European Journal of Heart Failure (2018) **20**, 1115–1124
doi:10.1002/ejhf.1140

RESEARCH ARTICLE

A flattening oxygen consumption trajectory phenotypes disease severity and poor prognosis in patients with heart failure with reduced, mid-range, and preserved ejection fraction

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Received 17 August 2017; revised 12 December 2017; accepted 27 December 2017; online publish-ahead-of-print 6 February 2018

Background In heart failure (HF), a flattening oxygen consumption (VO_2) trajectory during cardiopulmonary exercise test (CPET) reflects an acutely compromised cardiac output. We hypothesized that a flattening VO_2 trajectory is helpful in phenotyping disease severity and prognosis in HF with either reduced (HFrEF), mid-range (HFmrEF), or preserved (HFpEF) ejection fraction.

Methods and results Overall, 319 HF patients (198 HFrEF, 80 HFmrEF, and 41 HFpEF) underwent CPET. A flattening VO_2 trajectory was tracked and defined as an inflection of VO_2 linearity as a function of work rate with a second slope downward inflection >35% extent of the first one. Peak VO_2, the minute ventilation/carbon dioxide production (VE/VCO_2) slope, and the presence of exercise oscillatory ventilation (EOV) were also determined. Pulmonary artery systolic pressure (PASP) and tricuspid annular plane systolic excursion (TAPSE) were measured by echocardiography. A flattening VO_2 occurred in 92 patients (28.8%). PASP and TAPSE at rest were significantly higher and lower ($P < 0.001$), respectively. The primary outcome was the combination of all-cause death, heart transplantation and left ventricular assist device implantation. The secondary outcome was the primary outcome plus hospitalization for cardiac reasons. In the multivariate model including peak VO_2, VE/VCO_2 slope, EOV and VO_2 trajectory, a flattening VO_2 trajectory and EOV were retained in the regression for primary ($X^2 = 35.78$, and 36.36, respectively; $P < 0.001$) and secondary ($X^2 = 12.45$ and 47.91, respectively; $P < 0.001$) outcomes.

Conclusions Results point to a flattening VO_2 trajectory as a likely new and strong predictor of events in HF with any ejection fraction. Given the relation of right-sided cardiac dysfunction to pulmonary hypertension, this oxygen pattern might suggest a real-time decrease in pulmonary blood flow to the left heart.

Keywords VO_2 flattening • Heart failure with reduced ejection fraction • Heart failure with mid-range ejection fraction • Heart failure with preserved ejection fraction

Introduction

There is an extensive body of literature supporting the link between a number of multi-organ pathophysiologic processes and abnormal responses during cardiopulmonary exercise testing (CPET).[1] Moreover, a series of these abnormal CPET responses have demonstrated robust prognostic value especially in heart failure (HF) with reduced ejection fraction (HFrEF).[2] Indeed, a low peak oxygen consumption (VO_2), an elevated minute ventilation/carbon dioxide production (VE/VCO_2) slope, and exercise

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oscillatory ventilation (EOV) are firmly established as reflecting HF-specific pathology[3] and indicating elevated risk for adverse events.[4] However, these CPET measures, which are frequently utilized to guide the clinical management of HF, may not reflect the dynamic nature of oxygen (O_2) kinetics. That is to say real-time changes during CPET are not considered for peak VO_2, VE/VCO_2 slope, or EOV.

There has been a growing interest in the VO_2 trajectory during CPET, particularly in patients with suspected ischaemic heart disease.[5,6] A normal VO_2 trajectory would be linear in nature during CPET with progressively increasing workload to maximal exertion reflecting a progressive increase in left-sided cardiac output that parallels increasing workload.[7]

Along with previous demonstrations that a flattening VO_2 trajectory is an abnormal phenotype that may be precipitated by myocardial ischaemia development,[8] there is overall evidence that it occurs, in general, when there is a significant and quite sudden decline in left-sided cardiac output during exercise.[9,10] Specifically, this may happen in various cardiac diseases irrespective of the aetiology but it is primarily observed in HF.[9,10]

Left-sided pulmonary hypertension (PH) is highly prevalent and an ominous consequence of HF.[8] Interestingly enough, previous research studies have shown that HF patients with a greater reduction in aerobic capacity and ventilatory inefficiency (i.e. an elevated VE/VCO_2 slope and EOV) often present with significantly higher pulmonary pressures and poorer right-sided cardiac function at rest.[8,11] Patients with HF and PH are more likely to reach a potential juncture during exercise, where blood transitioning from the pulmonary circulation to the left side of the heart is compromised, resulting in a real-time drop in cardiac output. As such, it is reasonable to hypothesize that a flattening VO_2 trajectory in this patient subset is associated with higher pulmonary pressures and worsening right-sided cardiac function, irrespective of left ventricular ejection fraction (LVEF) classification. Our primary hypothesis was that a VO_2 flattening pattern may provide a strong independent predictor of outcome.

In addition to these outcome endpoints, we reasoned that an abnormal VO_2 trajectory flattening might help to better phenotype the clinical syndrome of HF based on LVEF categorization. We aimed at testing these hypotheses.

Methods

Study cohort

From 2003 to 2017, 319 consecutive patients with known HF enrolled through the Cardiomyopathy Programme at the Cardiopulmonary Laboratory at San Paolo Hospital, University of Milan, Italy, were screened for study enrolment at the time of referral for clinically indicated haemodynamic and functional assessment. These subjects are part of a multi-site registry that prospectively recruits HF patients undergoing comprehensive CPET evaluation. Notably, the few patients enrolled in our previous study on VO_2 flattening pattern including a population of patients with various cardiac diseases besides HF are not included in this registry.[9]

Subjects underwent two-dimensional (2D) echocardiographic/Doppler evaluation and CPET. Inclusion criteria were: (i) signs and symptoms of HF, and (ii) adequate echocardiographic windows. The diagnosis of HF was based on the recommended criteria of the European Society of Cardiology.[12] When LVEF was ≥50%, along with the additional proposed criteria, patients were considered to have HF with preserved ejection fraction (HFpEF); when LVEF was 40–49% they were classified as having HF with mid-range ejection fraction (HFmrEF), and when LVEF was <40% they were considered to have HFrEF. Patients with normal LVEF and isolated tricuspid regurgitation due to primary tricuspid valvular lesion were not included in the present investigation.[13] In patients with HFpEF, care was taken to identify the proper aetiology of coexistent PH excluding idiopathic pulmonary arterial hypertension. Accordingly, we referred to 3-point prediction score proposed and validated by Opotowsky *et al.*,[14] based on the measurements of E/e', the antero-posterior diameter of the left atrium, and notching and/or shortened acceleration time of pulmonary flow.

Thus, recruited patients were monitored in this prospective observational study. The study was approved by the local Ethical Institutional Review Board and informed consent was obtained from all subjects prior to enrolment.

Endpoints and event tracking

All subjects were followed up for the primary outcome [all-cause death, heart transplantation, left ventricular assist device (LVAD) implantation] and the secondary outcome of composite cardiac events (cardiac death, heart transplantation, LVAD implantation, rehospitalization for cardiac reasons), via hospital and outpatient medical chart review for up to a maximum of 193 months. As cardiac death we considered the one due to pump failure or sudden death. Hospitalization for cardiac reasons was considered admission to the HF Unit. Subjects were followed by the HF programme providing a high likelihood that all events were captured.

Echocardiography

Echocardiographic imaging was performed using a Philips IE33 and a 5.2 MHz transducer (Philips Medical Systems, Andover, MA, USA). Two experienced cardiologists obtained right heart echocardiographic measures according to the current guidelines.[15] A 2D and Doppler examination was performed using a pre-specified echocardiographic protocol by views specifically designed to optimize right ventricular imaging. To obtain tricuspid annular plane systolic excursion (TAPSE), the apical four-chamber view was used and an M-mode cursor was placed through the lateral tricuspid annulus in real time. Off-line, the brightness was adjusted to maximize contrast between the M-mode signal arising from the tricuspid annulus and the background. TAPSE was measured as the total displacement of the tricuspid annulus (in mm) from end-diastole to end-systole, with values representing TAPSE being averaged over three to five beats. Pulmonary artery systolic pressure (PASP) was estimated by Doppler echocardiography from the systolic right ventricular to right atrial pressure gradient using the modified Bernoulli equation. Right atrial pressure (assessed jugular venous pressure) was added to the calculated gradient to yield PASP. Moreover, the TAPSE/PASP ratio, a measure of right ventricular–pulmonary vascular (RV-PV) coupling[16] was calculated. Previously identified prognostic threshold of the TAPSE/PASP ratio </≥0.36 mm/mmHg was used to assess survival in the study population.[16] No subjects had significant right ventricular outflow tract obstruction. Inter-observer variability, assessed in a sample size of 20% of the total population, was 3.5% and

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3.4% for M-mode and 2D echocardiography, respectively, and 4.7% and 4.3% for Doppler variables in the two centres, respectively.

Blood analysis

N-terminal pro brain natriuretic peptide (NT-proBNP) was measured in all samples by immunoassay sandwich technique (pro-BNP II, Cobas, Roche, Burgess Hill, UK, with a lower sensitivity limit of 5 pg/mL).

Cardiopulmonary exercise test procedures

In all subjects, symptom-limited CPET was performed on a bicycle ergometer according to established guidelines.[17] Pharmacologic therapy was maintained during CPET. Individualized ramp protocols were designed. Ventilatory expired gas analysis was performed using a Sensormedics metabolic cart (Vmax, Yorba Linda, CA, USA). Before each test, the equipment was calibrated according to the manufacturer's specifications using reference gases. Standard 12-lead electrocardiograms were obtained at rest, each minute during exercise, and for at least 5 min during the recovery phase; blood pressure was measured using a standard cuff sphygmomanometer. Heart rate was determined at rest, at peak exercise, and after 1 min of recovery. An active cool-down period of ≥1 min was employed for all tests. Minute ventilation [VE at body temperature, pressure and saturated with water vapour (BTPS)], oxygen uptake [VO_2 at standard temperature, pressure and dry (STPD)], and carbon dioxide output (VCO_2, STPD) were acquired breath-by-breath, averaged over 30 s, and printed using rolling averages every 10 s. A flattening VO_2 trajectory was defined when an inflection was evident in the VO_2 as a function of work rate (WR). The VO_2/WR slope was automatically calculated using the software programme, defining the start and the end of the linear relationship by the operator. According to what proposed by Belardinelli *et al.*,[5] an abnormal VO_2/WR slope was identified when an inflection was evident in the VO_2 linearity as a function of WR. A significant inflection leading to 'VO_2 flattening' was considered when the second slope was reduced by >35% extent compared with the first one (*Figure 1A*), with duration of >30 s, at a predicted VO_2 < 85%. As displayed in *Figure 1A*, the first slope was calculated as the slope a–a' from start to inflection point while slope 2 as the slope b–b' from inflection point to peak.

Peak VO_2 and peak respiratory exchange ratio were expressed as the highest 10 s averaged sample obtained during the last 20 s of testing. We used the formula for VO_2 predicted normal value proposed by the Wasserman's group.[18]

VE and VCO_2 values, acquired from the beginning of exercise to peak, were input into spreadsheet software (Microsoft Excel, Microsoft Corp., Bellevue, WA, USA) to calculate the VE/VCO_2 slope via least squares linear regression ($y = mx + b$, m = slope). EOV during CPET was defined as previously described in detail.[2] Briefly, criteria for EOV included the presence of ≥3 regular oscillatory fluctuations in VE with a minimal average amplitude of 5 L/min persisting for at least 60% of the entire exercise.[2] EOV was identified by a single expert operator.

Test termination criteria consisted of symptoms (i.e. dyspnoea and/or fatigue), ventricular tachycardia, horizontal or downsloping ST-segment depression of >2 mm, or a systolic blood pressure drop of >20 mmHg during progressive exercise. A qualified exercise physiologist with physician supervision conducted each exercise test. Exercise response was also evaluated by performing the 6-min walk test (6MWT).

Statistical analysis

Continuous data are expressed as mean and standard deviation while categorical data are expressed as percentages. The unpaired *t*-test was used to assess differences in key continuous variables between subjects who did and did not demonstrate a flattening VO_2 trajectory. The X^2 test assessed differences in categorical data between these subgroups. Univariate and multivariate Cox regression analysis was used to assess the prognostic value of key CPET variables. For multivariate regression, a forward conditional model was used with stepwise entry and removal criteria set at 0.05 and 0.10, respectively. Maximal iterations were set at 20. Kaplan–Meier analysis was further used to assess the prognostic value of a VO_2 flattening trajectory response. The SPSS 22.0 (IBM, Armonk, NY, USA) statistical software package was used for all analyses. All tests with a *P*-value of <0.05 were considered statistically significant.

Results

Mean age of the study population was 63.0 ± 9.9 years and 78% were males. Average LVEF was 36.0 ± 11.1% and 62% of HF patients had an ischaemic aetiology. There were no major cardiac events, deaths, or undue cardiac stress during testing. Among 319 subjects, 198 (62.0%) were diagnosed with HFrEF, 80 (25.1%) with HFmrEF, and 41 (12.9%) with HFpEF. Overall, 92 (28.8%) patients demonstrated a flattening VO_2 trajectory during CPET; among them, 62 (67.4%) patients presented with HFrEF, 21 (23.0%) with HFmrEF, and 9 (9.8%) with HFpEF.

Clinical and echocardiographic characteristics of patients with and without VO_2 trajectory flattening are reported in *Table 1*. Patients with VO_2 trajectory flattening were older, had lower LVEF, higher plasma NT-proBNP, higher New York Heart Association class, and lower 6MWT distance. The distribution of males and females and the prevalence of coronary artery disease was similar between patients with and without VO_2 trajectory flattening, as well as HFrEF, HFmrEF and HFpEF aetiology ($P > 0.05$). No differences were observed in beta-blocker or renin–angiotensin system inhibitor use in patients with and without VO_2 trajectory flattening, whereas patients whose VO_2 trajectory flattened were less frequently on statin therapy and more frequently prescribed an aldosterone antagonist. TAPSE was significantly lower while PASP higher in subjects with flattened VO_2 ($P < 0.001$). Moreover, the TAPSE/PASP ratio was lower in those with VO_2 trajectory flattening ($P < 0.001$).

A typical VO_2 flattening pattern of a patient with HFpEF is displayed in *Figure 1B*. Significant differences in CPET responses were observed in the no VO_2 flattening vs. flattening group (*Table 2*). All patients reached metabolic criteria for maximal exercise test, with peak respiratory exchange ratio > 1.1. On average, subjects with a flattened VO_2 had an unfavourable CPET response, such as lower peak values for heart rate, heart rate recovery, peak VO_2, and peak end-tidal partial pressure of CO_2 ($P_{ET}CO_2$) as well as a higher VE/VCO_2 slope and EOV prevalence.

The trend of statistical significance differences in main clinical, echocardiographic and CPET variables between patients with and without VO_2 trajectory flattening was held in all three groups of HF patients, with the exception of LVEF in patients with HFmrEF

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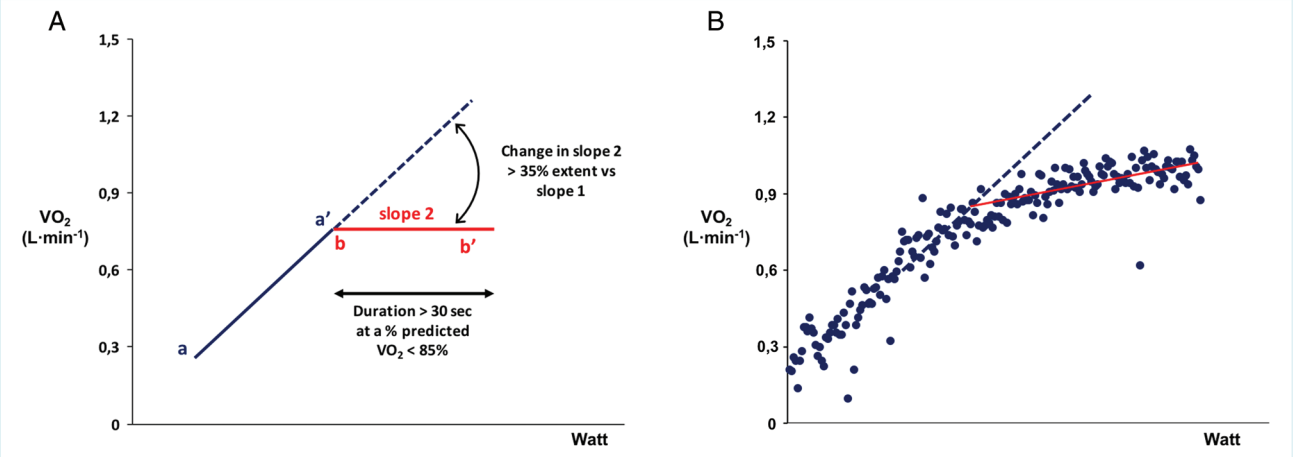

Figure 1 (*A*) Example of oxygen consumption (VO_2)/work rate flattening definition and (*B*) a representative case of VO_2 flattening in a patient with heart failure with preserved ejection fraction.

and HFpEF, which was similar (*Table 3*).

Overall, 71 patients died during the tracking period (25.8 ± 26.4 months), 17 for non-cardiac reasons; there were two cardiac transplantations, four LVAD implantations, and 41 rehospitalizations during the tracking period. Data on cardiac events and non-cardiac mortality in patients with HFrEF, HFmrEF and HFpEF during the follow-up period are reported in *Table 4*. A flattening VO_2 trajectory was a significant univariate predictor of primary [hazard ratio (HR) 4.0, 95% confidence interval (CI) 2.5–6.6, $P < 0.001$] and secondary outcomes (HR 3.8, 95% CI 2.6–5.7, $P < 0.001$), as well as mortality for cardiac reasons (HR 5.0, 95% CI 2.9–8.8, $P < 0.001$), whereas it did not predict significantly non-cardiac mortality ($P > 0.05$). In the multivariate model including peak VO_2, VE/VCO_2 slope, EOV and VO_2 trajectory, only a flattening VO_2 trajectory ($X^2 = 40.2$, $P < 0.001$) and EOV ($X^2 = 17.0$, $P < 0.001$) were retained in the regression for the cardiac death endpoint. In particular, multivariate Cox analysis showed a strong predictive value of VO_2 flattening for the primary and secondary outcomes (*Table 5*).

On Kaplan–Meier analysis, a flattening VO_2 trajectory significantly distinguished patients with and without the primary outcome (log-rank Mantel–Cox =34.3, $P < 0.001$) and secondary outcome (log-rank Mantel–Cox =51.2, $P < 0.001$) during the tracking period (*Figure 2*).

At the same analysis, the primary and secondary outcome was significantly more apparent in patients with a TAPSE/PASP <0.36 mm/mmHg in both patients with and without VO_2 trajectory flattening (log-rank Mantel–Cox =40.0 and 63.8, respectively, $P < 0.001$) (*Figure 3*).

Kaplan–Meier analysis showed that a flattening VO_2 trajectory significantly distinguished patients with and without the composite outcome of cardiac events during the tracking period in subgroups of patients with HFrEF (log-rank Mantel–Cox =31.9, $P < 0.001$), HFmrEF (log-rank Mantel–Cox =4.4, $P = 0.03$), and HFpEF (log-rank Mantel–Cox =16.5, $P < 0.001$) (*Figure 4*).

Discussion

The present findings demonstrate that almost one third of patients diagnosed with any type of HF exhibit a real-time flattening of the VO_2 trajectory. For the first time, this pattern is documented to hold strong predictive power outperforming more established CPET parameters, such as peak VO_2 and VE/VCO_2 slope. A flattening VO_2 trajectory emerged as associated with older age, higher plasma NT-proBNP level, lower LVEF, and a more unfavourable response of several CPET variables. In addition, in the flattening group, the TAPSE/PASP ratio, a measure of RV-PV uncoupling, was significantly lower discriminating a relevant haemodynamic feature that has been highlighted in a number of recent reports.[16,19,20] Remarkably, this background applies to all HF phenotypes, irrespective of LVEF.

Oxygen consumption flattening: pathophysiological insights

A flattening VO_2 trajectory represents an alarming phenotype indicative of ongoing haemodynamic instability. It has been described in a variety of cardiac disorders including HFrEF, HFpEF, mitral regurgitation,[9] and ischaemic heart disease.[5,6] The present study extends these findings to the entire spectrum of HF patients, suggesting that common pathophysiological mechanisms sustain this abnormal function phenotype. The normal VO_2 trajectory corresponds to a rate of increase of 10 mL/min/W, irrespective of age and workload, substantiating the aerobically generated ATP and providing a measure of cardiovascular efficiency.

The pathophysiological explanation of this phenomenon lies within the Fick principle and the classical interpretation offered is a reduction in left ventricular myocardial contractile response limiting cardiac output increase.[1]

In a study addressing VO_2 mean responsive time, a measure of early exercise VO_2 kinetics, a link between the degree of RV-PV uncoupling and VO_2 kinetics was observed and the right heart was

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Table 1 Clinical and echocardiographic characteristics of study patients with and without oxygen consumption trajectory flattening

	No flattening ($n = 227$)	Flattening ($n = 92$)	*P*-value
Age (years)	61.9 ± 10.1	65.9 ± 9.0	0.01
Female sex	51 (22.6%)	18 (19.6%)	0.65
BMI (kg/m^2)	26.9 ± 4.6	26.0 ± 3.8	0.09
CAD	139 (61.5%)	60 (65.2%)	0.61
NYHA class			
I	42 (18.7%)	4 (4.3%)	0.002
II	137 (60.9%)	31 (33.7%)	<0.001
III	42 (18.7%)	51 (55.4%)	<0.001
IV	4 (1.8%)	5 (5.4%)	0.12
NT-proBNP rest (pg/mL)	915.1 ± 637.9	1828.1 ± 865.0	<0.001
LVEF (%)	36.9 ± 11.1	33.9 ± 10.8	0.028
PASP (mmHg)	35.8 ± 9.3	48.3 ± 10.9	<0.001
TAPSE (mm)	18.6 ± 2.8	16.0 ± 3.1	<0.001
TAPSE/PASP (mm/mmHg)	0.56 ± 0.18	0.36 ± 0.15	<0.001
SAP (mmHg)	122 ± 10	119 ± 10	0.005
HR (b.p.m.)	73 ± 9	77 ± 9	<0.001
HFrEF	136 (59.9%)	62 (67.4%)	0.25
HFmrEF	59 (26.0%)	21 (23.1%)	>0.05
HFpEF	32 (14.1%)	9 (9.7%)	>0.05
6MWT (m)	370.9 ± 90.2	315.8 ± 84.5	<0.001
Medications			
Beta-blockers	148 (65.2%)	60 (65.2%)	1.00
ACE-inhibitors or ARBs	185 (81.5%)	74 (80.4%)	0.88
Aldosterone antagonists	101 (44.5%)	55 (59.8%)	0.019
Statins	137 (60.4%)	44 (47.8%)	0.055

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BMI, body mass index; CAD, coronary artery disease; HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HR, heart rate; LVEF, left ventricular ejection fraction; 6MWT, six-minute walk test; NT-proBNP, N-terminal pro brain natriuretic peptide; NYHA, New York Heart Association; PASP, pulmonary artery systolic pressure; SAP, systolic arterial pressure; TAPSE, tricuspid annular plane systolic excursion.

Table 2 Cardiopulmonary exercise test parameters in patients with and without oxygen consumption trajectory flattening

	No flattening ($n = 227$)	Flattening ($n = 92$)	*P*-value
Peak VO_2 (mL·min^{-1}·kg^{-1})	15.3 ± 4.4	12.5 ± 3.9	<0.001
VE/VCO_2 slope	31.5 ± 5.4	42.5 ± 9.3	<0.001
Peak $P_{ET}CO_2$ (mmHg)	35.0 ± 4.6	29.2 ± 4.4	<0.001
EOV	77 (33.9%)	62 (67.4%)	<0.001
Peak HR (b.p.m.)	128 ± 17	121 ± 16	0.001
HRR (b.p.m.)	18 ± 4	15 ± 4	<0.001
Peak SAP (mmHg)	179 ± 13	172 ± 16	<0.001

EOV, exercise oscillatory ventilation; HR, heart rate; HRR, heart rate recovery; $P_{ET}CO_2$, end-tidal partial pressure of carbon dioxide; SAP, systolic arterial pressure; VCO_2, carbon dioxide production; VE, minute ventilation; VO_2, oxygen consumption.

interpreted to have a central role in delayed kinetics.[21] Moreover, the link between right heart function and functional capacity was shown. In accordance with these findings, it has been demonstrated that patients who perform with a VO_2 trajectory flattening exhibit a pattern of reduced TAPSE and increased PASP at peak exercise, as well as reduced TAPSE/PASP ratio both at rest and peak exercise, which was related to reduced cardiac output at peak exercise. A finding that could not be explained by the heart rate response. Current findings are aligned with these previous observations pointing to RV-PV uncoupling as the key substrate.

In patients with more severe PH and right ventricular failure, one of the possible mechanisms of greater real-time VO_2 trajectory flattening with incremental workload increases may be slower blood flow from the right to the left side of the heart, further decreasing left ventricular cardiac output. However, in the condition of increased preload, such as during exercise, the severity of right ventricular failure may be accentuated due to distension of an already compromised right ventricle, which adds to the decrease in both right and left ventricular cardiac output. Right ventricular failure further leads to a decline in pulmonary perfusion and O_2 exchange, in the presence of normal ventilation, reducing VO_2 together with the WR increase. This combination of mechanisms may explain why flattening was more common in HFrEF. On the other hand, HFpEF is a cardiac condition that is preload sensitive. How much a failure of preload recruitment may be involved

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Table 3 Clinical, echocardiographic and cardiopulmonary exercise test characteristics of patients diagnosed with heart failure with reduced, mid-range, and preserved ejection fraction, with and without oxygen consumption trajectory flattening

HFrEF	No flattening ($n = 136$)	Flattening ($n = 62$)	*P*-value
NT-proBNP rest (pg/mL)	1006.4 ± 722.8	1864.1 ± 883.6	<0.001
6MWT (m)	359.0 ± 85.6	323.1 ± 86.2	0.007
LVEF (%)	29.9 ± 6.6	27.7 ± 5.8	0.03
PASP (mmHg)	36.7 ± 8.7	48.6 ± 10.3	<0.001
TAPSE (mm)	18.2 ± 2.6	15.8 ± 2.9	<0.001
TAPSE/PASP (mm/mmHg)	0.53 ± 0.16	0.35 ± 0.14	<0.001
Peak VO_2 ($mL \cdot min^{-1} \cdot kg^{-1}$)	14.8 ± 4.2	12.6 ± 3.8	<0.001
VE/VCO_2 slope	32.1 ± 5.3	43.1 ± 10.0	<0.001
Peak $P_{ET}CO_2$ (mmHg)	34.5 ± 4.5	28.9 ± 4.3	<0.001
EOV	56 (41.2%)	45 (72.6%)	<0.001
Peak HR (b.p.m.)	127 ± 15	121 ± 17	0.017
HRR (b.p.m.)	17 ± 4	15 ± 4	<0.001
Peak SAP (mmHg)	177 ± 12	171 ± 17	0.004
HFmrEF	**No flattening ($n = 59$)**	**Flattening ($n = 21$)**	***P*-value**
NT-proBNP rest (pg/mL)	789.1 ± 410.3	1482.2 ± 697.4	<0.001
6MWT (m)	403.4 ± 84.5	322.8 ± 76.1	<0.001
LVEF (%)	42.7 ± 2.6	42.5 ± 2.8	0.73
PASP (mmHg)	33.7 ± 9.6	43.7 ± 10.9	<0.001
TAPSE (mm)	19.3 ± 2.9	17.2 ± 3.5	0.008
TAPSE/PASP (mm/mmHg)	0.62 ± 0.19	0.43 ± 0.17	<0.001
Peak VO_2 ($mL \cdot min^{-1} \cdot kg^{-1}$)	16.5 ± 4.5	13.4 ± 3.7	0.006
VE/VCO_2 slope	30.8 ± 5.1	40.3 ± 8.0	<0.001
Peak $P_{ET}CO_2$ (mmHg)	35.8 ± 4.6	29.8 ± 5.1	<0.001
EOV	12 (20.3%)	10 (47.6%)	0.034
Peak HR (b.p.m.)	129 ± 18	123 ± 16	0.21
HRR (b.p.m.)	19 ± 4	17 ± 4	0.15
Peak SAP (mmHg)	182 ± 13	176 ± 17	0.86
HFpEF	**No flattening ($n = 32$)**	**Flattening ($n = 9$)**	***P*-value**
NT-proBNP rest (pg/mL)	757.4 ± 515.6	2395.4 ± 815.2	<0.001
6MWT (m)	459.5 ± 105.8	249.1 ± 67.8	0.006
LVEF (%)	56.2 ± 4.9	56.0 ± 4.2	0.93
PASP (mmHg)	35.2 ± 10.6	56.7 ± 10.7	<0.001
TAPSE (mm)	19.1 ± 2.9	14.7 ± 3.1	<0.001
TAPSE/PASP (mm/mmHg)	0.62 ± 0.19	0.43 ± 0.17	<0.001
Peak VO_2 ($mL \cdot min^{-1} \cdot kg^{-1}$)	15.1 ± 5.2	9.3 ± 3.3	0.003
VE/VCO_2 slope	30.1 ± 6.0	43.5 ± 6.7	<0.001
Peak $P_{ET}CO_2$ (mmHg)	35.9 ± 4.6	29.3 ± 2.8	<0.001
EOV	9 (28.1%)	7 (77.8%)	0.021
Peak HR (b.p.m.)	128 ± 20	110 ± 18	0.015
HRR (b.p.m.)	17 ± 5	15 ± 2	0.21
Peak SAP (mmHg)	182 ± 14	173 ± 19	0.10

EOV, exercise oscillatory ventilation; HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HR, heart rate; HRR, heart rate recovery; LVEF, left ventricular ejection fraction; 6MWT, six-minute walk test; NT-proBNP, N-terminal pro brain natriuretic peptide; PASP, pulmonary artery systolic pressure; $P_{ET}CO_2$, end-tidal partial pressure of carbon dioxide; SAP, systolic arterial pressure; TAPSE, tricuspid annular plane systolic excursion; VCO_2, carbon dioxide production; VE, minute ventilation; VO_2, oxygen consumption.

as a key mechanism in at least some of these patients remains unknown. It is also interesting to reason on what is the potential role of exercise-induced right ventricular underfilling as an additional mechanism at work in contributing to cardiac output failure. Again, given the preload sensitivity of the right ventricle in general, a lack of progressive preload recruitment during exercise would further inhibit TAPSE, leading to RV-PV uncoupling even at PASP not or minimally elevated. Future studies aimed at validating current findings should focus on defining the role of these peculiar contributory mechanisms, looking at specific patient subsets.

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Table 4 Follow-up of patients with heart failure with reduced (25.9 ± 24.3 months), mid-range (26.8 ± 32.3 months), and preserved ejection fraction (22.9 ± 23.6 months)

	HFrEF ($n = 198$)	HFmrEF ($n = 80$)	HFpEF ($n = 41$)	Total ($n = 319$)
Cardiac death	40 (20.2%)	6 (7.5%)	8 (19.5%)	54 (16.9%)
Cardiac transplantation	1 (0.5%)	0 (0%)	1 (2.4%)	2 (0.6%)
LVAD implantation	3 (1.5%)	0 (0%)	1 (2.4%)	4 (1.3%)
Rehospitalization for cardiac reasons	31 (15.7%)	5 (6.2%)	5 (12.2%)	41 (12.9%)
Non-cardiac death	10 (5.1%)	6 (7.5%)	1 (2.4%)	17 (5.3%)

LVAD, left ventricular assist device; HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction.

Table 5 Cox analysis for key cardiopulmonary exercise test variables in the prediction of cardiac death, and the primary and secondary outcomes

	X^2	Hazard ratio	95% CI	*P*-value
Cardiac death[a]				
Univariate analysis				
VO_2 trajectory flattening	40.59	5.00	2.86–8.80	<0.001
Peak VO_2	8.26	0.91	0.84–0.97	0.004
VE/VCO_2 slope	28.79	1.06	1.04–1.08	<0.001
EOV	38.80	0.18	0.10–0.33	<0.001
Multivariate analysis				
VO_2 trajectory flattening	40.20	3.16	1.74–5.75	<0.001
Peak VO_2	0.66			0.45
VE/VCO_2 slope	0.87			0.35
EOV	17.00	0.26	0.13–0.51	<0.001
Primary outcome[b]				
Univariate analysis				
VO_2 trajectory flattening	35.78	4.00	2.46–6.61	<0.001
Peak VO_2	10.34	0.90	0.85–0.96	0.001
VE/VCO_2 slope	24.57	1.05	1.03–1.08	<0.001
EOV	36.36	0.22	0.13–0.88	<0.001
Multivariate analysis				
VO_2 trajectory flattening	11.42	2.44		0.001
Peak VO_2	3.87			>0.05
VE/VCO_2 slope	0.08			>0.05
EOV	43.84	0.31		<0.001
Secondary outcome[c]				
Univariate analysis				
VO_2 trajectory flattening	51.11	3.84	2.58–5.70	<0.001
Peak VO_2	31.61	0.86	0.81–0.91	<0.001
VE/VCO_2 slope	48.99	1.06	1.04–1.07	<0.001
EOV	63.54	0.20	0.13–0.30	<0.001
Multivariate analysis				
VO_2 trajectory flattening	12.45	2.12	1.39–3.25	<0.001
Peak VO_2	16.14	0.90	0.86–0.95	<0.001
VE/VCO_2 slope	0.93			0.33
EOV	47.91	0.31	0.19–0.50	<0.001

CI, confidence interval; EOV, exercise oscillatory ventilation; VCO_2, carbon dioxide production; VE, minute ventilation; VO_2, oxygen consumption.
[a]Number of events = 54; censored cases = 260; censored cases before the earliest event = 5.
[b]Number of events = 77; censored cases = 237; censored cases before the earliest event = 5.
[c]Number of events = 101; censored cases = 217; censored cases before the earliest event = 1.

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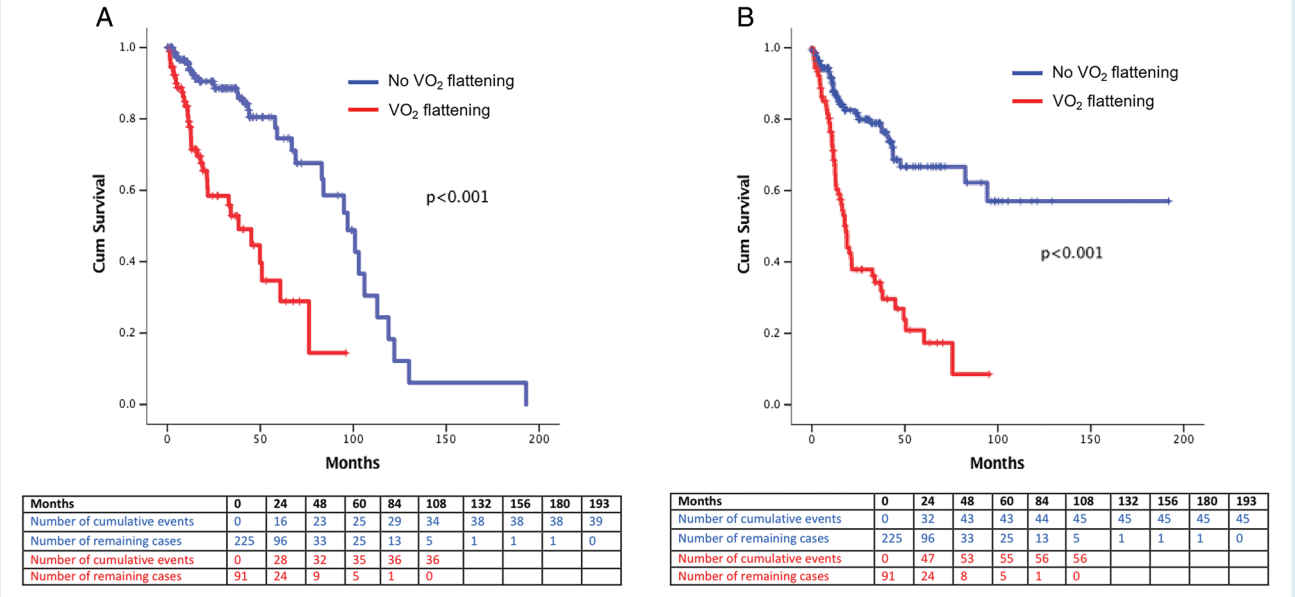

Months	0	24	48	60	84	108	132	156	180	193
Number of cumulative events	0	16	23	25	29	34	38	38	38	39
Number of remaining cases	225	96	33	25	13	5	1	1	1	0
Number of cumulative events	0	28	32	35	36	36				
Number of remaining cases	91	24	9	5	1	0				

Months	0	24	48	60	84	108	132	156	180	193
Number of cumulative events	0	32	43	43	44	45	45	45	45	45
Number of remaining cases	225	96	33	25	13	5	1	1	1	0
Number of cumulative events	0	47	53	55	56	56				
Number of remaining cases	91	24	8	5	1	0				

Figure 2 Kaplan–Meier analysis of oxygen consumption (VO_2) trajectory flattening in patients with and without the primary (*A*) and secondary (*B*) outcome during 25.8 ± 26.4 months of follow-up (both $P < 0.001$).

Clinical implications

Regardless of the underlying mechanisms, a novelty of this study with respect to the management and clinical decision-making of patients with HF is the prognostic significance of VO_2 trajectory flattening. CPET is a well established method showing an increasing role in the management of HF syndrome. Our study draws the attention to a new prognostic variable that adds and overcomes the role of low peak VO_2 and elevated VE/VCO_2 slope. Specifically, a flattening VO_2 trajectory emerged along with EOV, another CPET-derived variable more prognostic than peak VO_2 and VE/VCO_2 slope,[22,23] as the worse CPET phenotype, whose early identification may add to therapeutic strategies.

Definition of the phenotype at higher risk of events is implemented by the demonstration that RV-PV uncoupling, as assessed by TAPSE/PASP ratio < 0.36 mm/mmHg, is associated with a particularly poor prognosis.[16] Previous studies already demonstrated that right heart function is a crucial determinant of outcome in HF patients, regardless of left ventricular function or predominance of systolic or diastolic HF.[24,25] Thus, it appears that the worse outcome in patients with HF is dependent on right-sided cardiac function and increased pulmonary pressure, with a real-time decrease in left-sided cardiac output.

The observation that these findings apply to all HF subgroups irrespective of LVEF stratification is of particular value, considering the lack of prognostic criteria that may work in parallel for patients with HFrEF, HFmrEF, or HFpEF.

Limitations

A routine use of VO_2 trajectory flattening during CPET in the assessment of severity and prognosis of HF may be affected by determinants that have not been addressed in the present investigation, such as the presence of respiratory diseases, anaemia, and type of beta-blocker. We were unable to define the pattern of TAPSE/PASP ratio during exercise, which might further increase the evidence for a clear involvement of the right heart and its coupling with the pulmonary circulation. How much HF aetiology may play a role in the occurrence of VO_2 trajectory flattening remains also unknown. Another limitation of this study in the explanation of the pathophysiological mechanisms leading to VO_2 trajectory flattening is the lack of invasive haemodynamic evaluation. However, we used a strict echocardiographic protocol for non-invasive assessment, rejecting data without good quality to minimize potential errors. Sub-analyses on age and gender were not performed due to the limited numbers in the specific subsets of patients. We are unable to exclude that some of our patients might have suffered of occult pulmonary embolism. Nonetheless, this possibility is quite unlikely because we carefully checked the CPET patterns typical of pulmonary embolism and we could not find in any patient derived indicators such as the lack of a curvilinear decrease in dead space to tidal volume ratio with associated lower levels of $P_{ET}CO_2$ and marked shallow breathing with elevated respiratory rate even early during exercise. An additional limitation of this study is the tracking period variability, as our data are compelling and not definitive. Further data collection may bring stronger conclusions on the prognostic value of VO_2 flattening in the various subgroups of HF patients.

Conclusions

The present findings alert on the necessity to systematically detect the occurrence of a flattening VO_2 trajectory during incremental

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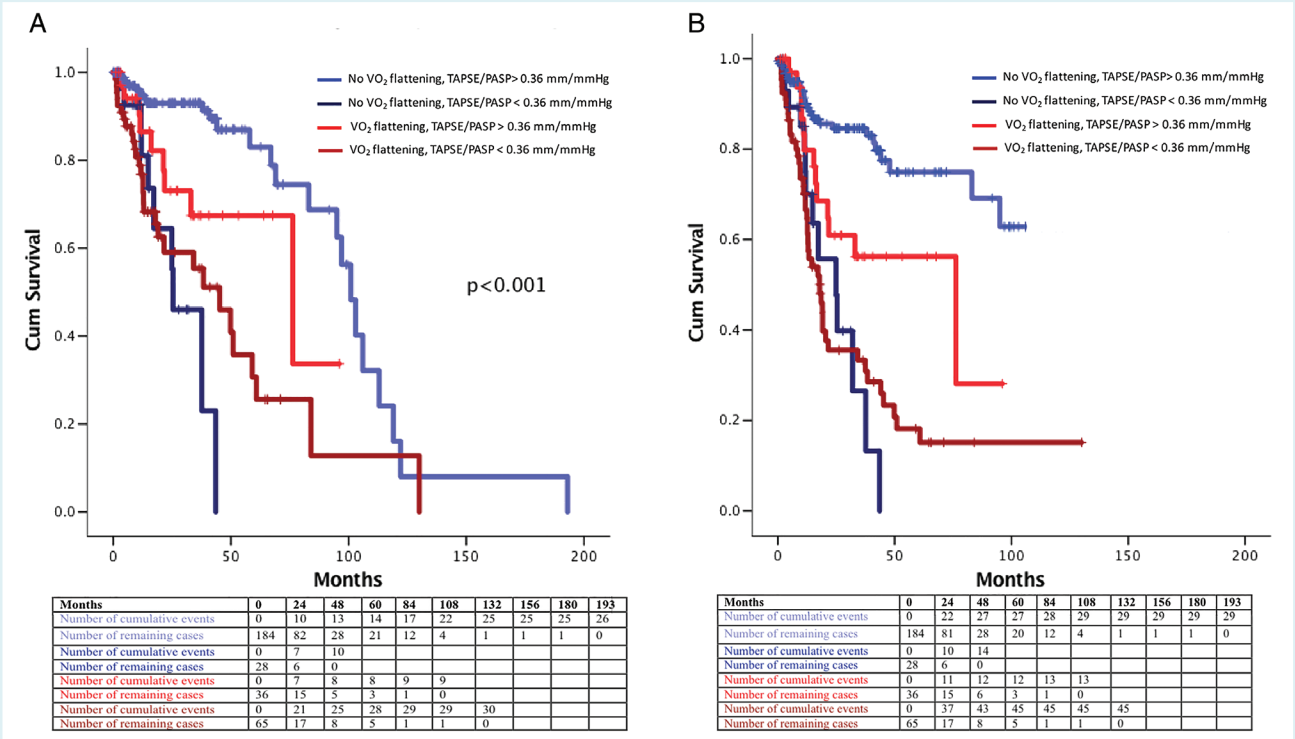
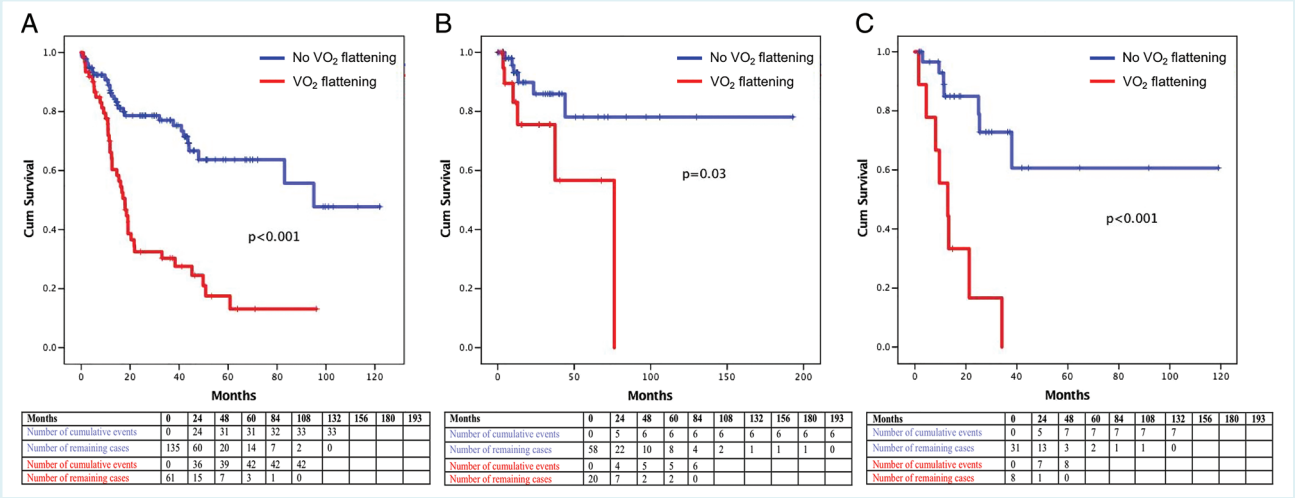


Months	0	24	48	60	84	108	132	156	180	193
Number of cumulative events	0	10	13	14	17	22	25	25	25	26
Number of remaining cases	184	82	28	21	12	4	1	1	1	0
Number of cumulative events	0	7	10							
Number of remaining cases	28	6	0							
Number of cumulative events	0	7	8	8	9	9				
Number of remaining cases	36	15	5	3	1	0				
Number of cumulative events	0	21	25	28	29	29	30			
Number of remaining cases	65	17	8	5	1	1	0			

Months	0	24	48	60	84	108	132	156	180	193
Number of cumulative events	0	22	27	27	28	29	29	29	29	29
Number of remaining cases	184	81	28	20	12	4	1	1	1	0
Number of cumulative events	0	10	14							
Number of remaining cases	28	6	0							
Number of cumulative events	0	11	12	12	13	13				
Number of remaining cases	36	15	6	3	1	0				
Number of cumulative events	0	37	43	45	45	45	45			
Number of remaining cases	65	17	8	5	1	1	0			

Figure 3 Kaplan–Meier analysis of oxygen consumption (VO_2) trajectory flattening in all heart failure patients divided by tricuspid annular plane systolic excursion to pulmonary artery systolic pressure (TAPSE/PASP) ratio ≥ 0.36 or <0.36 mm/mmHg according to the primary (*A*) and secondary (*B*) outcomes.



Months	0	24	48	60	84	108	132	156	180	193
Number of cumulative events	0	24	31	31	32	33	33			
Number of remaining cases	135	60	20	14	7	2	0			
Number of cumulative events	0	36	39	42	42	42				
Number of remaining cases	61	15	7	3	1	0				

Months	0	24	48	60	84	108	132	156	180	193
Number of cumulative events	0	5	6	6	6	6	6	6	6	6
Number of remaining cases	58	22	10	8	4	2	1	1	1	0
Number of cumulative events	0	4	5	5	6					
Number of remaining cases	20	7	2	2	0					

Months	0	24	48	60	84	108	132	156	180	193
Number of cumulative events	0	5	7	7	7	7	7			
Number of remaining cases	31	13	3	2	1	1	0			
Number of cumulative events	0	7	8							
Number of remaining cases	8	1	0							

Figure 4 Kaplan–Meier analysis of oxygen consumption (VO_2) trajectory flattening according to the cardiovascular composite outcome in patients with heart failure with reduced (*A*, follow-up of 25.9 ± 24.3 months), mid-range (*B*, follow-up of 26.8 ± 32.3 months) and preserved ejection fraction (*C*, follow-up of 22.9 ± 23.6 months).

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CPET. For the first time, a flattening VO_2 trajectory emerges as a novel unfavourable marker of outcome, likely more powerful than established CPET prognosticators such as peak VO_2 and VE/VO_2 slope. Given the relation between RV-PV uncoupling and a flattening VO_2 trajectory, it might reflect a right ventricular-induced decrease in left cardiac output. This information seemingly applies to the entire spectrum of HF syndromes, regardless of LVEF.

Funding

This study was supported by a grant of the Monzino Foundation, Milan, Italy.

Conflict of interest: none declared.

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