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Responses to exercise training in patients with heart failure. Analysis by oxygen transport steps

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ABSTRACT

Background: Exercise training (ET) increases exercise tolerance, improves quality of life and likely the prognosis in heart failure patients with reduced ejection fraction (HFrEF). However, some patients do not improve, whereas exercise training response is still poorly understood. Measurement of cardiac output during cardiopulmonary exercise test might allow ET response assessment according to the different steps of oxygen transport.
Methods: Fifty-three patients with HFrEF (24 with ischemic cardiomyopathy (ICM) and 29 with dilated cardiomyopathy (DCM) had an aerobic ET. Before and after ET program, peak oxygen consumption (VO_{2peak}) and cardiac output using thoracic impedancemetry were measured. Oxygen convection (QO_{2peak}) and diffusion (DO_2) were calculated using Fick's principle and Fick's simplified law. Patients were considered as responders if the gain was superior to 10%.
Results: We found 55% VO_{2peak} responders, 62% QO_{2peak} responders and 56% DO_2 responders. Four patients did not have any response. None baseline predictive factor for VO_{2peak} response was found. QO_{2peak} response was related to exercise stroke volume ($r = 0.84$), cardiac power ($r = 0.83$) and systemic vascular resistance (SVR_{peak}) ($r = -0.42$) responses. Cardiac power response was higher in patients with ICM than in those with DCM ($p < 0.05$). Predictors of $QO2_{peak}$ response were low baseline exercise stroke volume and ICM etiology. Predictors of DO_2 response were higher baseline blood creatinine and prolonged training.
Conclusion: The analysis of the response to training in patients with HFrEF according to the different steps of oxygen transport revealed different phenotypes on VO_{2peak} responses, namely responses in either oxygen convection and/or diffusion.

1. Introduction

Intolerance to exercise is one of the most common symptoms of chronic heart failure. It is remarkably reflected by the peak oxygen consumption (VO_{2peak}) which is considered to represent the limits of the cardiopulmonary system. Oxygen consumption at any time is given by the Fick equation (VO_2 = cardiac output x arteriovenous oxygen difference). For a long time, VO_{2peak} has proved to be a powerful prognostic marker. It is therefore commonly used in management strategies and the evaluation of new therapies. Other markers from the cardiopulmonary exercise test (CPET) that are independent of peak exercise, such as the relationship between minute ventilation and carbon dioxide production (VE/VCO_2 slope) and the oxygen uptake efficiency slope, have been shown to be additional prognostic markers of VO_{2peak} owing to their relationship with cardiac output during exercise [1].

Exercise training improves exercise tolerance and quality of life in patients with chronic heart failure. Some studies also suggest that exercise training improves clinical prognosis [2,3]. In addition, and more significantly, it has been shown that the lack of significant improvement in VO_{2peak} after training is an important predictor of poor prognosis [4]. But the characteristics of future responders and non-responders to training are currently poorly known. Patients showing signs of inappropriate peripheral muscle adaptation have low VO_{2peak} associated with low ventilatory threshold [5]. Conversely, those able to increase their cardiac output were reported to be responders in previous studies [6,7].

The recent development and validation of non-invasive cardiac output measurement has made it possible to refine the assessment of the specific cardiac limitations on exercise intolerance. Studies have highlighted the prognostic value of the response of cardiac output during exercise in patients with chronic heart failure. A recent study with

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impedance measurement of cardiac output during exercise showed that cardiac output at peak exercise was the strongest hemodynamic prognostic factor and was independent of other prognostic factors such as VO_{2peak} and VE/VCO_2 slope [8]. In addition, the measurement of cardiac output during exercise makes it possible to distinguish 2 of main determinants of VO_{2peak} or steps of oxygen transport: convection (the transport of oxygen from the pulmonary vein to the capillaries of the peripheral muscle, mainly determined by cardiac output during exercise) and peripheral diffusion (the ability of oxygen to diffuse from the capillary to the mitochondria during exercise) [9].

The aim of our study was to measure changes in VO_{2peak} and its determinants after training of patients with chronic heart failure with reduced ejection fraction (HFrEF) by non-invasive measurement of cardiac output assessed by impedancemetry during CPET, as well as to highlight the baseline characteristics of responders and non-responders to training.

2. Methods

2.1. Population

Between 2017 and 2018, we prospectively included 56 consecutive stable chronic heart failure patients referred to our cardiac rehabilitation center. CPET was performed before and after training. All patients had a left ventricular ejection fraction <40%. We excluded from our study cardiac transplant patients, patients implanted with a pacemaker (heart rate dependency) or with a ventricular assist device as well as patients with contraindications to cardiac rehabilitation according to the European guidelines [10]. The data collected about the cardiovascular clinical examination, electrocardiogram, resting echocardiography (left ventricular ejection fraction (LVEF) and end-diastolic diameter, mitral E/e'), biological examinations (renal function, BNP, hemoglobin, CRP) and the treatment of heart failure taken by the patient at the time of his/her inclusion were collected. All patients underwent a comprehensive cardiac rehabilitation program. No treatment has been changed and no revascularization procedure has been carried out between the 2 CPETs.

2.2. CPET

CPETs were performed under the supervision of a cardiologist, on an ergometer bicycle using a ramp protocol with an increased workload of 10 W per minute until exhaustion before and after training. Exercise ventilation and exhaled gases were measured. Breath by breath analysis of exhaled gases included oxygen consumption (VO_2), carbon dioxide production (VCO_2) and minute ventilation (VE). The 10-s average VO_2 at peak was recorded as the peak VO_2 (VO_{2peak}). Derived variables included ventilatory efficiency (VE/VCO_2), the maximum workload and total duration of the exercise were also reported. Heart rate (HR) at the peak (HR_{peak}), resting HR and the age-predicted maximal HR (APMHR) were used to calculate chronotropic index defined as (HR_{peak}- resting HR)/(APMHR- resting HR) using APMHR defined as 119 + resting HR/2 – age/2–5 [11].

2.3. Noninvasive stroke volume measurement

Cardiac output (Q), cardiac index (CI) and stroke volume (SV) were determined non-invasively during exercise test using a thoracic bioelectrical impedance device (PhysioFlow, PF-05 Lab1, Manatec Biomedical) commonly used in our center. This method has been previously described [12]. Peak HR, SV_{peak} and Q_{peak} are the values of HR, SV and Q assessed at peak exercise. We considered a gain of 7.2% in SV between pre- and after-training as the minimum clinically significant gain [12]. Cardiac power (CP) was defined as the product of cardiac index and mean blood pressure (MBP) (CP = CI x MBP). Systemic vascular resistance at the peak (SVR_{peak}) was defined as $SVR_{peak} = MBP/Q_{peak}$.

2.4. Exercise training program

The exercise-training program included 20 sessions of supervised training (60 min/day, 5 sessions per week over a period of 4–6 weeks). Each session included 30 min bicycle endurance and 30 min of other dynamic physical activity (calisthenics and/or resistance training). The endurance protocol was individualized according to the baseline CPET and included interval training (90% of peak VO_2 bouts of 1 min, and below VT during 4 min) 3 times a week and continuous training (at the VT level) twice a week. The intensity of exercise training was monitored using the related perceived exertion (Borg) scale. The intensity was regularly adjusted to maintain 12–14 level.

2.5. Calculation of variables from CPET: see details in supplementary data

AVD═VO_{2peak}/Q_{peak}: arteriovenous difference in oxygen content.

CaO_2: arterial oxygen content.

$CvO_2 = DAV - CaO_2$: venous oxygen content.

PvO_2: mean venous O_2 pressure (calculated from CvO_2).

$QO_{2peak} = Q_{peak}$ x CaO_2: central determinant of exercise capacity (or convection) is defined by the peak oxygen content brought to capillaries.

$DO_2 = VO_{2peak}$ /2 X PvO_2: Peripheral determinant is defined as the peripheral muscle oxygen diffusion at peak exercise. DO_2 is the muscle diffusion capacity of oxygen at peak exercise.

We applied this model to the whole body not using oxygen consumption and blood flow of the exercising muscles, but instead using total VO_{2peak} and cardiac output, considering the whole body as a single muscle as it has already been done by others [13,14]. Thus, the inferred DO_2 will also depend on the amount of cardiac output redistributed to the exercising muscles. The limitations of this assumption (the

Table 1
Baseline characteristics of patients.

	n (%)	mean ± SD
Anthropomorphic data		
Sex ratio (F/M)	8/45 (15/85)	
Age (y)		58.1 ± 13.2
BMI (Kg/m^2)		25.4 ± 9.9
Corporeal area (m^2)		1.9 ± 0.27
Cardiac disease		
Dilated cardiomyopathy	29 (55)	
Ischemic cardiomyopathy	24 (45)	
ICD	17 (32)	
Comorbidities		
Systemic hypertension	18 (34)	
Diabetes mellitus	8 (15)	
Atrial fibrillation	7 (13)	
Medications		
Betablockers	42 (79)	
ACEi/ARB	38 (71)	
Sacubitril + valsartan	6 (11)	
Spironolactone	37 (70)	
Furosemide	38 ((71)	
Lab tests		
Creatinin (μmol/L)		94 ± 34
Hemoglobin (g/dL)		13.1 ± 2.1
CRP (mg/L)		24 ± 62.4
BNP (pg/mL)*		446 ± 590
Total Cholesterol (mmol/L)		4.5 ± 1.4
Echocardiography		
LV ejection fraction (%)		28.6 ± 9.3
LV end-diastolic diameter (mm)		63.6 ± 8.6
Mitral E/e'		10.9 ± 4.7
Mitral regurgitation (grade)		1.4 ± 0.9
sPAP (mmHg)		37.2 ± 11

ACEi, angiotensin-converting enzyme inhibitors; ARB, angiotensine receptor blockers; BMI, body mass index; BNP, brain natriuretic peptide; ICD, implantable cardioverter defibrillator; LV, left ventricular; sPAP, systolic pulmonary artery pressure. * Patients treated by sacubitril/valsartan are excluded (tested by NT BNP).

application of this model) will be discussed in the paragraph Limitations in Discussion section.

Patients were considered as "responders" when their relative increase in VO_{2peak} after training was equal or more than 10% which may be considered as clinically relevant. A change of 7.2% in SV was considered as the minimum clinically significant gain [12]. Arbitrarily, we considered as QO_{2peak} and DO_2 responders, patients with an increase equal or more than 10% after training.

2.6. Statistical analysis

The Mann-Whitney test or the student test was used according to the normal distribution of the samples to compare the values of pre-training variables between the responding and non-responding groups. The signed Wilcoxon test or the student test was used to compare the values of paired variables before and after training according to the normality of the samples. Khideux test (with Yates correction if counts <5) was used to compare population counts according to qualitative variables. A link between 2 continuous variables was sought by determining the Pearson's correlation coefficient. Multivariate analysis for predictive factors was done using logistic regression. The variables selected for this test were those with a p value <0.2 in univariate analysis; whatever was a correlation or physiological link between several variables, only one of the variables was selected for multivariate analyses. These analyses were performed using XLSTAT (version 2019.3.2; Addinsoft).

2.6.1. Ethical standards

The authors assert that all patients gave signed informed consent to participate, in conformity with the ethical guidelines of the 1975 Declaration of Helsinki.

3. Results

3.1. Population

Of the 56 patients included, 53 patients had a usable impedance measurement signal and were selected for the study, among which 24 had ischemic cardiomyopathy (ICM) and 29 had dilated cardiomyopathy (DCM). The characteristics of patients before training are summarized in Table 1. Fig. 1 shows the interactions of central and peripheral oxygen transports that determine VO_{2peak} before training in the whole population.

3.2. Response to training

3.2.1. Resting echocardiography

Resting LVEF rose after training from 28% ± 8 to 32% ± 10 ($p = 0.001$). Mitral E/e' and systolic pulmonary artery pressure were not significantly different after training (10.9 ± 4.7 vs 11.5 ± 4.2 and 37.2 ± 11.1 vs 34.6 ± 10.3 respectively).

3.2.2. CPET

Table 2 describes the effects of training on CPET parameters and shows a significant increase in exercise capacity, stroke volume and cardiac output and decrease in VE/VCO_2 slope and vascular resistance. HR_{peak} increased slightly but significantly ($p = 0.03$) and was not influenced by betablocker treatment.

We identified 55% VO_{2peak} responders, 62% QO_{2peak} responders and 56% DO_2 responders (Fig. 2). Figs. 2 and 3 shows the different profiles of responders and non-responders in VO_{2peak} according to responses in QO_{2peak} and/or DO_2. Response in VO_{2peak} could be related to an isolated response on $QO_{2\ peak}$ (27%) or DO_2 (30%) or both (43%). Non responders in VO_{2peak} might have QO2peak or DO_2 increase but insufficiently to affect significant gain on VO_{2peak}.

Besides, the increase in QO_{2peak} was correlated to increase in SV_{peak} ($r = 0.85$) but neither to gain in HR_{peak} nor to improvement in resting LVEF%. By contrast, a significant correlation was found between the decrease in SVR_{peak} and the gain in QO_{2peak} ($r = 0.42$, $p = 0.001$), but not with gain in DO_2. Gain in cardiac power strongly correlated with gain in QO_{2peak} ($r = 0.83$, $p < 10^{-6}$). Response in QO_{2peak} tended to be favorized by the absence of response in DO_2, but this relationship did not reach statistical significance (Fig. 3). Details of calculated data of 3 patients are displayed in supplementary data.

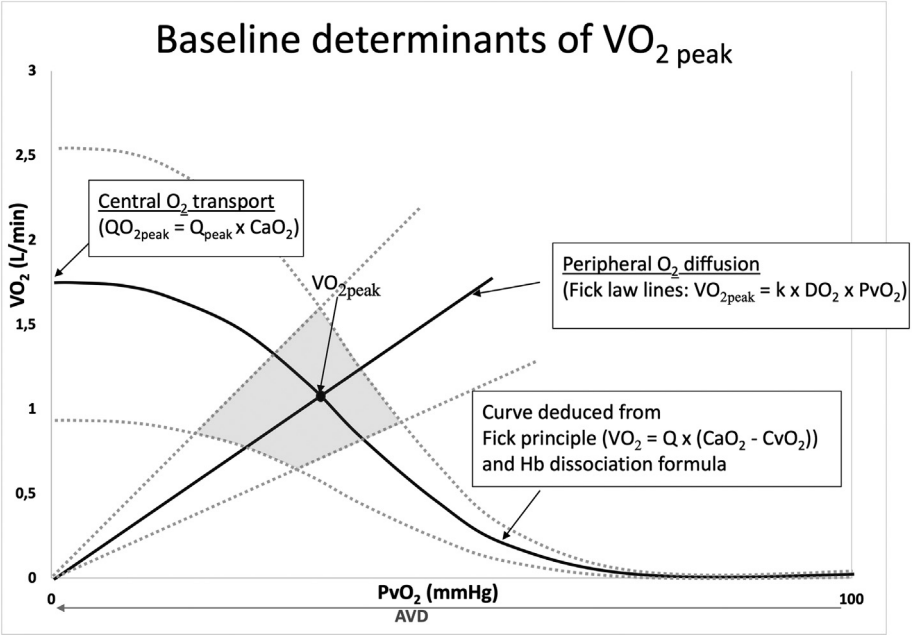

Fig. 1. Graphical representation of interactions between central and peripheral oxygen transports that determine VO2peak in patients before training. Note the curve lines that reflect both Fick principle and hemoglobin dissociation curve. The decrease in central transport automatically leads to a decrease in the PvO2 and therefore an increase in the AVD at the peak, partially limiting the effect on the VO2peak. Inversely, decrease in diffusive transport decreases the AVD. Solid lines: mean values of the population, dotted lines: values at one plus and minus one standard deviation. AVD: arteriovenous difference, PvO2: partial venous pressure of oxygen. VO2peak: oxygen uptake at peak of effort.

Table 2
comparison CPET and exercise hemodynamic data before and after training.

	Before training	After Training	p
Rest			
HR (b/mn)	80 ± 15	73 ± 11	0.0002
SBP (mmHg)	100 ± 18	102 ± 20	0.32
MBP (mmHg)	74 ± 15	76 ± 15	0.49
VO_2 (mL/kg/mn)	4.3 ± 0.9	4.9 ± 1.5	0.002
VE (L/mn)	13.6 ± 4.4	13.8 ± 3.9	0.35
SaO_2 (%)	98.6 ± 3.7	99.4 ± 2.0	0.09
SV (mL/m^2)	32.7 ± 11	35.4 ± 10.1	0.026
CI ($L/mn/m^2$)	2.5 ± 0.8	2.5 ± 0.6	0.60
SVR ($Dynes.m.s^{-5}$)	12.9 ± 2.9	12.6 ± 2.9	0.29
30 watts			
HR (b/mn)	91 ± 18	82 ± 13	0.0002
VO_2 (mL/kg/mn)	7.8 ± 1.0	7.7 ± 1.3	0.941
VE (L/mn)	23.3 ± 5.3	21.6 ± 4.1	0.029
O_2p (mL)	6.6 ± 1.7	7.1 ± 1.7	0.001
Ventilatory threshold			
Workload (watts)	42 ± 22	56 ± 25	<0.0001
HR (b/mn)	93 ± 17	90 ± 17	0.029
SBP (mmHg)	117 ± 27	126 ± 37	0.026
MBP (mmHg)	81 ± 23	85 ± 19	0.34
VO_2 (mL/kg/mn)	9.2 ± 2.5	11.2 ± 3	<0.0001
VE (L/mn)	24 ± 6	28 ± 8	<0.0001
O_2p (mL)	7.4 ± 2.5	9.6 ± 3.3	<0.0001
Peak exercise			
Workload (watts)	87 ± 38	109 ± 48	<0.0001
HR (b/mn)	111 ± 22	115 ± 24	0.03
SBP (mmHg)	134 ± 39	145 ± 36	0.08
MBP (mmHg)	94 ± 24	96 ± 29	0.18
VO_2 (ml/kg/mn)	14.8 ± 4.7	17.3 ± 6	<0.0001
VE (L/mn)	53 ± 17	66 ± 24	<0.0001
SaO_2 (%)	96.5 ± 5	97 ± 5	0.14
VE/VCO_2 slope	39.8 ± 10.2	37.7 ± 8.6	0.0008
O_2p (mL)	10.0 ± 3.2	11.3 ± 3.7	<0.0001
SV (mL/m^2)	46.1 ± 15.1	52.9 ± 14.7	0.001
CI ($L/mn/m^2$)	5.1 ± 1.9	6.1 ± 2.3	0.0001
CaO_2 (mL/100 mL)	17.4 ± 3.0	17.3 ± 2.2	0.32
CvO_2 (mL/100 mL)	6.5 ± 3.2	5.8 ± 3.2	0.07
AVD (mL/100 mL)	12.4 ± 4.8	12.3 ± 4.3	0.13
PvO_2 (mmHg)	31 ± 11	20 ± 8	<0.0001
QO_2 (L/mn)	1.7 ± 8.2	2.1 ± 9.1	0.0006
DO_2 (mL/mn/mmHg)	22 ± 8	28 ± 20	0.006
SVR ($dynes.m.s^{-5}$)	8.1 ± 3.6	6.9 ± 3.7	0.015
CP ($L/min/m^2.mmHg$)	2.1 ± 1.1	2.7 ± 1.5	0.005

AVD, arteriovenous difference in oxygen content; CaO_2, arterial oxygen content; CI, cardiac index; CP, cardiac power, CvO_2, venous oxygen content; DBP, diastolic blood pressure; HR, heart rate; MBP, mean blood pressure; O_2P, oxygen pulse; PvO_2, partial venous oxygen pressure; QO_2, oxygen delivery; VO_2, oxygen consumption; SBP, systolic blood pressure; SV, stroke volume; SVR, systemic vascular resistance; VE, minute ventilation.

3.3. Comparison responders – non responders and predictive factors (Tables 3 and 4)

3.3.1. Response in VO_{2peak}

VO_{2peak} responders had a higher resting systolic blood pressure than non-responders ($p = 0.008$). However, no significant difference in blood pressure was found at peak exercise. No other clinical, CPET and echocardiographic parameters were significantly different between responders and non-responders. Chronotropic index tended to be lower in responders than in non-responders but the difference did not reach significance ($p = 0.06$). In multivariate analysis, no baseline parameters predicted VO_{2peak} response after ET.

3.3.2. Response in QO_{2peak}

QO_{2peak} responders had a significantly lower pre training SV_{peak} (and Q_{peak}) than non-responders ($p < 0.01$). Within patients having a pre-training $SV_{peak} < 41$ ml/m^2, 81% were QO_{2peak} responders. This proportion fell to 50% of patients with pre-training $SV_{peak} > 41$ ml/m2. Moreover, considering response in SV_{peak} as a gain in $SV_{peak} > 7\%$, there was significantly less responders in SV_{peak} in patients with DCM than in patients with ICM ($p = 0.026$). Improvement of cardiac power was significantly greater in patients with ICM than in patients with DCM ($p < 0.05$) while no significant difference was found in decrease in SVR_{peak} between ICM and DCM patients (Fig. 4).

QO_{2peak} responders had no different HR_{peak} and chronotropic index than non-responders.

In multivariate analysis, predictors of response in QO_{2peak} were a lower SV_{peak} and having an ICM (Table 4)

3.3.3. Response in DO_2

DO_2 responders had significantly higher systemic vascular resistance at rest, serum creatinine and total training time than non-responders (respectively $p = 0.047$, $p = 0.011$ and $p = 0.026$). In multivariate analysis, only serum creatinine and total exercise time were predictive of DO2 response (Table 4).

We found a well correlation between DO2 and blood creatinine in patients with blood creatinine below 120 μmol/L ($r = 0.58$, $p = 0.0002$), without any correlation between blood creatinine and BMI.

4. Discussion

To our knowledge, this study is the first to analyze the responses to training in HFrEF patients according to differentiated determinants of oxygen transport. We have highlighted 3 groups of responder profiles of roughly equivalent prevalence: both QO_{2peak}-DO_2 responders, QO_{2peak}-only responders and DO_2 -only responders. Among the VO_{2peak} non-responders, only a minority did not respond in either QO_{2peak} or DO_2.

Potential factors which might explain training response variability are training modalities (type, intensity, duration, frequency), cardiac function, autonomic or vascular function, non-cardiac factors, drugs and heritability (genetic and epigenetic background) [15].

Previous studies have highlighted the importance of central or peripheral determinants in the response to exercise training. Wilson et al. in 1996 measured Q_{peak} using invasive method and showed that patients with severe hemodynamic dysfunction during exercise usually do not improve with training, which suggests that these patients are primarily limited by circulatory factors [6]. Other authors emphasized the role of a severe muscular deconditioning as a main limiting factor, especially in severe HF [5]. Schmidt et al. identified chronotropic incompetence as a predictive factor of nonresponse [7], a result that was not found in our study.

Even if we could not find predictive factors for VO_{2peak} response, perhaps due to the low number of patients in our study, we evidenced predictive factors for response in each determinant of VO_{2peak}: low SV_{peak} and the ICM etiology appeared to be associated with QO_{2peak} response and high creatinine levels and prolonged training predicted DO_2 response.

4.1. Oxygen convection

Sixty two percent of our patients increased oxygen delivery due to an increase in cardiac output that was not due to raised HR but to gain in stroke volume. The observations of the meta-analysis by van Tol et al. [16], showing a 20% increase in cardiac output and only a 4 beats/min increase in maximal HR after aerobic training, are consistent with our observations.

However, a causal link with a positive effect of training on intrinsic myocardial function remains difficult to establish.

Several studies have shown that exercise training induced a decrease in total peripheral vascular resistance improving SV and cardiac output during exercise [17,18], notably by improving endothelium-dependent vasodilatation [19] and by increasing vagal tone [20]. Our results argue for the important role played by the significant decrease in overload in improving post-training SV_{peak}. In the Erbs et al. study [18], the greatest improvement in SV_{peak} was observed in the

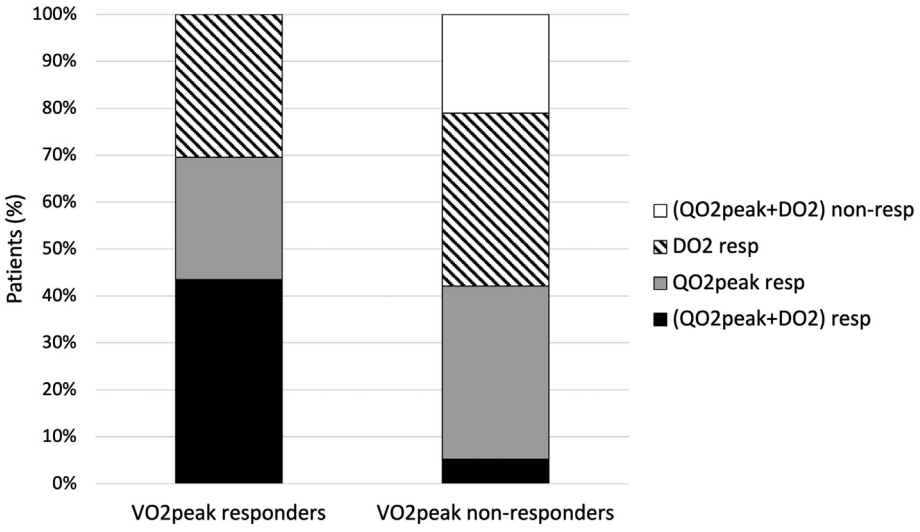

Fig. 2. Profiles of VO2peak responders according to QO2peak and DO2 response (see details in text); resp.: responders. DO2: peripheral oxygen diffusion, $QO2_{peak}$: oxygen delivery at peak effort, $VO2_{peak}$: oxygen uptake at peak effort.

most symptomatic patients and, as in our series, with the lowest baseline SV_{peak}.

Furthermore, we showed in this study that patients with ICM better improved SV_{peak} after training than those with DCM. One of the few studies that compared the response to training according to the etiology of heart disease found a better VO_{2peak} in patients with DCM than in those with ICM [21]. But numerous studies have shown a benefit of training in terms of cardiac output at exercise in patients with ICM [16,22]. Moreover, Belardinelli et al. showed that the presence of hibernating myocardium in case of ICM predicted the improvement of cardiac reserve after training due to the improvement of the endothelial and vasculogenesis [23]. The improvement of LVEF at peak exercise of patients with ICM, without an increase in tele-diastolic volume or a decrease in arterial pressure, argued for an improvement in myocardial contractility after training [22]. Conversely, the increase in post-training SV_{peak} was not linked to an increase in myocardial energy metabolism in patients with DCM, suggesting a training effect primarily on total peripheral vascular resistances [19,24]. So, the existence of hibernating myocardium in ICM would favor an intrinsic contractile response in addition to the decrease in afterload. The significantly better increase in cardiac power in our patients with ICM than those with DCM reinforces this hypothesis.

Finally, like in other studies, the gain in LVEF at rest did not appear to be related to the gain in oxygen delivery in our patients [25].

4.2. Oxygen diffusion

The diffusion of oxygen from the peripheral muscle microcirculation to the mitochondria was improved after training in more than half of our patients. Like the QO_{2peak} response, a DO_2 response alone is not always sufficient to significantly increase VO_{2peak}. In a previous invasive study [26], in which some patients increased their VO_{2peak} by 40% after training, the increasing muscle diffusion and increasing oxygen supply to the muscle related to a better redistribution of cardiac output toward the exercising muscles. A concomitant increase in fiber cross-sectional area, capillary-to-fiber ratio, and mitochondrial volume density was observed in these patients. We showed that total training duration positively impacted the DO_2 response. Consistently, analysis of biopsies collected during a 12-week resistance training program in young men showed significant muscle hypertrophy and angiogenesis by the second week that continued to develop until the 12th week [27].

We found that a lower blood creatinine was associated with a poorer diffusion response. Blood creatinine is a very approximate marker of

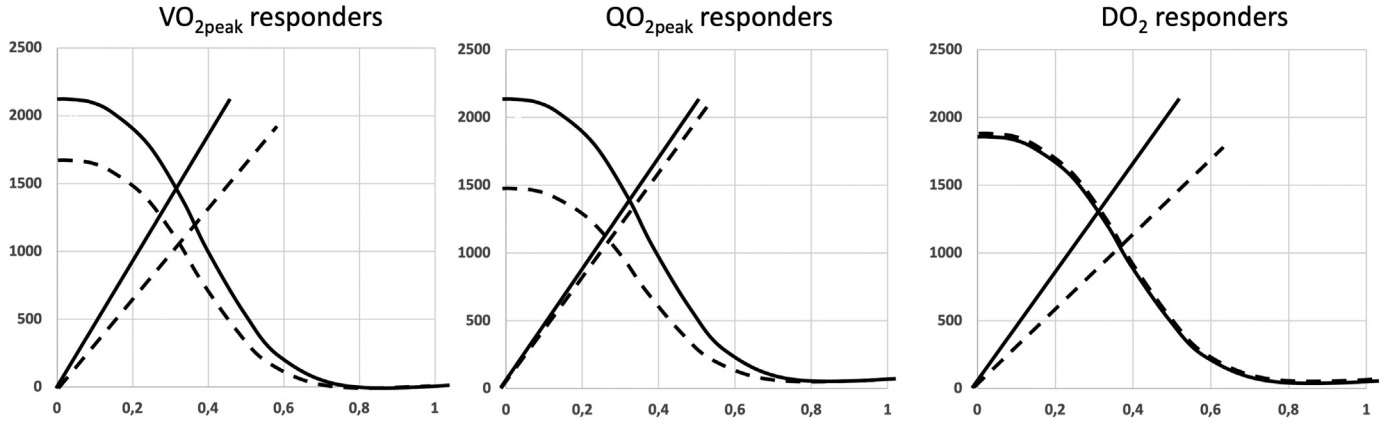

Fig. 3. Graphical representation of interactions of central and peripheral oxygen transports that determine VO2peak in responders in VO2peak, QO2peak, DO2. Dotted lines: mean values of the population before training, solid lines: mean values of the population after training. DO2: peripheral oxygen diffusion, $QO2_{peak}$: oxygen delivery at peak effort, $VO2_{peak}$: oxygen uptake at peak effort.

kidney function as it could be influenced, among others, by muscle mass. Numerous studies have shown in healthy subjects or subjects with chronic disease an inverse correlation between creatinine level and functional limitation [28]. In patients with CHF, there is good evidence of muscle atrophy promoted by tissue and systemic inflammation [29]. Anker et al. showed that in cachectic heart failure patients VO_{2peak} depend on the oxygen supply to the muscle in contrast to non-cachectic patients [30]. In our study we found a correlation of DO_2 gain with blood creatinine level. We therefore postulate that a low blood creatinine level in our patients reflects at least partly a low muscle mass which limits the adaptation of muscle diffusion to training.

4.3. Limitations

One of the limits of this study is that the cardiac output was measured by thoracic bioelectrical impedancemetry, a non-invasive method. This method is well correlated with the Fick method in most cardiac diseases and its reliability has already been evaluated in normal adult and pediatric populations at maximal effort [31,32,12]. Interestingly, compared to 2 other noninvasive methods, Physiofow® device appeared to provide the lowest number of impossible or implausible values (i.e. values of cardiac output that induce a calculated CvO2 < 0 mL/L, or < 20 mL/L observed in elite endurance athletes

Table 3
comparison between responders and non-responders in VO_{2peak}, QO_{2peak}, DO_2.

	VO_{2peak}			QO_{2peak}			DO_2		
	Non-resp 45%	Resp 55%	p	Non-resp 37.7%	Resp 62.3%	p	Non-resp 42.8%	Resp 57.2%	p
Anthropomorphic									
Sex ratio F/M (n)	3/21	5/24	–	4/16	4/29	–	5/13	2/22	–
Age (y)	59 ± 11	53 ± 14	0.14	59 ± 13	54 ± 13	0.72	58 ± 16	57 ± 11	0.87
BMI (Kg/m^2)	25 ± 6	27 ± 12	0.50	26 ± 7	26 ± 12	0.89	24 ± 4	25 ± 7	0.62
Baseline CPET									
rest									
HR (b/mn)	79 ± 15	80 ± 16	0.84	77 ± 13	82 ± 16	0.24	79 ± 16	78 ± 15	0.94
SBP (mmHg)	93 ± 11	106 ± 21	**0.008**	105 ± 22	97 ± 15	0.14	98 ± 15	100 ± 13	0.94
MBP (mmHg)	73 ± 9	75 ± 18	0.06	78 ± 10	74 ± 10	0.11	73 ± 8	76 ± 9	0.21
CI (L/mn/m^2)	2.6 ± 0.9	2.5 ± 0.8	0.25	2.8 ± 0.9	2.4 ± 0.7	0.25	2.9 ± 0.8	2.6 ± 0.8	0.13
SV (mL/m^2)	33.3 ± 14.0	32.2 ± 18.0	0.34	37 ± 14	30 ± 8	0.4	36.8 ± 11.6	34.3 ± 9.8	0.49
SVR (dynes.m.s-5)	12.7 ± 3.2	13.0 ± 2.6	0.72	12.5 ± 2.8	13.1 ± 2.9	0.71	11.5 ± 2.4	13.2 ± 2.9	**0.047**
peak									
VO_2 (mL/Kg/mn)	15.4 ± 4.6	14.3 ± 4.8	0.4	14.8 ± 3.9	14.8 ± 5.1	0.97	16.1 ± 5.0	13.5 ± 4.0	0.09
HR (b/mn)	115 ± 22	108 ± 23	0.3	110 ± 21	112 ± 24	0.79	111 ± 24	109 ± 23	0.71
SaO_2 (%)	97 ± 5	96 ± 5	0.97	98 ± 3	95 ± 6	0.13	96 ± 5	97 ± 5	0.45
SBP (mmHg)	132 ± 38	136 ± 42	0.45	142 ± 46	130 ± 35	0.11	128 ± 31	141 ± 46	0.57
MBP (mmHg)	94 ± 24	95 ± 23	0.92	99 ± 27	92 ± 21	0.32	91 ± 21	97 ± 5	0.30
CI (L/mn/m^2)	5.2 ± 2.1	5.0 ± 1.9	0.58	6.8 ± 1.8	4.5 ± 1.6	**0.012**	5.3 ± 1.8	5.4 ± 1.7	0.68
SV (mL/m^2)	46.7 ± 16.8	45.5 ± 14.0	0.8	52.7 ± 13.8	40.7 ± 13.1	**<0.003**	48.7 ± 14.6	50.3 ± 12.7	0.71
QO_{2peak} (L/mn)	1.8 ± 0.9	1.7 ± 0.8	0.67	2.1 ± 1.0	1.4 ± 0.6	**0.007**	1.8 ± 0.8	1.9 ± 0.8	0.70
DO_2 (mL/mn/mmHg)	19.4 ± 14.2	26.2 ± 23.9	0.46	19.3 ± 15.1	26.22 ± 23.4	0.68	27.6 ± 26	16.9 ± 9	0.36
SVR (dynes.m.s^{-5})	8.7 ± 4.5	7.7 ± 2.8	0.36	7.5 ± 3.8	8.5 ± 3.5	0.36	6.9 ± 2.2	8.1 ± 4.0	0.23
VE (L/mn)	54 ± 21	52.6 ± 14	0.86	53 ± 17	53 ± 18	0.86	53 ± 19	50 ± 13	0.98
CP (L/min/m^2.mmHg)	2.1 ± 1.2	2.1 ± 1.1	0.98	2.6 ± 1.3	1.8 ± 0.9	**0.013**	2.1 ± 1.2	2.3 ± 1.1	0.42
VE/VCO2 slope	40 ± 11	39.2 ± 10	0.66	40 ± 11	40 ± 10	0.99	38 ± 8	40 ± 11	0.52
Cardiac disease									
DCM (%)	63	49	0.3	70	45	0.08	39	62	0.34
ICM (%)	37	51	0.3	30	55	0.08	61	38	0.34
Comorbidities									
Hypertension (%)	33	34	0.94	35	33	0.90	22%	46%	0.11
DM (%)	12	17	0.64	15	15	0.98	17%	21%	0.73
Echocardiography									
LVEF (%)	28 ± 7	28 ± 9	0.97	29 ± 7	27 ± 9	0.35	27 ± 8	29 ± 9	0.87
LV EDD (mm)	65 ± 10	62 ± 8	0.25	63 ± 6	63 ± 10	0.67	62 ± 8	61 ± 7	0.87
Mitral E/e'	11 ± 6	11 ± 4	0.95	11 ± 5	11 ± 5	0.79	12 ± 6	11 ± 5	0.62
sPAP (mmHg)	41 ± 13	35 ± 10	0.18	41 ± 12	36 ± 12	0.19	33 ± 8	39 ± 12	0.11
MI (grade)	1.0 ± 1.1	1.1 ± 0.9	0.66	1.0 ± 1.1	0.9 ± 1.0	0.94	1.0 ± 1.0	1.1 ± 0.8	0.86
Medication									
Bisoprolol (%)	71	86	0.18	85	75	0.41	77	83	0.66
Spironolactone (%)	75	66	0.46	75	66	0.52	55	71	0.32
Furosemide (%)	79	66	0.27	75	70	0.68	66	75	0.57
ACE (%)	71	72	0.90	80	67	0.28	73	75	0.84
Sacubitril/valsartan (%)	13	12	–	12	13	–	5	28	–
Lab test									
Hb (g/dL)	13.4 ± 2.1	12.9 ± 2.1	0.41	13.6 ± 2.4	12.9 ± 1.9	0.28	13.4 ± 2.2	12.9 ± 2.0	0.41
Creatinin (μmol/L)	94 ± 42	93 ± 27	0.89	105.5 ± 41	87 ± 28	0.11	79 ± 24	107 ± 41	**0.011**
BNP(pg/mL)	568 ± 760	526 ± 387	0.5	636 ± 817	482 ± 353	0.69	669 ± 886	464 ± 370	0.88
CRP (mg/L)	13 ± 16	35 ± 84	0.83	35.8 ± 97.5	18.1 ± 26.3	0.59	13.4 ± 15.5	17.5 ± 26.5	0.55
Cholest T (mmol/L)	4.3 ± 1.5	4.7 ± 1.3	0.41	4.7 ± 1.4	4.4 ± 1.4	0.50	4.5 ± 1.5	4.2 ± 1.5	0.55
Training									
Total time (h)	45 ± 16	49 ± 22	0.9	45 ± 14	48 ± 22	0.45	40 ± 15	54 ± 23	**0.026**

The *p* values in bold are significant (<0.05).
ACE, angiotensin-converting enzyme; BMI, body mass index, BNP, brain natriuretic peptide, CI, cardiac index; CP, cardiac power, DBP, diastolic blood pressure; DM, diabetes mellitus; DCM, dilated cardiomyopathy; DO_2, peripheric oxygen diffusion; h, hours; Hb, hemoglobin, HR, heart rate; ICM, ischemic cardiomyopathy; LV, left ventricular; MBP, mean blood pressure; MI, mitral insufficiency; n, number of patients; non-resp, non-responders patients; O_2P, oxygen pulse; PvO_2, partial venous oxygen pressure; QO_{2peak}, oxygen delivery at peak; resp., responders patients; SBP, systolic blood pressure; SaO_2, peripheric oxygen saturation; sPAP, systolic pulmonary artery pressure; SV, stroke volume; SVR, systemic vascular resistance; VE, minute ventilation; VO_{2peak}, oxygen consumption at peak.

Table 4
Pre-training predictors of response in VO_{2peak}, QO_{2peak} and DO_2 (multivariate analysis).

	OR	CI (95%)	Pr > Khi2
VO_{2peak} responders			
None			
QO_{2peak} responders			
SV_{peak}	0.89	0.83–0.97	0.009
DCM	0.10	0.1–0.69	0.02
DO_2 responders			
Total training time	1,1	1.005–1.22	0.04
Creatinin	1.07	1.001–1.15	0.04

CI, confidence interval; DCM, dilated cardiomyopathy; DO_2, peripheric oxygen diffusion; OR, odds, QO_{2peak}, oxygen delivery at peak; SV, stroke volume; VO_{2peak}, oxygen consumption at peak.

during maximal exercise) [33].Nevertheless, an overestimation of stroke volume has been observed in patients with hyperiflation [34] and also in heart failure [35] but with an earlier version of the calibration system and was not found in a recent study [36].

In our study muscle diffusion is estimated not on hemodynamic parameters of the exercising muscles but on the whole-body oxygen consumption and total cardiac output. Thus, the inferred DO_2 will also depend on the amount of cardiac output redistributed to the exercising muscles. This approximation has already been made in previous works [13,14]. The PvO_2 thus calculated is probably slightly different from that of the blood issued from the exercising muscles. Indeed, the arteriovenous difference would tend to be greater in the exercising muscle and therefore the exercising muscle PvO_2 would tend to be lower. At the opposite, the increase in oxygen supply by preferential redistribution of cardiac output to the exercising muscle tends to increase the muscular PvO_2. At constant PvO_2, muscular DO_2 is estimated in our study by simplified Fick's law using the VO_{2peak} of the whole body but not the VO_{2peak} of the exercising muscles. This might therefore lead to a modest overestimation of the actual muscle diffusion. We verified this hypothesis by simulating "whole body" diffusion calculations (with different muscle cardiac output and muscle diffusions) from a model using experimental observations of total and local VO_2 measurement and cardiac output redistribution [37] (data not shown): we found that an increase in blood flow toward the muscles (at constant cardiac output) that was shown to be associated with DO_2 improvement after training in these patients [26], limits the difference between muscle DO_2 and "whole body" DO_2.

The number of hours of training performed was considered sufficient to expect a response to training in all patients. However, the combination of the training exercises proposed in our study and the small size of the overall population did not allow us to distinguish the effects of the different modalities of training. Finally, we have not yet carried out any long-term follow-up to know whether QO_2 or DO_2 gains are predictive factors of clinical prognosis. Finally, we were not able to highlight the probable effects of heart failure treatments on the different types of response to training, which may have interfered with our results.

5. Conclusion

The analysis of the response to training in patients with HFrEF according to the different steps of oxygen transport revealed different phenotypes on VO_{2peak} responses, namely responses in either convection and/or diffusion. This study emphasizes the usefulness of routine noninvasive cardiac output measurement during CPET in refining the phenotypes of ET responses according to oxygen transport steps.

Further studies including more patients could refine the predictive factors of these different responses to different training modalities. It might be hypothesized that the number of exercise training responders could be increased by adapting training programs according to these predictive baseline characteristics. Lastly, the prognostic value of different responses to exercise training deserves further large studies.

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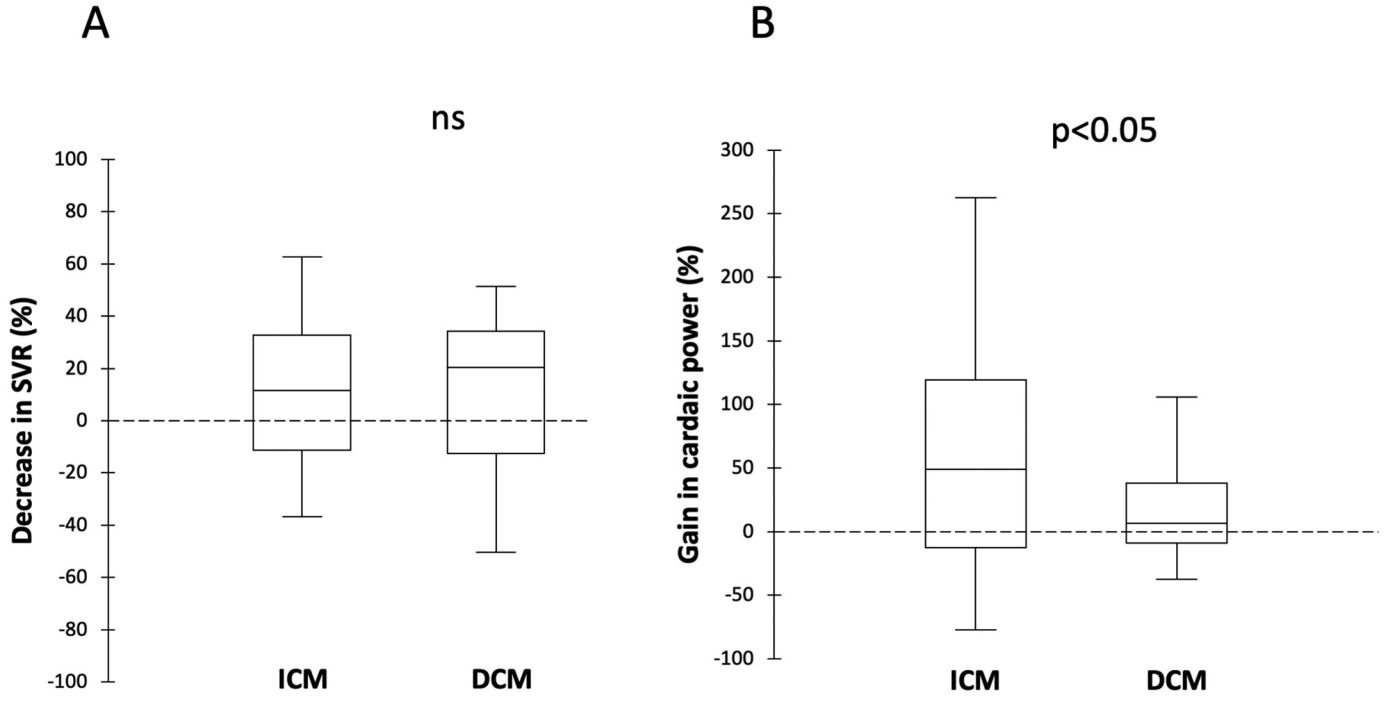

Fig. 4. Comparison of impact of training on SVR (A) and on cardiac power (B) at peak between patients with ICM and those with DCM. The training lowered the SVR without significant differences between the two populations. Training further increased cardiac power in ICM patients. DCM: dilated cardiomyopathy, ICM: ischemic cardiomyopathy, SVR: systemic vascular resistance.

Declaration of Competing Interest

None

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None

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2021.02.004.

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