysiological background of delayed  $\text{VO}_2$  kinetics in HF. In fact, submaximal  $\text{VO}_2$  kinetics reflect the ability of the heart to increase cardiac output and the capacity of skeletal muscles to increase oxygen utilisation (online supplemental graphical abstract). This, in turn, is determined by peripheral vascular function and the metabolic capacity of skeletal muscles.<sup>27</sup> In fact, previous studies showed that peripheral vascular function is impaired<sup>28,29</sup> and related to prolonged recovery after submaximal exercise in HF patients.<sup>30</sup> Peripheral vascular function is, among others, influenced by neurohumoral and systemic inflammatory processes. Impaired peripheral haemodynamics, reflected in impaired  $\text{VO}_2$  kinetics, could therefore point towards a proinflammatory state

and an unbalanced neurohumoral system, which also impairs myocardial adaptation to CRT.

In turn, significant improvements in  $\tau\text{VO}_2$  recovery were seen during the follow-up. Because CRT primarily alters cardiac function, actual changes in  $\tau\text{VO}_2$  recovery 'following CRT' are most likely predominantly owed to improved local oxygen delivery at the skeletal muscle level. Further research is warranted to assess whether CRT can alter local oxygen utilisation as well.

### Submaximal exercise-capacity and age

Age is a well-documented independent cause of CRT non-response, but the actual reason for this has remained largely unexplained.<sup>3,31</sup> In our study, older age was associated with both echocardiographic non-response and prolonged peripheral oxygen uptake recovery kinetics, irrespective of sex or HF aetiology. This link is not surprising, since decreased skeletal muscle performance has been shown to be age-dependent before.<sup>32,33</sup> However,  $\text{VO}_2$  recovery kinetics were more strongly associated with non-response, also when corrected for differences in age, NYHA class and peak exercise capacity. Submaximal exercise capacity may, therefore, be a more specific marker of response to CRT than age, while also being more objective than assessment of NYHA functional class. Moreover, submaximal  $\text{VO}_2$  recovery kinetics can be assessed as a continuum, as opposed to NYHA functional class.

Although current prediction models of CRT-response incorporate age and indices of electrical and mechanical dyssynchrony,<sup>31</sup> clinical information of exercise capacity is currently lacking and perhaps insufficiently explored in this context. To date, no literature has related  $\text{VO}_2$  kinetics to CRT response. Our results, therefore, point for the first time towards the potential role of impaired oxygen uptake kinetics as a mechanism of non-response. Clearly, future studies are warranted to investigate whether performing submaximal exercise tests in patients with dyssynchronous HF can be of added value in the refinement of patient selection criteria.

### Clinical implications

To our knowledge, this is the first study that shows that submaximal exercise parameters can be used to predict CRT response. Although we acknowledge that larger prospective studies are warranted to establish definite cut-off values, the utility of submaximal  $\text{VO}_2$  kinetics for predicting echocardiographic response after CRT was superior to  $\text{VO}_2$  peak. Previous research<sup>34</sup> has suggested  $\text{VO}_2$  peak to be more predictive than submaximal prognostic markers such as the 6 min walking test.<sup>35,36</sup> However, submaximal  $\text{VO}_2$  kinetics provides physicians with reliable prognostic and objective information on the functional status of the individual patient, that is, the ability to adapt to and recover from daily activities. Assessment of  $\text{VO}_2$  kinetics may, therefore, be a more accurate and potentially better reproducible method to determine one's submaximal exercise capacity as opposed to better known and more widely implemented indices such as the

6 min walking test.<sup>15 37</sup> It also does not require achieving peak exertion, which is unobtainable in as many as half of all patients with HF.<sup>8</sup> In addition, assessment of  $\text{VO}_2$  kinetics is non-invasive, objective, affordable and can easily be performed repetitively over time as an indicator of clinical status.

### Limitations

First, as a relatively small number of patients were included, statistical power was limited. As such, a type 2 error should not be ruled out for conventional exercise parameters, and no adequately powered subgroup analyses could be performed. Therefore, especially results concerning exercise-related predictors should be interpreted with caution, and larger prospective trials are warranted before finite conclusions can be drawn whether potential predictors should be applied in clinical practice. Nonetheless, to our best knowledge, incorporation of submaximal exercise-related predictors has not been performed previously, and therefore, extends our current knowledge of eligible CRT patients. Second, a relatively short follow-up duration was carried out, possibly resulting in overestimation of the percentage of non-responders as a consequence of a potential delayed effect. Alternatively, some patients illustrate temporary effects after CRT that diminish over time, and our response percentages were similar to those observed in larger trials.<sup>8 9</sup> Third, day-to-day reproducibility of recovery kinetics are superior relative to onset kinetics, rendering them most clinically suitable.<sup>15</sup>

### CONCLUSION

This study showed that delayed onset and recovery of peripheral oxygen uptake kinetics at baseline are associated with non-response in CRT, whereas parameters measured during maximal exertion were not. Although this association was independent of age, prolonged recovery from submaximal exercise may also—in part—explain the relative lack of reverse remodelling as more frequently seen in older individuals. Since assessment of  $\text{VO}_2$  kinetics is feasible, objective and easy to perform, requiring only a short bout of submaximal exercise, this method is promising for use in clinical practice. However, additional research in larger populations, allowing for multivariate analysis, is needed to establish definite cut-off values, and show whether submaximal exercise testing can be of added value in the clinical decision process of CRT as a whole.

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