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Evaluation of exercise capacity by means of cardiopulmonary exercise testing (CPET) in older adult cancer patients undergoing antineoplastic treatments

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Background and aims. Functional capacity measured with cardiopulmonary exercise testing (CPET) is extensively studied in patients with cardiovascular diseases. In the current prospective study, we aim at exploring the role of CPET in oncologic patients and at evaluating exercise capacity and its variation with the administration of oncologic treatments.
Material and methods. We analyzed 77 maximal CPETs from older adult cancer patients and assessed exercise capacity. CPETs were performed before starting (t0), during (t1) and at the end of (t2) oncologic treatments. The main outcome was death for all causes.
Results. CPETs performed at t0 and t1 showed a reduced percent predicted peak V_{O2}, compared to CPETs performed at t2. In addition, at t2 we observed higher peak achieved workload and longer exercise time compared to t0 and t1. Intriguingly, achieved workload and oxygen uptake at Anaerobic Threshold were lowest in CPETs performed at t1, while Respiratory Exchange Ratio (RER) was higher in t1. Predicted V_{o2}/HR and oxygen pulse (V_{o2}/HR), were higher after therapy and lower during oncologic treatments. These abnormalities were even more evident in CPETs of patients who underwent anthracyclines-based treatments, and when comparing patients who then died later during follow-up (G1) *vs* patients who survived (G2).
Conclusions. CPET can be useful to evaluate exercise capacity and muscular metabolic alterations in older adult cancer patients. The effectiveness of this technology in predicting survival or the increased incidence of cardiovascular events in cancer patients is not fully understood; further studies are needed to define the role of CPET in assessing the benefits of aerobic exercise and its potential "therapeutic" prescription in cancer patients.

Key words: cardio-oncology, exercise, cardiotoxicity, cardiopulmonary, cancer

INTRODUCTION

Antineoplastic therapies have significantly increased overall and progression-free survival of oncologic patients thanks to the latest advances in therapeutic protocols. Along with these innovations, research has been focusing into better recognition of cancer drugs side-effects, including cardiovascular events (CVEs) associated to antineoplastic treatments [1]. Clinical manifestations of CVEs include thromboembolic and vasospastic ischemia, arrhythmias, hypertension, left ventricular (LV) dysfunction, and even heart failure (HF) [2-5]. Currently, echocardiographic measurements of LV ejection fraction (LVEF) and serum biomarkers are the most used parameters for the evaluation of cardiac function in oncologic patients [6,7]. This is particularly relevant in older adult patients, who have more "opportunity" to develop cancer and cardiovascular diseases, often in association [8-12].

Functional capacity measured using cardiopulmonary exercise testing (CPET) has been extensively studied in patients with cardiovascular diseases. Functional capacity is intended as the integrated efforts of skeletal-muscular, pulmonary and cardiovascular systems in performing daily living activities that require sustained aerobic metabolism and is already known to provide important prognostic information in a wide number of medical settings [13], such as patients with HF [14-20], pulmonary hypertension [21-24], or with cardiac amyloidosis [25]. Functional capacity is also useful to determine right-to-left exercise induced shunting [26], or to evaluate pre-operability in lung reductive surgery [27] and response to treatment in subjects with chronic obstructive pulmonary disease (COPD), pulmonary hypertension, pulmonary vascular disease, interstitial lung disease or cystic fibrosis [28-31]. Thus, as functional capacity is the ability of an individual to perform aerobic work, oxygen consumption (VO_2) is the most accurate and standardized parameter used for its measurement. CPET offers the most integrated evaluation of muscular, pulmonary and cardiovascular systems during a maximal effort exercise [32]. Moreover, maximal oxygen consumption (VO_{2peak}) measured throughout maximal effort can strongly relate with incident HF and all-cause mortality, being a good candidate in the early identification of CVEs [33,34]. Furthermore, beside VO_{2peak}, CPET is able to provide a wide range of integrated parameters that can be useful to identify other conditions such as ventilatory inefficiency and physical deconditioning [27,32]. Currently, a number of studies are investigating the importance of the assessment of VO_{2peak} and/or other parameters of functional capacity in the oncologic and cardiotoxicity setting [35,36].

In the current prospective study, we aim at exploring the role of CPET in oncologic patients and at evaluating exercise capacity and its variation with the administration of oncologic treatments.

MATERIALS AND METHODS

Study design and population

This is a single center prospective study based in our Internal Medicine Unit for Oncologic Patients in the Department of Translational Medical Sciences, "Federico II" University, Naples, Italy. The protocol was approved by the local ethic committee, the study was conducted following the Helsinki Declaration principles and all patients signed a written informed consent to participate to the study. The vast majority of patients included in our study were consecutive subjects who were referred to our Unit from major Oncology University Clinics such as the Hematology and the Oncology Divisions of the Department of Clinical Medicine and Surgery at "Federico II" University of Naples, and the Division of Onco-Hematology, Department of Precision Medicine, "Luigi Vanvitelli" University of Campania, Naples, Italy. A few patients were referred from smaller Oncology Units in the Naples area.

We evaluated exercise performance before, during and after administration of oncologic drugs and/or radiotherapy. Inclusion criteria were: age > 65 years; patients newly diagnosed with cancer with indication to oncologic treatments, or patients already on anticancer treatment, or patients who had been previously administered with anticancer treatments.

Exclusion criteria were: severe COPD and/or HF at first

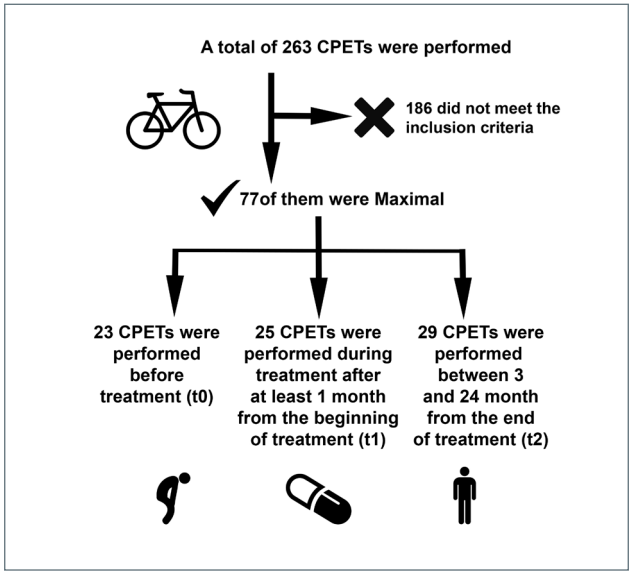

Figure 1. Study design.

clinical evaluation; age < 65 y.o., inability to perform the CPET, Respiratory Exchange Ratio (RER) < 1.05. CPETs were performed before starting (t0), during (t1) and at the end of (t2) oncological treatments, within 24 months after the end of the therapies (Fig. 1). Cut-offs were chosen according to literature [27,37].

Cardiopulmonary exercise test

CPET was performed on electromagnetically braked cycle ergometer using a the Wasserman formula for ramp quantification (VO2unloaded (mL/min) = 150 + (6× weight, kg) | V˙O2peak (mL/min) = (height: cm, age: years)×20 | Ramp (w/min) = V˙O2peak – V˙O2unloaded/100) [32] with metabolic chart of breath-by-breath respiratory gas exchange, 12-lead electrocardiogram, blood pressure cuff, and pulse oximetry (SpO2). All tests were conducted according to AHA and ERS guidelines [28,37]. CPET parameters were compared with normal values proposed by Wasserman, also expressed as percentage predicted [3].
The following parameters were chosen to assess exercise capacity: maximal oxygen uptake (peak V_{O2}), V_E/V_{CO2}slope, $\Delta V_{O2}/\Delta W$ slope, peak Heart Rate (HR), achieved Workload (WL), SBP, DBP, percent predicted peak V_{O2}, oxygen uptake at Anaerobic Threshold (V_{O2}AT), percent predicted V_{O2} at AT, Oxygen pulse (V_{O2}/HR), predicted V_{O2}/HR, exercise time.

Outcomes

The main outcome was death for all causes.

Statistical analysis

We performed Shapiro-Wilk test to verify the normal distribution of our data and a Levene's test to verify heteroskedasticity. Discrete variables are expressed as absolute number and percentage; continuous variables are expressed as mean and standard deviation when normally distributed and as median (25^{th}-75^{th} interquartile range) when not normally distributed. Chi-square test was used to compare discrete variables among time points. One way analysis of variances (ANOVA), with post-hoc pairwise comparisons with Bonferroni adjustment, and Kruskal-Wallis rank test (K-W rank test), with Dunn's test with Bonferroni correction for post hoc pairwise comparisons were used to examine differences in CPET parameters between t0, t1 and t2, for normally and not normally distributed variables, respectively. We performed repeated measures ANOVA for paired analysis. Two-way ANOVA was performed to evaluate the effects of outcome and t0-t1-t2 interaction on exercise capacity, then we divided CPETs by outcome and by timing (t0, t1, t2) in a two-way ANOVA for normal distributed data and a K-W test for non-normal distributed data, focusing our attention on pairwise comparison death vs no-death at t0, t1 and t2. A p-value ≤ 0.05 was considered statistically significant. Statistical analysis was performed using STATA 15.1 (Stata Corporation, College Station, Texas).

RESULTS

From January 2015 to February 2020, a total of 263 subjects were referred to our Unit and performed CPETs, with a median follow-up time of 15 [5; 22] months. We analyzed 77 CPETs, maximal for Anaerobic Threshold, with RER > 1.05, that met the inclusion criteria. 23 CPETs were performed by 23 patients before starting oncologic treatments (t0), 25 CPETs were performed by 25 patients during oncologic treatments, at least after 1 month from initiation of oncologic treatments (t1). Then, at t2, we included 29 CPETs performed by 29 patients at least 3 months after and within 24 months after termination of oncologic treatments (Fig. 1). Nine patients performed CPETs at all time points t0, t1 and t2, 10 patients performed CPETs only at t1 and t2, 1 patient performed CPET only at t0 and t1, 4 patients performed CPETs only at t0 and t2.

Clinical characteristics of the study sample

Data on cardiovascular and cancer characteristics, including cancer stage and antineoplastic protocols are presented in Table I.

CPET and cardiovascular follow-up of oncologic patients

Peak V_{O2} and percent predicted peak V_{O2} were higher in CPETs performed at t2 compared to t0 and t1. Peak of achieved workload and oxygen uptake at Anaerobic Threshold were lower and RER was higher during therapy (t1), while maximal exercise time was higher after therapy (t2), suggesting higher fatiguability at t1, with a recovery at t2. Predicted V_{o2}/HR and oxygen pulse (V_{o2}/HR) were higher after therapy and lower during oncologic treatments. Results are shown in Table II.
Nine patients performed CPETs at all time points (t0, t1 and t2). Eight patients were affected by hematologic cancer; 7 were treated with anthracyclines-based therapies and 1 with target therapies. One patient was affected by gastrointestinal cancer and treated with antimetabolites. In this group, after termination of oncologic treatments (t2) we observed significantly higher predicted peak V_{O2} exercise time, Oxygen pulse V_{O2}/HR and predicted V_{O2}/HR compared to t0 and t1 (Tab. III).

CPET and outcome of oncologic patients

We then compared CPET data according to patients' survival: group 1 (G1, dead during follow-up) and group

Table I. Clinical characteristics of the study sample.

	T0 (n = 23)	T1 (n = 25)	T2 (n = 29)	P-value
Age, years	69.3-3.97	69.76-3.86	70.45-3.99	0.57
Female, n (%)	10 (43%)	15 (60%)	13 (45%)	0.43
Cancer site, n (%)				
Gastrointestinal	6 (26%)	11 (44%)	11 (38%)	0.31
Breast	2 (8%)	2 (8%)	5 (17%)	0.49
Hematological	9 (40%)	7 (28%)	11 (38%)	0.66
Melanoma	6 (26%)	5 (20%)	2 (7%)	0.16
Cancer stage, n (%)				
I-II	5 (22%)	12 (48%)	12 (41%)	0.15
III	12 (52%)	4 (16%)	11 (38%)	0.02
IV	6 (26%)	9 (36%)	6 (21%)	0.42
Antineoplastic protocol, n (%)				
Anthracyclines	7 (30%)	8 (32%)	13 (45%)	0.48
Antimetabolites	5 (22%)	5 (20%)	8 (28%)	0.78
Pyrimidine analogues + bevacizumab	0 (0%)	7 (28%)	2 (7%)	0.03
Target therapy	5 (22%)	5 (20%)	6 (20%)	0.98
Immunotherapy	6 (26%)	0 (0%)	0 (0%)	0.01
Comorbidities, n (%)				
Diabetes	5 (21.7%)	1 (4%)	3 (10.3%)	0.16
Hypertension	10 (43.4%)	13 (52%)	9 (31%)	0.39
Dyslipidemia	8 (34.8%)	8 (32%)	6 (20.6%)	0.58
Smoking habit	9 (39%)	6 (24%)	3 (10.3%)	0.07
COPD	3 (13%)	1 (4%)	1 (3.44%)	0.34
Cardiovascular therapy, n%				
Beta-blockers	9 (39%)	10 (40%)	13 (44.8%)	0.81
Diuretics	2 (8.7 %)	0 (0%)	4 (13.8%)	0.14
CCBs	3 (13 %)	4 (16%)	0 (0%)	0.10
ARBs or ACE-Is	8 (34.8%)	11 (44%)	18 (62%)	0.13
No cardiologic therapy	8 (34.8%)	9 (36%)	4 (13.8%)	0.16
Patients who showed CVEs during follow-up	0 (0%)	7 (28%)	0 (0%)	0.01
Patients dead for all causes during follow-up	9 (39%)	11 (44%)	4 (13.8%)	0.06

Abbreviations: COPD: chronic obstructive pulmonary disease; CCBs: Calcium-channel blockers; ARBs: Angiotensin II Receptor Blockers; ACE-Is: Angiotensin Converting Enzyme-inhibitors; CVEs: cardiovascular events.

2 (G2, still alive at the end of the study), and performed a two-way ANOVA for normal distributed data and a K-W test for non-normal distributed data, focusing our attention on pairwise comparison G1 *vs* G2 at t0, t1 and t2 (Tab. IV).

In all patients, there was an increase in exercise time from t0 to t2. Interestingly, G2 patients showed a longer exercise time compared to G1 at t0. Achieved workload was generally higher in G2 patients, with an initial decrease from t0 to t1, and a subsequent increase from t1 to t2. RER was higher in G1 patients, at each time point. Heart rate was higher in G2 patients at each time point.

Finally, percent predict V_{O2}peak and oxygen uptake at AT was lower in G1 patients, especially at t0.

DISCUSSION

In our study, CPETs performed before starting (t0) and during (t1) oncologic therapies showed a reduced percent predicted peak V_{O2}, compared to CPETs performed after completing oncologic treatments (t2). In addition, at t2 we observed higher peak achieved workload and longer exercise time compared to t0 and t1. At t2 Predicted V_{o2}/HR and oxygen pulse (V_{o2}/HR), ΔVO2/ΔW slope were higher. Intriguingly, achieved workload and peak V_{O2} at Anaerobic Threshold (AT) were lowest in CPETs performed at t1, while RER was higher in t1. These abnormalities were supported by paired data in patients who performed CPETs at all time points (t0, t1, t2, Tab. III), subgroup analysis by outcome analysis (Tab. IV).

Table II. Cardiopulmonary exercise testing variables according to the timing.

	T0 (23)	T1 (25)	T2 (29)	P-value
RER	1.16 [1.13-1.28]	1.19 [1.14-1.26]	1.12 [1.1-1.2]	**0.04**
peak VO2, ml/kg/min	18.2 [16.5-24.2]	18.1 [16-22.3]	20.1 [17.5-26.9]	**0.03**
%-predicted peak VO2, %	70.3 ± 20.4	70.8 ± 18.37	81.18 ± 16.72	0.06
VO2-AT, ml/kg/min	14.34 ± 4.94	13.1 ± 3.69	16.61 ± 4.39	**0.01**
%-predicted VO2-AT, %	51.78 ± 21	52 ± 15.46	58.55 ± 13.51	0.24
VE/VCO2 slope	28.44 ± 3.15	29.4 ± 5.11	28.36 ± 4.73	0.65
Ex time, min	8.22 ± 1.91	8.99 ± 1.74	9.87 ± 1.20	**< 0.01**
Workload, Watts	109 [73-119]	80 [73-108]	125 [95-145]	**< 0.01**
Maximal HR, bpm	126 ± 18.2	134 ± 16.6	138 ± 19.4	0.055
VO2/HR, ml/kg/min/bpm	11 [10-13]	9 [6-11]	12 [10-13]	**< 0.01**
%-pred VO2/HR, ml/kg/min/bpm	91.35 ± 20.65	86.32 ± 22.46	99.9 ± 18.68	0.06
ΔVO2/ΔW slope	8.5 [8-10.3]	8.2 [7.6-9.6]	9.3 [8.6-9.9]	0.16
fcmt	79 [72-85]	85 [80-92]	85 [81-88]	**0.04**
EF %	58.05 ± 3.22	57.34 ± 3.35	57.44 ± 4.05	0.78

Abbreviations: RER: Respiratory Exchange Ratio; V_{02}-AT: peak V_{02} at anaerobic threshold; HR: Heart rate.

Table III. Cardiopulmonary exercise testing variables according to the timing, paired-data analysis.

Variable	T0	T1	T2	P-value
RER	1.19 ± 0.11	1.22 ± 0.14	1.13 ± 0.07	0.12
peak VO2, ml/kg/min	21.65 ± 6.17	20.9 ± 2.39	24.6 ± 4.43	0.13
%-predicted peak VO2, %	71± 23	70 ± 13.9	83.33 ± 10.73	**0.046**
VO2-AT, ml/kg/min	16.7± 5.48	14 ± 3.99	17.22 ± 4.2	0.22
%-predicted VO2-AT, %	55.89 ±22.19	51.3 ± 20.7	58 ± 11.72	0.5
VE/VCO2 slope	26.8 ± 5.28	26.8 ± 4.81	27.05 ± 3.77	0.98
Ex time, min	8.4 ± 1.81	8.43 ± 2.14	10.22± 1.09	**0.01**
Work load, Watts	105.78 ± 18	107 ± 21	123.44 ± 32	0.17
Maximal HR, bpm	147 ± 23	145 ± 10	150 ± 14.89	0.78
VO2/HR, ml/kg/min/bpm	9.44 ± 1.81	9.88 ± 1.69	11.48 ± 2.7	**0.02**
%-pred VO2/HR, ml/kg/min/bpm	85 ± 20	86 ± 16.48	100 ± 12.6	**0.02**
ΔVO2/ΔW slope	9.28 ± 1.39	8.65 ± 1.42	9.7 ± 0.43	0.22
fcmt	81.55 ± 11.9	83 ± 7	81.8 ± 7.53	0.13
EF %	58.22 ± 3.8	56.7 ± 2.78	59.11 ± 4.25	0.28

Abbreviations: RER: Respiratory Exchange Ratio; V_{02}-AT: peak V_{02} at anaerobic threshold; HR: Heart rate.

These results suggest that during oncologic therapies (t1) exercise capacity is worse than before starting (t0) and after completing (t2) such therapies in the whole patients' populations. In particular, we show that t1 patients reach maximal RER earlier at lower exercise time, lower workload and lower oxygen uptake at AT. These differences are also present when comparing patients who died during follow-up (G1) vs patients who survived (G2), and seem to be related with patients' age, cancer site and cancer stage. We observed that smoking tended to be less common in T2 patients, but we did not find differences in VE/VCO2 slope, which suggest the presence of impaired ventilation [38]. Moreover, we excluded severe COPD patients to avoid bias. The above-mentioned alterations in CPETs parameters are usually associated with worse prognosis in HF [39]

Table IV. Cardiopulmonary exercise testing variables according to the outcome (death for all causes) and timing.

	T0		T1		T2		P-value
	G1 (9)	G2 (14)	G1 (11)	G2 (14)	G1 (4)	G2 (25)	
VO2-peak, ml/kg/min	18.2 [17.6-20.7]	20.4 [16.5-25.3]	15.7 [13.1-22.3]	18.1 [16.8-24]	19.3 [17.7-23.6]	20.3 [17.5-26.9]	0.25
VO2-peak % predicted, ml/kg/min	46 [46-53]	71 [63-88]	61 [55-75]	73 [58-93]	61.5 [54-77]	87 [69-92]	**< 0.01**
VO2-AT, ml/kg/min	11.5 [11.5-12.5]	15.4 [13.1-20.3]	11.7 [8.6-15.5]	13.45 [11.5-14.9]	13.7 [12.5-26.9]	17.1[13.3-19.6]	**< 0.01**
VO2-AT % pred, ml/kg/min	26 [26-43]	61 [57-80]	51 [37-56]	57 [44-70]	44 [39-54]	60 [50-70]	**< 0.01**
VE/VCO2 slope	29.2 [26-29.2]	27.8 [27.3-29]	32 [25.7-38.5]	28 [27 -30]	29.95 [29-35.7]	26.9 [24-31.6]	0.23
Ex time, min	6 [6-6.4]	9 [7.85-10.75]	8.25 [8-9.3]	9.45 [8-10.5]	10.4 [9.67-10.5]	10 [9.15-10.6]	**< 0.01**
Workload, Watts	73 [73-109]	113.5 [104-125]	77 [73-102]	104.5 [61-128]	117.5 [89-126]	125 [95-145]	**0.01**
RER	1.44 [1.28-1.46]	1.14 [1.12-1.15]	1.23 [1.18-1.27]	1.18 [1.13-1.25]	1.18 [1.18-1.19]	1.12 [1.09-1.21]	**< 0.01**
Maximal HR, bpm	134 [104-145]	121 [112-121]	139 [100-139]	139 [130-153]	116 [111-127]	142 [124-155]	**< 0.01**
VO2/HR, ml/kg/min/bpm	9 [8-11]	13 [10-13]	8 [6-10]	9.5 [7-12]	13.5 [10-15]	12 [10-13]	**< 0.01**
VO2/HR % predicted, ml/kg/min/bpm	58 [58-86]	100 [96-107]	79 [72-93]	80 [78-114]	83 [80-92.5]	104 [88-119]	**< 0.01**
ΔVO2/ΔW slope	8 [8-8.5]	10 [8.5-11]	8.2 [7-11]	8.6 [8-9.6]	9.3 [9.3-9.5]	9.3 [8.4-9.9]	**0.03**
Cancer site, n (%)							
Gastrointestinal	5 (55.6%)	1 (7.1%)	9 (81.8%)	2 (14.3%)	4 (100%)	7 (28%)	**0.01**
Breast	0 (0%)	2 (14.3%)	0 (0%)	2 (14.3%)	0 (0%)	5 (20%)	0.57
Hematological	2 (22.2%)	7 (50%)	0 (0%)	7 (50%)	0 (0%)	11 (44%)	**0.03**
Mela1noma	2 (22.2%)	4 (28.6%)	2 (18.2%)	3 (21.4%)	0 (0%)	2 (8%)	0.54
Cancer stage, n (%)							
I-II	0 (0%)	5 (35.7%)	2 (18.2%)	10 (71.5%)	0 (0%)	12 (48%)	**0.027**
III	5 (55.6%)	7 (50%)	1 (9.1%)	3 (21.4%)	3 (75%)	8 (32%)	**0.01**
IV	4 (44.4%)	2 (14.3%)	8 (72.7%)	1 (7.1%)	1 (25%)	5 (20%)	**0.01**
Antineoplastic protocol, n (%)							
Anthracyclines	2 (22.2%)	5 (35.7%)	0 (0%)	8 (57.2%)	0 (0%)	13 (52%)	**0.01**
Antimetabolites	5 (55.6%)	0 (0%)	4 (36.4%)	1 (7.1%)	3 (75%)	5 (20%)	**0.01**
pyrimidine analogues + bevacizumab	0 (0%)	0 (0%)	5 (45.4%)	2 (14.3%)	1 (25%)	1 (4%)	**0.01**
Target therapy	0 (0%)	5 (35.7%)	2 (18.2%)	3 (21.4%)	0 (0%)	6 (24%)	**0.04**
Immunotherapy	2 (22.2%)	4 (28.6%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	**0.01**
Age	66 [66-67]	69.5 [67-75]	72 [68-75]	68.5 [65-70]	72 [67.5-75]	70 [68-74]	0.18

Abbreviations: RER: Respiratory Exchange Ratio; V_{02}-AT: peak V_{02} at anaerobic threshold; HR: Heart rate.

and PH patients [40]. Higher fatiguability can be a signal of complex interactions between cancer and the cardiopulmonary system. First, we have to consider cardiovascular toxicity of cancer therapies, hence exercise capacity may be impaired, as we observed in t1 patients. Many anticancer agents cause endothelial dysfunction [41], that can alter vasodilation and oxygen delivery to the skeletal muscle [42,43]. Interestingly, impaired peak VO2 and precent predicted peak VO2 seem to be associated with trastuzumab cardiovascular toxicity in

breast cancer patients [44]. After anthracycline treatment skeletal muscle composition may be altered [45], with intramuscular fat accumulation, which may also explain reduced exercise tolerance [46,47].
Importantly, we observed percent predicted peak V_{O2} reduction not just in CPETs performed during oncologic therapies, but also already in CPETs performed by cancer patients before oncologic therapies (t0). Different reasons may underly this finding. Reduced hemoglobin concentration is frequently present in cancer patients [8] and can affect oxygen delivery [48]. Deconditioning due to reduced physical activity, especially after surgery, can be associated with lower oxygen uptake [49]. Also, inflammation [50,51] and muscle wasting [52] can lead to exercise impairment, and may be due to systemic effects of cancer. Anker and coworkers hypothesized that cancer wasting can also involve cardiac tissue, resulting into cardiac cachexia [53] that, together with other systemic alteration characterizing such patients [51,54], can be part of a real heart failure-like syndrome [55]. Moreover, the pro-inflammatory cytokines from cancer cells may lead to metabolic dysfunction [10,11,56], with increased cytosolic glycolysis and reduced oxidative phosphorylation [57], resulting in increased lactic acidosis [58] that can contribute to higher ventilatory demand [59], higher RER and muscle fatiguability observed in our study. All these alterations can cause higher metabolic demand and inadequate oxygen delivery, resulting in cancer related fatigue (CRF), whose etiology is yet to be fully clarified and is most likely multifactorial, and a specific diagnostic algorithm is yet to be defined [60,61]. Functional capacity measured with CPET seems to be a promising marker of cardiac, pulmonary and skeletal muscle dysfunction [17,62] and could be a useful diagnostic tool for CRF, too.

FUTURE PERSPECTIVES

Beside their role in the evaluation of exercise capacity in oncologic patients, parameters obtained from CPETs could also be studied for prevention and treatment of CVEs during antineoplastic protocols [36,63,64]. Preclinical studies have shown that exercise can reduce doxorubicin-induced mitochondrial damage [65-67], while there is clinical evidence that exercise prescription can improve peak V_{O2} [34,68-70], whose impairment is usually related to worse outcome in HF [39] and PH patients [40]. Cardio-Oncology rehabilitation is an emerging non-pharmacologic approach to prevent and even treat chemotherapy-induced cardiotoxicity or cardiovascular disease in cancer patients [71,72]. While CRF is associated with treatment-related toxicities and augmented risk of mortality in cancer patients, the efficacy of exercise to treat cardiotoxicity is still unclear [64,73,74]. Randomized controlled trials are evaluating whether an exercise-based cardiac rehabilitation can prevent chemotherapy induced cardiotoxicity in breast cancer patients [75,76]. The OptiTrain trial showed that high-intensity exercise during chemotherapy in breast cancer patients was associated with lower levels of NT-pro-BNP and that there was reduced peak V_{O2} in patients with higher levels of cTnT and NT-pro-BNP, even after 2-years follow-up [36].

LIMITATIONS AND CONCLUSIONS

The major limitation to our study is the rather small sample size. In addition, patients were treated with very heterogeneous therapies and different forms of cancer were included. In our study, cancer type distribution does not completely overlap cancer type distribution in Italy, being our population mostly composed of patients with hematologic and gastro-intestinal cancers. Moreover, patients included in the analysis are relatively young and that might not be fully representative of the geriatric population.
In addition, we only collected scattered data regarding the biochemical and bio-humoral characteristics of the patients at the start of the study, such as troponin levels or natriuretic peptides, hence we could not correlate them to the rest of our data. On the other hand, we focused on maximal CPETs to avoid the bias due to VO2 peak reduction in non-maximal exercise.
Despite these limitations, CPET can be useful to evaluate exercise capacity and muscular metabolic alterations in cancer patients, especially before and during chemotherapy. The effectiveness of this technology in predicting survival or the increased incidence of cardiovascular events in cancer patient is not fully understood. Further studies are needed to define the potential role of CPET in assessing the benefits of aerobic exercise and its potential “therapeutic” prescription in cancer patients.

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Conflict of interest statement
TT received funding from Amgen, MSD, Novartis, Sanofi, BMS. CGT has received funding from Amgen, MSD and personal fees from Vivalyfe, Solaris, Univers Formazione, Myocardial Solutions, Medtronic, Astra Zeneca, Summeet, outside of the submitted work, and is listed as an inventor on two heart failure patents. The other authors have nothing to disclose.

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Author contributions
AnC, UA, AlC: share first co-authorship, conceptualization, data curation, and writing – original draft and revised versions; AnC: statistical analysis; PP, GC, MI, FF, LC, ET, RP, LF, CC, MP, CdC, MF, EM, SN, TT: data collection, data curation; RB, GM, NC: methodology, supervision; VM, CGT: conceptualization, data curation, formal analysis, methodology, supervision, validation, visualization, writing – original draft, and writing – review & editing; PA: review & editing; VM, CGT: share senior authorship.

Ethical consideration
This study was approved by the Institutional Ethics Committee of Università degli Studi di Napoli "Federico II" (approval number: 215/21).
The research was conducted ethically, with all study procedures being performed in accordance with the requirements of the World Medical Association's Declaration of Helsinki.
Written informed consent was obtained from each participant/patient for study participation and data publication.

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