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Cardiopulmonary exercise testing and heart failure: a tale born from oxygen uptake

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Since 50 years, cardiopulmonary exercise testing (CPET) plays a central role in heart failure (HF) assessment. Oxygen uptake (VO_2) is one of the main HF prognostic indicators, then paralleled by ventilation to carbon dioxide (VE/VCO_2) relationship slope. Also anaerobic threshold retains a strong prognostic power in severe HF, especially if expressed as a percent of maximal VO_2 predicted value. Moving beyond its absolute value, a modern approach is to consider the percentage of predicted value for peak VO_2 and VE/VCO_2 slope, thus allowing a better comparison between genders, ages, and races. Several VO_2 equations have been adopted to predict peak VO_2, built considering different populations. A step forward was made possible by the introduction of reliable non-invasive methods able to calculate cardiac output during exercise: the inert gas rebreathing method and the thoracic electrical bioimpedance. These techniques made possible to calculate the artero-venous oxygen content differences ($\Delta C(a\text{-}v)O_2$), a value related to haemoglobin concentration, pO_2, muscle perfusion, and oxygen extraction. The role of haemoglobin, frequently neglected, is however essential being anaemia a frequent HF comorbidity. Finally, peak VO_2 is traditionally obtained in a laboratory setting while performing a standardized physical effort. Recently, different wearable ergo-spirometers have been developed to allow an accurate metabolic data collection during different activities that better reproduce HF patients' everyday life. The evaluation of exercise performance is now part of the holistic approach to the HF syndrome, with the inclusion of CPET data into multiparametric prognostic scores, such as the MECKI score.

Cardiopulmonary exercise testing (CPET) has been introduced in heart failure (HF) evaluation strategy since almost half a century. At that time, only oxygen uptake (VO_2), both at peak exercise and at anaerobic threshold (AT) was considered. At first, the VO_2 at maximal effort was named 'VO_2 max' and only later the term 'peak VO_2' was proposed recognizing the conceptual differences between the two, being VO_2 max defined as the VO_2 value reached during a maximal exercise when a further VO_2 increase cannot be observed albeit an increase in workload, while peak VO_2 being simply the highest VO_2 achieved in a symptom-limited ramp protocol exercise test. Accordingly, the former can be elicited mostly (if not only) in well trained endurance athletes while the latter has a broader, clear application in the clinical field including in the exercise evaluation of HF patients. Regardless, Weber and Janicki[1]

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proposed the first classification of exercise performance for HF patients based on their peak VO_2 (named by the authors VO_2 max) which was paralleled by VO_2 at AT. This implies a fix relationship between peak exercise and AT suggesting that AT is always achieved in a maximal exercise test. Weber and Janicki classification, following the Fick principle, considers VO_2 as an essentially haemodynamic parameter. These authors proposed five classes—from A to E—with a progressively reduced exercise performance and a greater haemodynamic impairment. Fifteen years later Mancini *et al.*[2] proposed 14 mL/min/kg as a peak VO_2 cut-off value to identify HF patients at low (>14 mL/min/kg) and high (<14 mL/min/kg) risk provided that AT was identified. Of note, a value of 12 mL/min/kg is nowadays considered as a more accurate cut-off value for heart transplant listing by most recent guidelines.[3] Later, different risk categories were recognized grouping patients according to their peak VO_2. A step forward was done in this field by Corrà *et al.*[4] who, at the beginning of the XXI century, described three risk categories for HF patients identifying, specifically, a low risk group with peak $VO_2 \geq$ 18 mL/min/Kg and a high risk group with peak$VO_2 \leq$ 10 mL/min/kg. In case of observed values between 10 and 18 mL/min/kg, risk must be assessed by the analysis of the ventilation to carbon dioxide (VE/VCO_2) relationship slope, being high in case of VE/VCO_2 slope $\geq$ 34 and intermediate if below this threshold. The Corrà *et al.*[4] approach introduced the concept of maximal or near maximal exercise performance as a respiratory exchange ratio (RER, VCO_2/VO_2) $\geq$ 1.05, thus excluding the need of AT identification. This was an important step forward since in patients with severe HF, albeit a maximal exercise test, AT may not be identified, being the beginning of anaerobic metabolism uneven among the various muscle fibres. Importantly, patients with a not identified AT have a worst prognosis compared with patients with identified AT, regardless of AT value.[5] This concept was recently re-emphasized by Carriere *et al.*[6] who showed that the non-identification of AT and of the respiratory compensation point (RCP), which indicated the end of the isocapnic buffering period and the beginning of unbuffered acidosis, has a strong negative prognostic power. An intermediated prognosis was reported for HF subjects with identified AT but not identified RCP while a more favourable outcome was described for patients in case both thresholds were detected, regardless of the absolute value of AT and RCP. As regards AT, an open issue is how to calculate and report it. Recently Salvioni *et al.*[7]clearly showed that expressing the AT as a percent of predicted value improve the prognostic value of this variable, especially in more severe patients. Differently, when AT is expressed as a percentage of the peak VO_2 actually reached during the exercise the prognostic power of this parameter is lower.

Also in the case of peak VO_2 a different approach in its analysis was introduced considering the percentage of predicted value instead of an absolute value.[8] This allows a better comparison between gender and patients of different age and races.[9] Several VO_2 predictors have been adopted since, built considering different populations. At present, the most frequently applied is the Hansen and Wasserman prediction equation[10] albeit, particularly in Germany a prediction equation derived from a population study in Pomerania, the so-called SHIP study[11] has been successfully developed. With the same end, in the US, the FRIEND registry has been built. The concept of reporting data as a percentage of predicted is still underused albeit it allows an easier comparison among HF patients. For example, guidelines for heart transplant on top of the VO_2 absolute value, 12 mL/min/kg, also suggest to use peak values expressed as a percentage of the predicted according to age, sex, height and weight, especially in young subjects (< 50-years-old). On this regard, also other CPET derived parameters such as the VE/VCO_2 slope and cardiac output (Q_c) should be reported as a percentage of predicted albeit this is very rarely occurring.[12,13] However, the absolute peak VO_2 value is still very important when analyzing severe HF patients or when comparing the effects of a clinical intervention. For instance, evaluating the MECKI score database, a large cohort of HF with reduced ejection fraction patients prospectively enrolled in 28 Italian HF units since 1993, which at present comprehend 7948 HF patients with an median follow up of 4.06 (1.76–7.47) years, the analysis of patients with low peak VO_2 ($\leq$12 mL/min/kg $n = 2410$) allows us to differentiate the prognosis among subjects with peak VO_2 ranging from 12 to 10 mL/min/kg ($n = 1279$), vs. 8 to 10 ($n = 763$) and < 8 mL/min/kg ($n = 368$) (*Figure 1*).

An important issue regarding cut-off values for VO_2 but also for other CPET derived parameters is how their prognostic meaning changes over time. Indeed, grouping patients according to their year of enrolment in the MECKI score database showed a different prognosis despite an equal peak VO_2 for patients recruited before year 2001 ($n = 440$), between 2001 and 2005 ($n = 1288$), between 2006 and 2010 ($n = 2368$) and between 2011 and 2015 have with the same peak VO_2 a different prognosis.[14] *Figure 2* shows that the cardiovascular risk, defined as the composite of cardiovascular death, or urgent heart transplant, or left ventricle assist device (LVAD) implantation, for a patient with a peak $VO_2 = 10$ mL/min/kg moved from almost 40% for the patients studied before 2001, to 20% for patients recruited between 2001 and 2005 and to 12% for patients enrolled more recently.[14] It is likely, but still unproved, that the recent introduction of several new drugs and devices for HF treatment will further reduce the risk in now-a-days HF patients.

A further step forward in the understanding of the different faces of VO_2 has was achieved with the possibility to separately evaluate, in a sizable population, Qc and the artero-venous oxygen content differences [$\Delta C(a\text{-}v)O_2$]. This was made possible by the introduction of non-invasive methods to calculate Qc during exercise. Among the various techniques proposed in the past, there are currently two methods which are reliable and easy to perform, the inert gas rebreathing (IGR) method and the thoracic electrical bioimpedance (i.e. Physioflow®) Physioflow method. The first measure pulmonary blood flow and to obtain Qc pulmonary shunt flow most be estimated. This can be problematic in case of exercise-induced hypoxia.[15] In brief, the IGR method, utilizing the Innocor rebreathing system (Innovision A/S, Odense, Denmark) uses an oxygen-enriched mixture of an inert soluble gas (0.5% nitrous oxide-N2O) and an inert insoluble gas (0.1% Sulphur Hexafluoride-SF6) from a pre-filled bag. Patients breathe into a respiratory valve, activated at the end of the expiration so that the patient rebreaths from the pre-filled bag for a period of 10–20 s. Photo-acoustic analyzers measure gas concentration over a 5-breath interval. SF6 is insoluble in blood, and it is used to determine lung volume. On the other hand, N_2O is soluble

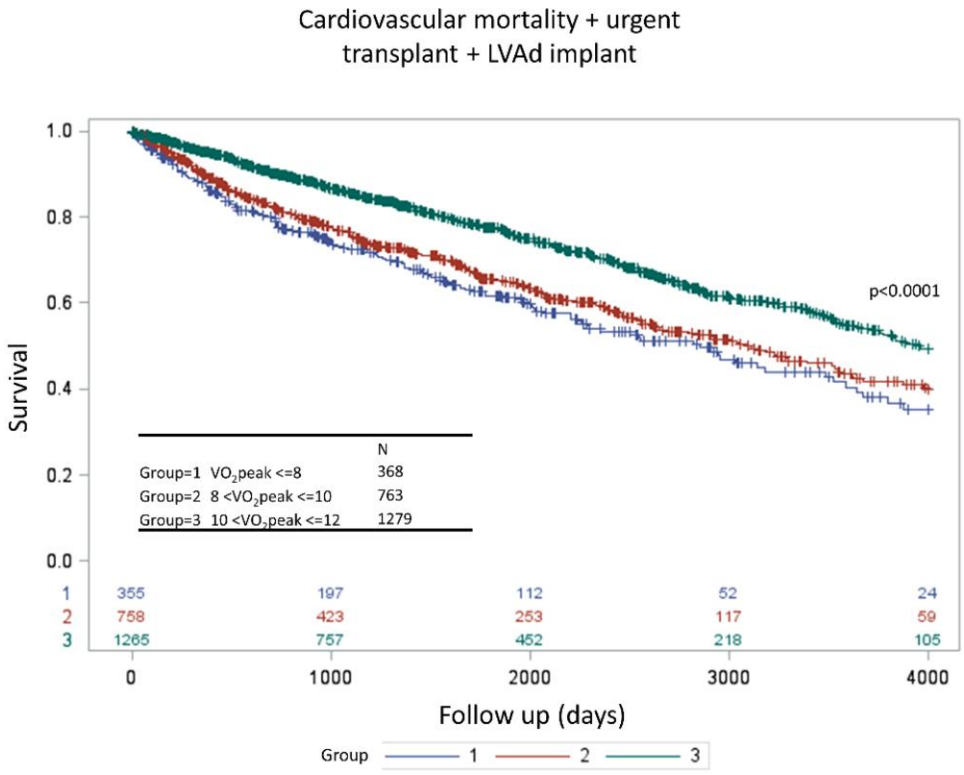

Figure 1 Survival rate according to peak VO_2 in a heart failure population with severe exercise impairment.

in blood, and its concentration decreases during rebreathing with a rate proportional to pulmonary blood flow, that is the blood flow that perfuses the active part of the alveoli. CO is equal to PBF when the arterial oxygen saturation measure (SpO_2) is high (>98% using the pulse oxymeter), showing the absence or the presence of only a negligible pulmonary shunt flow.

The second method is based on impedance cardiography and involves placing six electrodes on the thorax, which are connected to an electronic processing unit. In brief, a low magnitude high frequency alternative current is transmitted through the chest. The device measures the baseline impedance to this current together with variations induced by breathing and the cardiac flow. The impedance baseline is combined with an estimation of the volume of the thorax and the distance between electrodes to estimate thoracic fluid content, which is used as a reference to analyze the pulsatile components of the signals. This method is based on the assumption that, as blood flows out of the heart, phase shifts are created in alternating radiofrequency electrical currents applied across the patient's chest wall. Such phase shifts are measured continuously and have been shown to relate almost linearly to blood flow in the aorta. As a matter of facts, the Physioflow method provides continuous monitoring of heart rate and stroke volume, deriving cardiac output by stroke waveform morphology analysis.

Of note, the utilization of an invasive method for Qc determination, either thermodilution o direct Fick method, albeit rather fashionable is hampered by the invasive nature of the technique and by the fact that are frequently performed in the cath lab on supine patients. As a result, a comparison with exercise performed on pedalling sitting (cycle-ergometer) or running (treadmill) is questionable at least.

Consequently, in clinical practice is now-a-days possible to report VO_2 and its two components Qc and $\Delta C(a\text{-}v)O_2$ on a graph which has on the Y axis Qc and on the × axis $\Delta C(a\text{-}v)O_2$, so that the lines are isoVO_2 lines. On *Figure 3*, as an example, the combined effects of 3 different HF therapeutic interventions, cardiac rehabilitation, edge to edge mitral valve repair and cardiac resynchronization is reported in 234 cases (*Figure 3*). As clearly showed splitting VO_2 in its two components allows a better understanding of the cause of its change.

It is also possible and useful to go inside the $\Delta C(a\text{-}v)O_2$ which value is mainly related to haemoglobin (Hb) concentration, pO_2, muscle perfusion and oxygen extraction. The role of Hb is pivotal but frequently neglected when analyzing either VO_2 and $\Delta C(a\text{-}v)O_2$. Indeed, in HF anaemia is a comorbidity frequently present. In a previous study of our group, in a sizable population of 704 HF patients the correlation of peak VO_2 and resting Hb has a slope of ~0.97 mL/min/Kg/g/dL meaning that, on the average, at peak exercise each reduction of 1 gr of Hb implies a peak VO_2 reduction of ~109 mL/min.[16] A similar value can be reached by averaging the results of 4 studies in which CPET was performed before and after Hb increase.[16] Specifically, considering data derived from two CPETs performed before and after iron deficit treatment the $\Delta VO_2/\Delta Hb$ was 0.94 mL/min/kg/g/dL. However, knowing peak exercise Qc and Hb values a more precise calculation can be done to evaluate peak VO_2 reduction due to anaemia. Indeed, each gr of Hb binds 1.34 mL of O_2. Assuming a peak exercise O_2 extraction of 70% means that each gram of Hb delivers ~1 mL of O_2 to the muscle. If peak

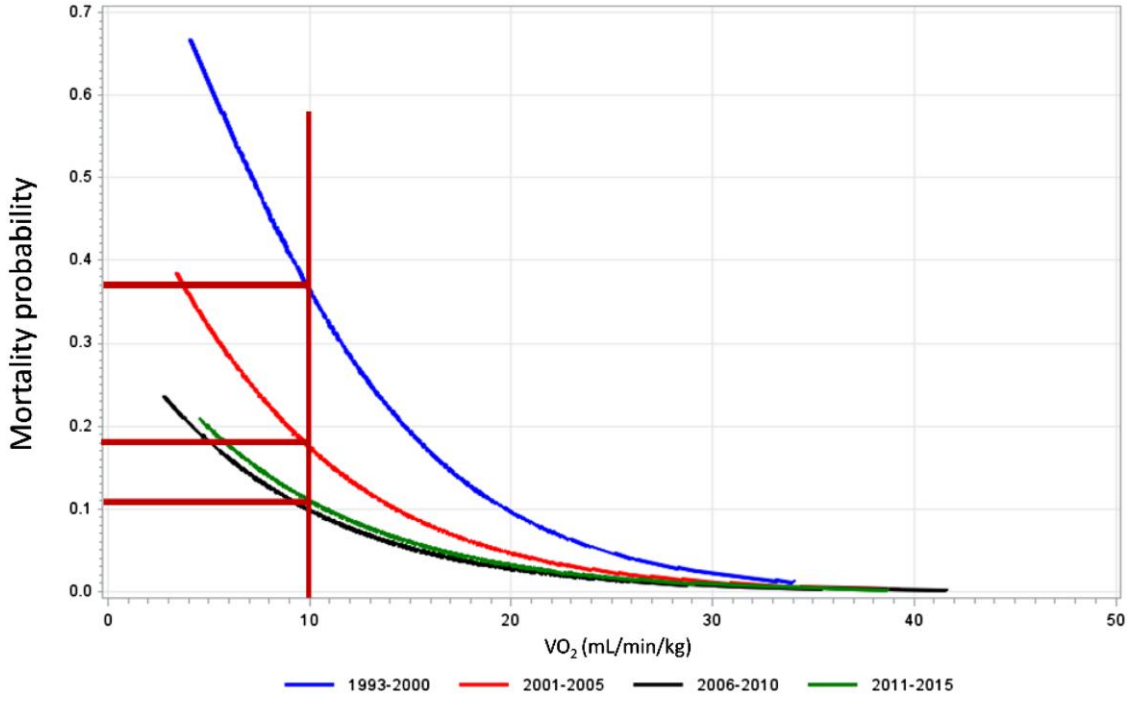

Figure 2 Graphical analysis of risk of the study outcome according to peak oxygen uptake (VO_2) risk was the composite of cardiovascular death, urgent heart transplantation, and left ventricular assist device implantation. (Reproduced from Paolillo et al., Eur J Heart Fail. 2019.[14]).

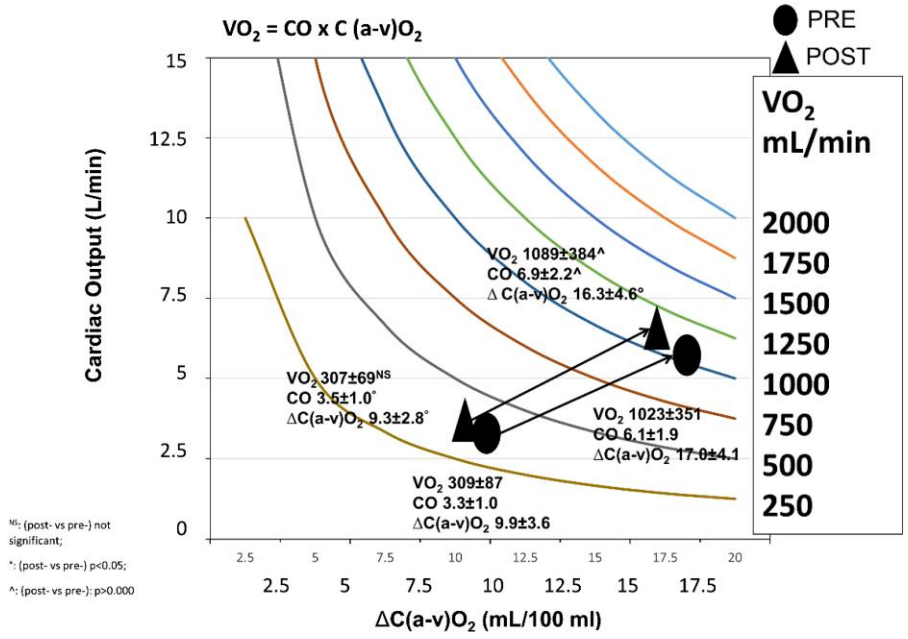

Figure 3 Example of the combined effects of three different HF therapeutic interventions, cardiac rehabilitation, edge to edge mitral valve repair, and cardiac resynchronization, on VO_2 and its components at rest and at peak exercise. PRE = basal evaluation pre-intervention; POST = evaluation after intervention.

exercise Qc is 10 L/m and that the patient has Hb concentration = 10/dL, which means that he has a 5 gr/dL Hb deficit, the VO_2 reduction due to anaemia is ~500 mL/min. It should be underlined that this analysis does not consider exercise-induced haemoconcentration, as well as possible differences in blood flow distribution during exercise. Regardless, albeit grossly, it indicates how much anaemia is relevant in determining peak VO_2 in HF. Knowing the predicted Qc[13] allows also to calculate the amount of the decrease in VO_2 due to Qc reduction. Thus, we can estimate the independent role of the heart, the muscles and Hb concentration in generating VO_2.

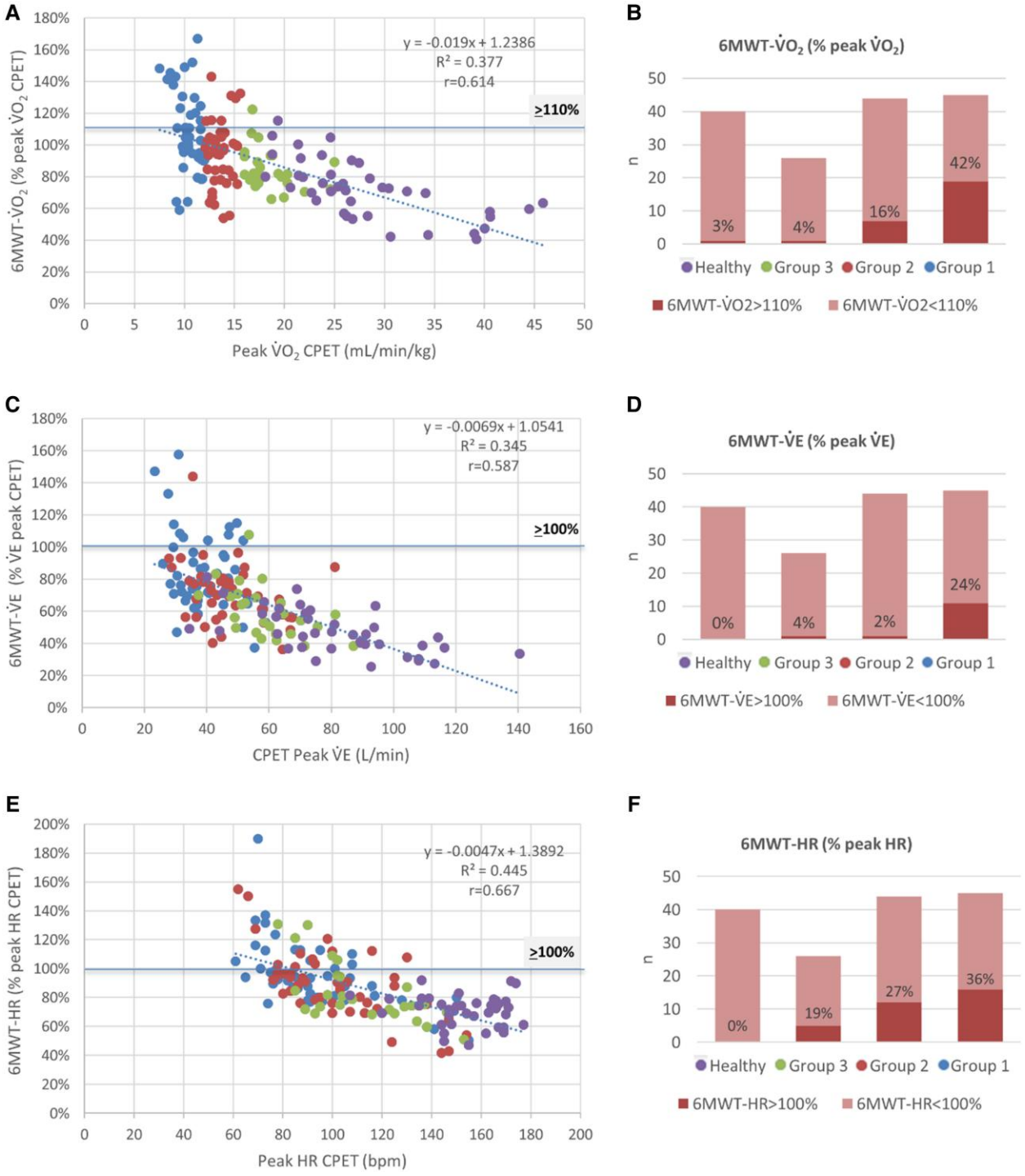

Figure 4 (*A*) The correlation between oxygen uptake (peak$\dot{V}O_2$) at cardiopulmonary exercise test (CPET) and 6 min walking test-$\dot{V}O_2$ expressed as a percent of the CPET peak $\dot{V}O_2$ (6MWT-$\dot{V}O_2$%) is shown. In (*B*), we show the percentage of subjects overcoming the 110% of CPET peak $\dot{V}O_2$ for each subgroup (healthy, Group 1 = peak $\dot{V}O_2$ < 12 mL/kg/min, Group 2 = peak $\dot{V}O_2$ 12–16 mL/kg/min, and Group 3 = peak $\dot{V}O_2$ > 16 mL/kg/min). (*C*) The correlation between peak ventilation ($\dot{V}E$) and 6MWT-$\dot{V}E$ expressed as % of peak $\dot{V}E$ at CPET (6MWT-$\dot{V}E$ %) is shown. In (*D*), the percentage of subjects overcoming the 100% of CPET peak $\dot{V}E$ for each subgroup is reported. (*E*) The correlation between peak heart rate (HR) and 6MWT-HR as % of peak HR at CPET (6MWT-HR%). In (*F*), the percentage of subjects overcoming the 100% of CPET peak HR for each subgroup. (Reproduced from Mapelli et al., ESC Heart Fail. 2022.[19]).

Peak VO_2 is traditionally obtained in a laboratory setting while performing a standardized physical effort (i.e. a maximal ramp protocol with a cycloergometer), being this the gold standard method to obtain reliable, meaningful, prognostic values. However, in HF patients, this may not represent their typical daily life activities. With this regards, different wearable ergo-spirometers have been developed during the last decades and used to

allow an accurate metabolic data collection during different activities, able to reproduce HF patients' everyday life.[17,18] In brief, with this method daily activities can be divided in three different groups: (1) activities where exercise time and work intensity are both variable and self-adjusted (i.e. climbing a stair at the patient's own pace); (2) activities with fixed execution time but variable intensity (i.e. swiping the floor for 4 min); (3) activities where both exercise intensity and time are fixed (i.e. 4 min of walking on a treadmill). This experimental model allowed researchers to characterize the different metabolic behaviour of healthy subjects and HF patients in performing different activities, underlying the compensatory mechanisms they put in place to complete the activity through a reduction—when possible—in exercise intensity or speed, even in case of significant functional limitation. Surprisingly, for patients with more advanced HF, some mundane activities such as making a bed could result in a supramaximal exercise from a metabolic point of view, as evidenced by a complete erosion of the so termed 'VO_2 reserve' (defined as the difference between peak VO_2 reached by the subject during a maximal CPET and the VO_2 he achieves during the activity). These experimental findings were also confirmed in a population of LVAD carriers[18] and similarly, in a recent report by Mapelli *et al.*[19] we showed that VO_2 measured during 6MWT is frequently higher that peak VO_2 achieved by a ramp exercise protocol particularly in patients with peak $VO_2 < 12$ mL/min/kg (*Figure 4*) showing that 6MWT can be a maximal and even supra maximal exercise test.

The evaluation of exercise performance is now part of the holistic approach to the HF syndrome. Indeed, several parameters regarding HF *per se* or its comorbidities have a recognized prognostic value. However, due to the huge variability of HF phenotypes and to the intrinsic variability of the disease itself, no parameter can be used alone to precisely assess the patient's prognosis. In the last 20 years, several prognostic scores have been developed for the general HF population or for specific HF groups. Very few of such scores include exercise performance; among those the MECKI score[20] and the Heart failure Survival Score (HFSS)[21]. At present, the most recent ESC HF guidelines recognize and suggest the use of MECKI Score, Seattle HF model and MAGICC score as a necessary step in the setting of severe HF.[22] Of note, only the former, the MECKI score, includes cardiopulmonary exercise data (peak VO_2 as a percent of the predicted, and VE/VCO_2 slope as an absolute value) together with 4 other easy-to-obtain variables (ejection fraction, haemoglobin, serum sodium, renal function assessed by MDRD equation). Several comparisons among scores[23–26] showed the superior prognostic power of the MECKI score.

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Data availability

No new data were generated or analysed in support of this research.

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