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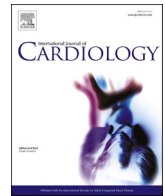


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Signal-morphology impedance cardiography is a non-invasive tool for predicting responses to exercise-based cardiac rehabilitation

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ABSTRACT

Exercise Based Cardiac Rehabilitation (EBCR) is highly beneficial to improve the outcome and quality of life of patients suffering from cardiac diseases. Most of the time, it increases cardiorespiratory and muscle capacity. However, not all patients elicit these benefits because of the high variability in their response to EBCR. In this context, the present study aimed to determine the potential of a specific parameter, the Contractility index (CTi), to predict the response of cardiac patients to EBCR. This parameter is acquired during the baseline Cardiopulmonary Exercise Test (CPET), using Signal-Morphology based Impedance Cardiography (SM-ICGTM). Methods: 58 cardiac patients (59.7 ± 10.2 years old) were retrospectively enrolled in this study and admitted to EBCR, and 57 could be analyzed. Results: The patients were divided into 2 groups based on their CTi response during CPET (normal versus altered or compromised). After the EBCR program, there was an overall increase in peak oxygen uptake (VO_{2peak}) (+13.6 ± 22.9 %). EBCR induced a higher VO_{2peak} improvement in patients with normal CTi response compared to their counterparts with altered or compromised CTi profiles (+24.1 ± 21.4 % vs. + 3.36 ± 19.5 %, *p* < 0.01). Patients with a normal CTi response during the baseline CPET were more likely to have a greater than 5% improvement in VO_{2peak} (odds ratio 8.7, *p* = 0.012) and benefit from EBCR, as compared to the patients in the altered or compromised CTi group. Conclusion: This study demonstrated the predictive potential of the CTi profile observed during the baseline CPET to anticipate the response to EBCR in cardiac patients.

1. Introduction

The benefits of exercise based cardiac rehabilitation (EBCR) are now well established, both in terms of reducing mortality and rehospitalization rates associated with coronary artery disease [1] or heart failure [2,3,11]. However, there is a high inter-individual variability in the degree of response to EBCR. Some patients remain non-responders and sometimes even see their peak oxygen uptake ($\dot{V}O_{2peak}$) decrease significantly, resulting in a less favorable prognosis [10,12]. A clinically accepted criterion for determining the response to EBCR is the change in $\dot{V}O_{2peak}$ between cardiopulmonary exercise testing (CPET) performed before and after EBCR ($\Delta\dot{V}O_{2peak}$). The threshold above which a patient is considered a responder according to the $\Delta\dot{V}O_{2peak}$ criteria varies

according to the authors [4,8,9]. The possible mechanisms explaining the response or lack of response to EBCR have recently been described, mainly in terms of oxygen diffusion [4], peripheral and ventilatory responses [5], but also in terms of cardiopulmonary changes assessed by stress echo in combination with $\dot{V}O_2$ [6], or even hemodynamic changes measured by signal-morphology impedance cardiography (SM-ICGTM) [7]. In this context, it remains difficult to identify parameters that could be used as a predictive tool to anticipate the response to exercise training in patients with cardiac disease. This is unfortunate, as they would help to better target patient populations suitable for EBCR, adapt the exercise training programme (modalities, duration and/or intensities), improve short-term outcomes and possibly also long-term patient adherence to lifestyle changes, which is essential to an overall improvement in

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outcomes [13]. Prediction of training response has been the subject of numerous studies focusing on central or peripheral physiological parameters, training modalities, and genetic or medical treatment-related factors. Despite some interesting results, no study seems to have definitively settled the issue. In particular, it seems that patients with impaired cardiac function, as evidenced by low maximal values of cardiac output (\dot{Q}) or stroke volume (SV), have a higher probability of a negative response to training, whether on $\dot{V}O_{2peak}$ or its determinants [4,14]. Belardinelli et al. identified changes in early left ventricular filling rate, as measured by radionuclide ventriculography, as a predictor of changes in $\dot{V}O_{2peak}$ [15]; one study identified resting systolic arterial blood pressure as a factor [4], others identified patients' peak heart rate (HR) [6]. Chronotropic incompetence may also be a factor, but has not been confirmed in a more recent study [4,18].

Other studies focused on muscle deconditioning to explain the non-response [16,17]. The type of training proposed has also been analyzed [9]. An interesting study mentions left ventricular contractile reserve measured by stress echo as having some potential predictive value [6]. The genetic or epigenetic (circulating microRNAs) makeup of patients may also play an important role [19,20]. These methods, although sometimes promising in terms of predictive value, often appear difficult to implement in routine clinical practice because they require special skills and/or complex equipment and procedures [6,20]. Conversely, hemodynamic responses to exercise can now be assessed routinely and quite easily in a non-invasive and validated manner using a technology called Signal-Morphology based Impedance Cardiography (SM-ICGTM). This technology has been used to improve the diagnosis during exercise testing in coronary artery disease [21,22], pulmonary hypertension [23] or ventricular dysfunction [24]. A SM-ICGTM specific parameter is the contractility index (CTi), of which the calculation is based on the velocity of the blood volume variation during the systole; reflected by the variations in heart impedance ($\frac{dZ}{dt}$). The aim of this study was to determine the predictive potential of the CTi profile, assessed during baseline CPET, on the response to cardiac rehabilitation in patients with cardiac disease.

2. Materials and methods

2.1. Study population

Fifty-eight patients were retrospectively included in this study. They were referred to the Leopold Bellan Prevention and Rehabilitation Center (Tracy le Mont, France) for in or out-patient EBCR between March 2019 and March 2020. All patients provided written informed consent for data analysis in this retrospective study. The study was conducted in accordance with the tenets of the Declaration of Helsinki. The exclusion criteria were not specific to this study and were set in accordance with the French recommendations for EBCR [31,32]. All of these patients underwent at least one complete CPET with SM-ICGTM exercise hemodynamics on admission. They also all underwent a CPET after their EBCR was completed. All patients completed a full rehabilitation programme in accordance with the guidelines of the French Society of Cardiology for cardiac rehabilitation in adults [31,32]. Their treatments were not modified and no patient underwent a revascularization procedure during the rehabilitation programme (Table 1). Exercise training was performed once or twice a day, 5 times a week for 4 weeks, for a total of 20 aerobic and 12 resistance sessions. Briefly, the aerobic exercise sessions consisted of 20–50 min of a continuous cycling at the first ventilatory threshold (VT1) using a cycloergometer. The exercise intensity was regularly increased to reach the target heart rate [33]. Resistance training consisted of 2 sets of 10–15 repetitions of lower limb exercises (leg press, quadriceps leg extension, and standing calf raise) and 2 sets of 10–15 repetitions of upper limb exercises (lateral raise, triceps pushdown, and dumbbell curl), at 30–50 % of 1 repetition maximum [33]. Patients were considered responders (Resp) to EBCR if

Table 1
Study population characteristics.

	Entire group (%)	Normal CTi profile	Altered + Compromised CTi profiles
Number (%)	57 (100)	28 (49.1)	29 (50.9)
Sex (Female/Male (%))	2/55 (3.5/96.5)	1/27 (3.6/96.4)	1/28 (3.4/96.6)
Age (years)	59.5 ± 10.3	58.4 ± 12.2	61.1 ± 8.0
Weight (Kg)	87.4 ± 15.2	88.7 ± 14.3	85.9 ± 16.7
Height (cm)	175.1 ± 7.9	174.6 ± 7.7	175.4 ± 8.3
BMI (kg.m ⁻²)	28.6 ± 4.3	29.1 ± 4.2	27.9 ± 4.3
Pathological context			
CAD (n (%))	32 (56.1)	17 (60.7)	15 (51.7)
CHF (n (%))	5 (8.8)	1 (3.6)	4 (13.8)
Valvular disease (n (%))	7 (12.7)	3 (10.7)	4 (13.8)
Risk factors (n (%))	11 (20.0)	6 (21.4)	5 (17.2)
Peripheral Arterial disease (n (%))	1 (1.8)	1 (3.6)	
Marfan disease (n (%))	1 (1.8)		1 (3.5)
Physiological parameters			
Baseline $\dot{V}O_{2peak}$ (mL.min ⁻¹ .kg ⁻¹)	20.3 ± 5.7	19.8 ± 5.4	22.3 ± 6.0
Baseline Resting Left Ventricular Ejection Fraction (Echo) (%)	54.56 ± 10.92	55.83 ± 13.01	53.08 ± 8.77
Duration of EBCR (weeks)	n = 54 4.0	n = 29 4.0	n = 25 4.0

Legend: CTi: contractility index, BMI: body mass index, CAD: coronary artery disease, CHF chronic heart failure, $\dot{V}O_{2peak}$: peak of oxygen uptake, EBCR: exercise based cardiac rehabilitation. * Significant difference between Normal and Altered+Compromised CTi profile groups (p<0.05)

they displayed an increase in $\dot{V}O_{2peak}$ value equal to or greater than 5 %, or non-responders (N-Resp) if not [18]. This is consistent with the rest-retest coefficient of variability of $\dot{V}O_{2peak}$, which is usually reported to be less than 4 % [34].

2.2. Cardiopulmonary Exercise Test (CPET)

All subjects performed a cardiopulmonary exercise test (CPET) in the upright position on an electronically braked cycloergometer (ERGOLINE 900, Schiller Medical SAS, Bussy St. Georges, France) in an air-conditioned room before and after the EBCR program. After 3 min of rest and 3 min of warm-up at 20 watts, each subject performed a 1-min incremental exercise test to voluntary exhaustion with a 10-watt work increment, as previously described [4,33]. Seat and handlebar height were adjusted for each subject according to personal preference. The cadence was fixed at 60 rpm and kept constant at all times. Respiratory Frequency (RF), Tidal Volume (TV), minute ventilation (\dot{V}_E), $\dot{V}O_2$ and carbon dioxide production ($\dot{V}CO_2$) were measured at rest and during exercise using a fixed gas analyzer (Quark-CPET, Cosmed, Rome, Italy). The software of the device was set to automatically eliminate ectopic values and to average the data every 5 s. The values of $\dot{V}O_{2peak}$ and Maximal Tolerated Power (MTP) were defined as previously proposed in the literature [35]. The First Ventilatory Threshold VT1 was determined as the breakpoint in the curve of the $\dot{V}CO_2$ versus $\dot{V}O_2$ plot (V-slope method) [33,36].

2.3. Cardiac hemodynamics during CPET

\dot{Q}_c , SV, and CTi values were determined during CPET by morphological analysis of the beat-to-beat cardiac impedance signal using an advanced transthoracic impedance cardiograph, a technology called SM-ICG™ (PhysioFlow®, PF-05 Lab1, Manatec Biomedical, Macheren, France). The PhysioFlow® software used was version 2.8.0 and the electrodes were those marketed by the manufacturer (PhysioFlow® PF50). The patients' skin was shaved if necessary and prepared with some Nuprep® abrasive gel (Weaver and Company, Aurora, CO, USA). The manufacturer's instructions for use were strictly followed. After signal processing, which included a sophisticated built-in noise reduction filter called HD-Z™, the heart signals were analyzed beat by beat and the results were averaged over 5 s. This method of measuring exercise hemodynamics has been described previously [37] and has been validated for accuracy, reproducibility and sensitivity, including at maximal exercise [23,37–39]. It has been widely used in research on exercise hemodynamics [40].

2.4. Contractility Index (CTi) Profiles during CPET

The . maximal rate of change of the impedance waveform ($\frac{dZ}{dt} \max$), computed as the peak of the first mathematical derivative over time of the impedance waveform during systole (also called $\frac{d(HD-Z)}{dt} \max$ by the manufacturer of PhysioFlow®), is a representation of the maximum ejection flow velocity during systole ($\frac{dV}{dt}$). It is a well-known parameter in impedance cardiography [41]. The $\frac{dZ}{dt} \max$ values are recorded during each cardiac cycle and graphically represented by the software in the form of trend curves averaged over 5 s under the name CTi (Fig. 1). A normal contractility profile during exercise is characterized by a rapid increase in CTi followed by a slower increase or plateau. This pattern has been described previously using other methods to assess myocardial contractility in healthy subjects [42]. The PhysioFlow® software allows manual scrolling of portions of these trend curves to evaluate a slope and average over the selected portion. This function is useful for determining slope changes and, in particular, the possible CTi slope inversion that can occur for at least one minute prior to the recovery phase of the

exercise test (negative slope after the positive slope observed at the start of exercise). This change in slope (altered CTi profile) appears to be a sign of an abnormal response to exercise of the ejection flow provided by left ventricular function. Sometimes the CTi does not increase during exercise (slope is zero or close to zero) or even collapses at the beginning of exercise (negative slope), which seems to be a sign of deteriorated left ventricular function (compromised CTi profile) (Fig. 1). The normal CTi profile defined a first subgroup of patients, whereas the altered and compromised CTi profiles defined a second subgroup of patients (abnormal CTi profile). In order to minimize operator bias, the CTi profiles' analysis was conducted by two independent operators. In case of disagreement, a third operator would intervene. Both analyses were conducted in a blinded manner.

2.5. Statistical analysis

Statistical analyses were performed with JASP (version 0.17.1 for Apple Silicon, JASP Team, VU Amsterdam, Amsterdam, The Netherlands). All data are expressed as mean and standard deviation (\pm SD). According to the normality of the data evaluated by Shapiro-Wilk and equality of variance (Levene's test), independent samples Student *t*-test or Mann-Whitney test was performed to evaluate $\Delta \dot{V}O_2$ peak and baseline LVEF values between both groups. Associations between CTi and CPET responses were evaluated using logistic regression, adjusting for several potential confounders, including duration of EBCR, age, chronic disease, baseline $\dot{V}O_2$ peak and LVEF values [40]. The dependent variable was CTi responses to CPET. Adjusted models (covariates with $P < 0.10$) were fitted to estimate the effect of CTi on $\dot{V}O_2$ peak in all subjects. The odds ratio (OR) was calculated for the associations [43]. The significance level was set at p -value < 0.05 for 95 % confidence interval.

3. Results

A majority of these patients had a form of coronary artery disease (CAD) or displayed risk factors for CAD (Table 1). Sometimes the pathology was severe with multiple stenosis and these patients underwent

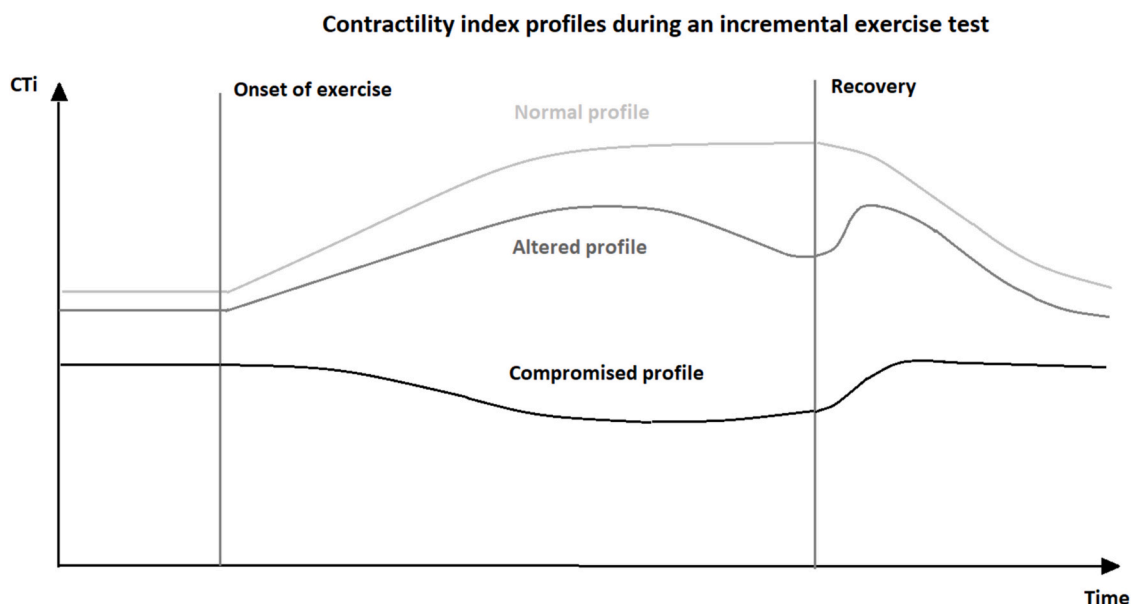


Fig. 1. Different CTi profiles obtained during exercise using the SM-ICG™ technique.

CTi: contractility index. Examples of CTi response of cardiac patients using SM-ICG™ during a CPET. These curves present the kinetics of CTi during exercise. Patients were classified into 3 categories according to their CTi response to CPET: 1) Normal profile is characterized by a rapid increase in CTi at the start of exercise followed by a plateau or pseudo-plateau, 2) Altered profile corresponds to an increase then a fall in CTi before the end of exercise, and 3) Compromised profile is characterized by no response or a decrease in CTi during exercise.

prior revascularization interventions (surgical or stents). The rest of the group is diverse (CHF, valvular surgery, etc.). 54 of the 58 patients had their LVEF recently measured by Echo, with an average value close to 54 % for the whole group. Only 7 out of these 54 patients presented with a mildly reduced ejection fraction (41 to 49 %) and 5 displayed a reduced ejection fraction (equal to or under 40 %). A post EBCR evaluation of LFEF could be performed on 30 of the 54 patients that had a baseline LVEF measured. All SM-ICG™ recordings were considered acceptable in terms of signal quality, except one (the signal was lost after some time, making the hemodynamic trends near maximal exercise uninterpretable). This left 57 patients for analysis in this study. On average, the entire group of 57 patients increased their $\dot{V}O_{2peak}$ ($+13.6 \pm 22.9$ %) and also their MTP ($+23.9 \pm 14.3$ %). The two subgroups, divided according to their CTi profiles, appear homogeneous in terms of size, demographics, disease, physiological parameters and duration of the EBCR program (Table 1). The EBCR program induced a higher $\dot{V}O_{2peak}$ improvement in patients with normal CTi response compared to their counterparts with altered or compromised CTi profiles ($+24.1 \pm 21.4$ % vs. $+3.36 \pm 19.5$ %, $p < 0.001$). Incidentally, this result correlates with a higher mean MTP increase in patients with normal compared to altered or compromised CTi profile groups ($+29.7 \pm 11.7$ % vs. $+18.1 \pm 14.3$ %, $p < 0.001$). Logistic regression analysis showed that patients with a normal exercise CTi profile were 8.7 times more likely to have a greater than 5 % improvement in $\dot{V}O_{2peak}$ (odds ratio 8.7, $p = 0.012$) compared to patients with an altered or compromised exercise CTi profile (Fig. 2). Neither baseline $\dot{V}O_{2peak}$ values, age nor number of EBCR days explained the changes in $\dot{V}O_{2peak}$ with exercise training (Fig. 2). Clinically, the 28 patients with normal CTi rarely did not respond to EBCR (less than 5 % increase in $\dot{V}O_{2peak}$, $n = 3$), but mostly responded positively to CR (more than 5 % increase in $\dot{V}O_{2peak}$, $n = 25$) (Fig. 3). In patients with altered or compromised CTi profiles, responses to EBCR were mixed. It should be noted that the patients who lowered their exercise CTi from the onset of exercise (compromised CTi profile) all experienced a decrease in $\dot{V}O_{2peak}$ after EBCR (Fig. 3). It is to be noted that there is no statistical relationship between baseline $\dot{V}O_{2peak}$ and $\Delta\dot{V}O_{2peak}$ (Pearson's $r = -0.381$, $p = 0.005$), and none between baseline resting LVEF and baseline $\dot{V}O_{2peak}$ (Pearson's $r = 0.406$, $p = 0.002$), $\Delta\dot{V}O_{2peak}$ (Pearson's $r = -0.085$, $p = 0.540$), or even

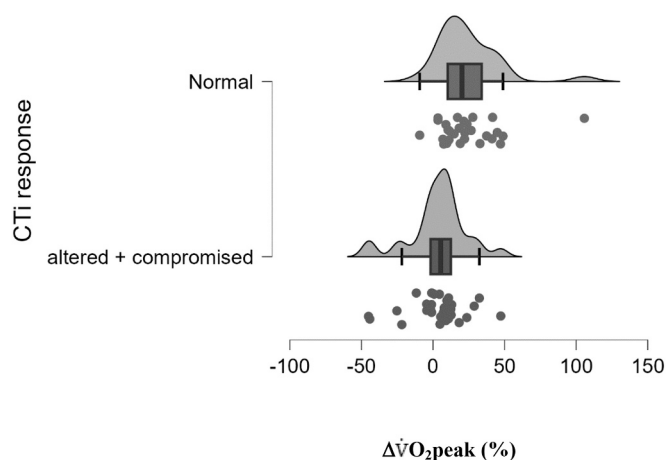


Fig. 2. Changes in peak value of oxygen uptake with exercise based cardiac rehabilitation.

CTi: contractility index, $\Delta\dot{V}O_{2peak}$ (%): changes in peak of oxygen uptake expressed in % of baseline value of peak of oxygen uptake. The graph on top represents the response in $\Delta\dot{V}O_{2peak}$ (%) for the normal CTi response group ($n = 28$). The graph below represents response in $\Delta\dot{V}O_{2peak}$ (%) for the altered+compromised CTi response group ($n = 29$).

exercise CTi profiles (Table 1). Interestingly, there is also no statistical relationship between the changes in resting LVEF (before and after EBCR) and $\Delta\dot{V}O_{2peak}$ (Pearson's $r = 0.224$, $p = 0.233$).

4. Discussion

The originality of the present study is to determine the predictive potential of the CTi profile assessed during baseline CPET for the response to cardiac rehabilitation in patients with cardiac disease. In this initial evaluation study, the focus was not on a specific pathology or type of patient, although a clear majority of CAD patients were included.

The decision to consider a rate of increase in $\dot{V}O_{2peak}$ greater than 5 % as a qualifying response to training can be controversial. Some studies have chosen higher rates, in the order of +10 %, which may be very clinically significant and also closer to a statistical median [2,4]. However, using this criterion, only half of the study population would have been “responders”, compared to 70 % using the +5 % criterion. Other studies have defined a +0 % threshold for a positive EBCR response [8] (78 % of patients had a positive response to EBCR in this particular study). We believe that a 5 % criterion remains a good compromise: it is a “real” improvement (beyond technical and physiological variability) and is also clinically relevant for these patient groups and not based on a purely statistical approach. It should be noted that in our group of patients, the average response in terms of $\Delta\dot{V}O_{2peak}$ ($+13.6 \pm 22.9$ %) is consistent with the expected range of improvement observed in comparable studies (from +8.5 % to +16.0 %) [29,45]. According to our results, a normal CTi profile, reflecting a healthy contractile function of the heart during exercise, seems to be a favorable predictor for improvements in patients’ performance with training. Some patients with an altered or compromised CTi profile during exercise were responders and others were not. It is to be noted that the confidence intervals remain relatively large, highlighting a significant variability in the response to EBCR in both groups. This observation may be related to the nature of the myocardial injury, its severity, and its timing before the patient entered the CR program, which hypothesis would require further investigations. It is also to be noted that resting LVEF was not significantly correlated to these CTi profiles, suggesting again that the hemodynamic response to exercise matters more from a clinical standpoint, rather than resting evaluations.

Furthermore, it is possible that a very impaired CTi response (i.e., no increase at all during exercise) could be a negative predictive factor, but the small number of patients with this profile in this study ($n = 7$) precludes a definitive conclusion. It has previously been suggested that the absence of an increase in contractility during exercise is a sign of severely impaired cardiac function [30], and therefore a possible severe limitation to exercise capacity improvement with training. Conversely, a normal CTi response to exercise could imply that cardiac function is not a limiting factor for training-induced improvements in all physiological determinants of exercise capacity. These results and their potential clinical implications may be viewed by some clinicians as counterintuitive: it is often described that EBCR benefits sicker patients more than those in better health, but our data show that baseline resting LVEF or even baseline $\dot{V}O_{2peak}$ is not predictive of $\Delta\dot{V}O_{2peak}$ (which result is consistent with the literature). Other clinicians might even find them potentially counterproductive (if not ethically implemented): pre-selecting “healthier patients” based on CTi response might very significantly improve outcomes in the selected population, but then the therapeutic nature of EBCR might be questioned as a significant number of patients would be excluded. Further studies could be designed in order to determine if optimizing pre-EBCR therapeutic strategies would improve the patients’ exercise CTi pattern and thus potentially qualify more patients for a successful rehabilitation. Even if in real life patients have increasingly complex cardiovascular profiles and a higher incidence of comorbidities, further studies could focus on more specific patient groups, such as heart failure or CAD patients. This could allow a

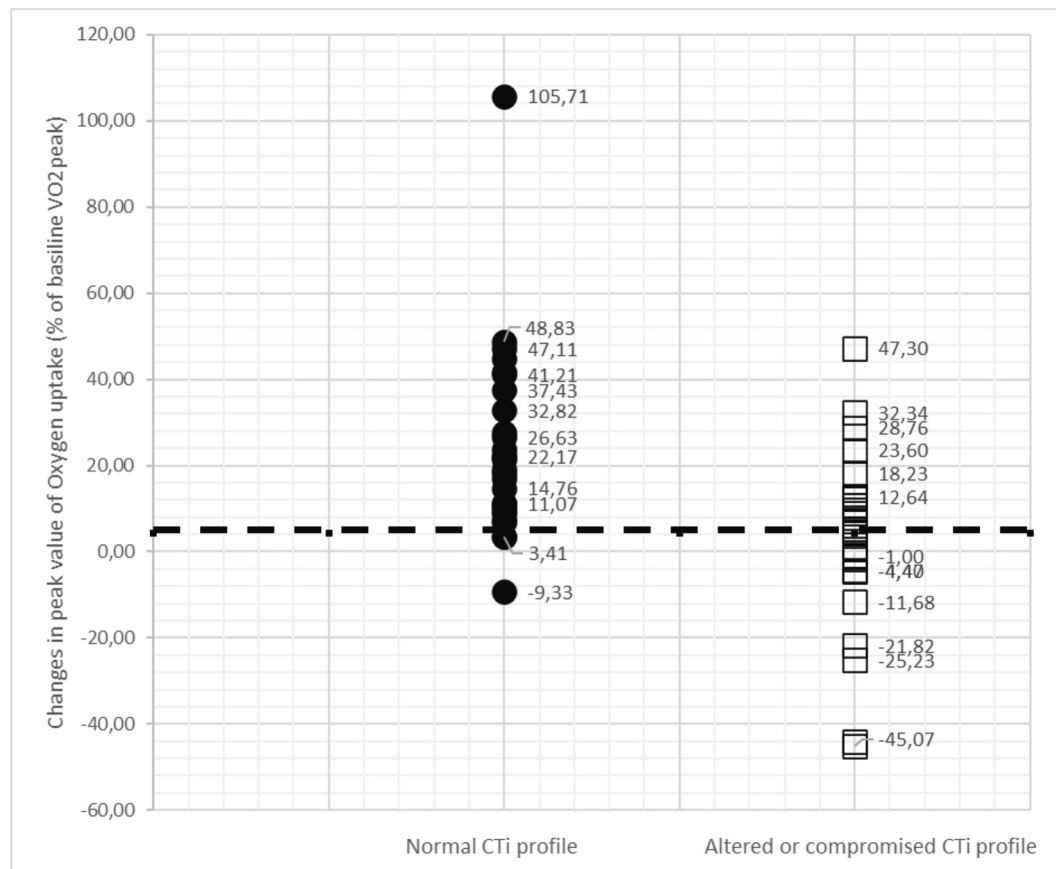


Fig. 3. Individual responses to cardiac rehabilitation.

CTi: contractility index, $\Delta\dot{V}O_2$ peak (%): changes in peak of oxygen uptake expressed in % of baseline value of peak of oxygen uptake. Each point and square represent a patient ($n = 57$). The dotted line represents the response threshold line ($\Delta\dot{V}O_2$ peak = 5 %). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

more detailed analysis of the predictive power of CTi profiles according to specific pathologies. The predictive power could also be improved by combining the CTi profile criteria with other metrics from the $\dot{V}O_2$ test or even cardiac ultrasound (e.g., LVEF). But it is to be noted again that baseline resting LVEF alone displayed no predictive value for the outcome of EBCR in this study.

4.1. Study limitations

The present study presented a certain number of limitations. Firstly, the relatively small sample size that could be analyzed, even if the differences are statistically significant and despite the small number of patients excluded from the study. Unfortunately, only two women were included in this study, which reflects the patient mix in this rehabilitation center at the time of data collection and also the general under-representation of women in EBCR [45]. Secondly, the relative heterogeneity of the population studied could be questioned. However, the diversity of pathologies, drug treatments and even the (limited) individualization of training protocols did not seem to be a limitation of this study, which reinforces its interest. Thirdly, the monocentric nature of this study could be discussed, but it ensures homogeneity in the protocols and in the interpretation of the exercise tests, and also in the supervision of the training protocol. The nature of the parameter used, CTi (or $\frac{dZ}{dt}$ max) could also be discussed. It is undoubtedly related to cardiac contractility, but not a direct measure of this contractility. However, $\frac{dV}{dt}$ max, which is closely related to $\frac{dZ}{dt}$ max, has been successfully studied previously using different sensors, most of the time invasive [27,28]. CTi remains a parameter specific to the SM-ICG™ system that is

difficult to correlate with other technologies, even if it is a strong contributor to the calculation of SV values and trends, which have been validated in comparative studies before, and also in application studies [29,30]. Interestingly, the strong predictive value of more conventional SM-ICG™ exercise hemodynamic parameters (i.e. Cardiac Index) has been established independently of other prognostic factors in several types of heart failure patients [25,26]. Finally, the determination of slope changes in CTi is purely graphical and relies on the averaging tool offered by the PhysioFlow® software, which is controlled by the physician in charge of interpretation (scrolling). An automated slope analysis could be welcome to limit potential analysis errors, especially by inexperienced users, and to guarantee reproducibility. However, the comparison between the expert analysis and the analysis by the team with no prior exposure to CTi profiles showed that only in 5 cases out of 58 recordings the interpretation could have been clearly different, leading to a potential reclassification of the CTi profile by the expert in 1 case out of 5 (a borderline case actually). However, these reclassifications were further analyzed and they did not alter the predictive power of the CTi profiles. These findings limit the potential for an operator bias.

5. Conclusion

This study highlights the value of adding noninvasive, continuous exercise hemodynamic measurements to $\dot{V}O_2$ testing in the routine evaluation of cardiac rehabilitation patients, at least in the initial assessment CPET. The exercise CTi profiles observed during this baseline CPET, as measured by SM-ICG™, appear to have a strong predictive value to anticipate the response to EBCR, confirming the original study

hypothesis. It is also likely to be of interest as an independent criterion of rehabilitation outcome. Finally, the hemodynamic patterns and profiles observed during this baseline test could potentially be used as a tool to personalize exercise prescription.

Statement of authorship

All the author take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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CRedit authorship contribution statement

Frank Bour: Writing – original draft, Methodology, Formal analysis. **Evan Milstein:** Methodology, Visualization. **Antoine Poty:** Data curation. **Yves Garaud:** Supervision, Investigation. **Damien Vitiello:** Writing – review & editing, Supervision. **Pierre Marie Leprêtre:** Writing – review & editing, Writing – original draft, Supervision, Funding acquisition, Conceptualization.

Declaration of competing interest

Frank Bour is co-inventor of the SM-ICGTM technology and co-founder and managing director of Manatec Biomedical, the company that develops and manufactures the PhysioFlow[®] device based on this technology.

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