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Beyond VO2: the complex cardiopulmonary exercise test

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Abstract:	Cardiopulmonary exercise test (CPET) is a valuable diagnostic tool with a specific application in heart failure (HF) thanks to the strong prognostic value of its parameters. The most important value provided by CPET is the peak oxygen uptake (peak VO2), the maximum rate of oxygen consumption attainable during physical exertion. According to the Fick principle, VO2 equals cardiac output (Qc) times the arteriovenous content difference [C(a–v)O2], where Ca is the arterial oxygen and Cv is the mixed venous oxygen content, respectively; therefore, VO2 can be reduced both by impaired O2 delivery (reduced Qc) or extraction (reduced arteriovenous O2 content). However, standard CPET is not capable of discriminating between these different impairments, leading to the need for “complex” CPET technologies. Among non-invasive methods for Qc measurement during CPET, inert gas rebreathing and thoracic impedance cardiography are the most used techniques, both validated in healthy subjects and patients with HF, at rest and during exercise. On the other hand, the non-invasive assessment of peripheral muscle perfusion is possible with the application of near infra-red spectroscopy, capable of measuring tissue oxygenation. Measuring Qc allows, by having hemoglobin values available, to discriminate how much any VO2 deficit depends on muscle, anemia or heart.

Cover letter

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Milan, April 21st, 2023

Prof. Massimo Piepoli

Editor in Chief

European Journal of Preventive Cardiology

Dear Prof. Piepoli,

My colleagues and I are submitting the manuscript entitled "**Beyond VO_2: the complex cardiopulmonary exercise test**" for possible publication in *European Journal of Preventive Cardiology* in the special issue "**Heart failure research achievement at CENTRO CARDIOLOGICO MONZINO, IRCCS**".

We revised the manuscript according to the reviewers' indication.

I look forward to receiving your feedback and comments.

Sincerely yours,

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Editor:

- This article merits a graphical Abstract/central figure to summarise its main message and to enhance its visibility

We agree with your observation, thank you. A central illustration was added.

- Please consider to discuss also the following papers: 10.1093/eurjpc/zwac255; 10.1093/eurjpc/zwac116; 10.1093/eurjpc/zwac099; 10.1093/eurjpc/zwac042; 10.1093/eurjpc/zwac018; 10.1093/eurjpc/zwab125; 10.1093/eurjpc/zwaa141).

Thank you, these references have been added throughout the text.

Reviewer #1:

This article is from the cardiorespiratory pathophysiology laboratory at the Centro Cardiologico Monzino led by Professor Agostoni. This is a review article and not a 'Full Research Article' as assigned in the 'Article Type'. This group has an excellent track record of published work on the CPET and are well placed to offer this article that discuss the argument that the standard CPET is limited by its ability to discriminate between the multiple different impairments both centrally (with reduced cardiac output, Qc) and peripherally (with reduced peripheral extraction) that leads to a reduced peak VO2. They suggest that complex' CPET technologies could be employed to assess Qc continuously with techniques such as inert gas rebreathing techniques and with thoracic impedance cardiography. Additionally, they discussed the utilisation of NIRS to allows non-invasive and repeatable assessment of muscle perfusion impairment in HF patients.

In general, the article is well written. However, there are areas that could help improve the article:

1. References need to be more contemporary. Apart of the one reference (Reference 44. Corrieri N et al ESC Heart Failure 2021), all the references were relatively old with ahandful of 2020 references.

Thank you, some more recent references have been added throughout the text.

2. HFrEF and HFpEF. This article did not consider the different HF types. Yet, exercise intolerance is a universal symptom of both HFrEF and HFpEF. Indeed, in the face of numerous recent diagnostic and therapeutic advancements in the field of HF, the addition of CPET provides unique haemodynamic data that are not available from imaging studies with echo and cardiac MR. Some discussion involving HFpEF will be welcomed especially with the recognition that like in HFrEF, additional CPET measurements such as the VE/VCO2 slope, O2 pulse slope curve and the duration of the VO2 recovery offers a better understanding of the overall pathophysiology in HFpEF. and provides a yet stronger risk stratification profile.

We agree with your comment. A section on HFpEF has been added.

3. Pulmonary capillary wedge pressure (PCWP) during exercise. Besides Qc and peripheral extraction, a rise in PCWP is increasingly recognised as a contributor to exercise intolerance especially in HFpEF. A brief discission on this will add interest among the readers.

Your observation is correct. We have added the following sentence among the limitations of our paper: "The non-invasive measures are not able to discriminate an increase in wedge pressure, which can only be inferred from an elevated VE/VCO2 slope as a rise in pulmonary pressure due to augmented left side pressure".

4. Quantification of multi-organ system reserve capacity. While I appreciate that this article focuses on complex CPET technologies that allow assessment of Qc and peripheral extraction, I wonder whether the authors would consider discussing quantification of multi-organ system reserve that contributes to reduced exercise capacity in HF. An example of such an article is the recent paper by Nayor M et al. JACC HF 2020, Pages 605-617

Thank you for the observation. We have reinforced the concept by adding the following sentence as well as the suggested reference:
"A comprehensive assessment of the patient is important to evaluate the different comorbidities and correctly identify the origins of the functional limitation"

Reviewer #2:

The Cardiopulmonary exercise test (CPET) provides joint data analysis that allows complete assessment of the cardiovascular, respiratory, muscular and metabolic systems during exertion, being considered gold standard for cardiorespiratory functional assessment. The authors analyzed in detail different and integrated tools that allow to give answers aimed at discriminating the causes of a reduction in VO2 values. An integrated non-invasive approach for assessment patient is increasingly needed to achieve a more detailed analysis of etiology for VO2 consumption reduction. It is highlighted how the "complex" technologies could bel helpful for more specific etiological definition of reduced pVO2.

General overview
The main goal in patient with heart failure is a more individualized non invasive assessment of the patient pathology and this is the strenght message of this paper. The envise is an expanding role for CPET in evaluating patients with heart failure (HF) and other pathologies (e.g. pulmonary, valvular).
Good exposure about different non invasive methodologies of non invasive assessment of Cardiac output and skeletal muscle oxygenation although cited works in bibliograpfhy about near infrared spectroscopy studies contain not extensive samples.

Thank you for the positive comments. As regards published works on NIRS application, we added the following sentence in the appropriate paragraph:
"with few relevant publications, as the application in this field is just in its early stages"

Specific comments
Introduction is exaustive , the authors intorduce well the overview on importance of CPET in evaluation of exertional dyspnea and definition of complex CPET analysis for better stratificiation patient with cardiac a pulmonar pathologies.

We appreciate your comment.

Cardiac output description by using INNOCOR technology may have some reference about heart failure , other that related to pulmonary hypertension.

Thank you for your comment. We have added a sentence and references on heart failure and the effects of various therapies.

Interesting reference on preliminar data about partitioning CO ventilated and non ventilated lung zones during execrise , it makes the work projected on new promising data.
NIRS has been used extensively to evaluate the changes in muscle oxygenation and blood volume during a variety of exercise models. It was shown that there is a strong correlation between the lactate threshold during incremental cycle exercise and the reduction in muscle oxygenation measured by NIRS. Relevant citation about LVAD (38) and Levosimendan (13) studies.

Thank you again for your positive feedback.

Complex cardiopulmonary testing is a very challenge for the future in terms of application and etiological definition of exertional dyspnea. New technologies could lead to the creation of an integrated analysis system capable of providing all peak VO2, CO and muscle O2 extraction in a single software.

We agree with your statement, the following sentence has been added at the end of the conclusions: "It is desirable that, in the future, these technologies could be integrated into a single software."

Images
Quality of images is good and captions are appropriate.

Thank you for your kind comments.

Beyond VO_2: the complex cardiopulmonary exercise test

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Conflict of interest: none

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ABSTRACT

Cardiopulmonary exercise test (CPET) is a valuable diagnostic tool with a specific application in heart failure (HF) thanks to the strong prognostic value of its parameters. The most important value provided by CPET is the peak oxygen uptake (peak VO_2), the maximum rate of oxygen consumption attainable during physical exertion. According to the Fick principle, VO_2 equals cardiac output (Q_c) times the arteriovenous content difference [$C(a–v)O_2$], where Ca is the arterial oxygen and Cv is the mixed venous oxygen content, respectively; therefore, VO_2 can be reduced both by impaired O_2 delivery (reduced Q_c) or extraction (reduced arteriovenous O_2 content).

However, standard CPET is not capable of discriminating between these different impairments, leading to the need for "complex" CPET technologies. Among non-invasive methods for Q_c measurement during CPET, inert gas rebreathing and thoracic impedance cardiography are the most used techniques, both validated in healthy subjects and patients with HF, at rest and during exercise. On the other hand, the non-invasive assessment of peripheral muscle perfusion is possible with the application of near infra-red spectroscopy, capable of measuring tissue oxygenation. Measuring Q_c allows, by having hemoglobin values available, to discriminate how much any VO_2 deficit depends on muscle, anemia or heart.

Keywords: Heart failure; complex cardiopulmonary exercise test; cardiac output measurement

Introduction

Cardiopulmonary exercise test (CPET) is a valuable tool, capable of complete evaluation of physiological adaptation to exercise, examining metabolic, respiratory, cardiovascular, muscular, and cellular responses (1). CPET is an extremely useful in cases of dyspnea or exercise intolerance of unknown origin, able to discriminate between cardiogenic and pulmonary source. However, thanks to the strong prognostic value of its parameters, it also represents a fundamental instrument in the prognostic stratification and follow-up of patients with heart failure (HF). According to the most recent HF guidelines (2): CPET is recommended as part of the evaluation for heart transplantation and/or mechanical circulatory support, to optimize prescription of exercise training and to identify the cause of unexplained dyspnea and/or exercise intolerance (2). Performing CPET is also useful in the following cases: evaluation of hypertensive patients (3), patients with chronotropic incompetence (4), patients with congenital heart disease (5), functional characterisation of healthy subjects (6).

The most important value provided by CPET is the peak oxygen uptake (peak VO_2), the maximum rate of oxygen consumption attainable during physical exertion. Peak VO_2 continues to be considered the most useful parameter in assessing prognostic stratification among HF patients (7-11).

The minute ventilation-carbon dioxide production relationship (VE/VCO_2 slope) has recently demonstrated prognostic significance in patients with HF, and in some studies, it has outperformed peak VO_2 (12, 13).

Another critical value is the ventilatory anaerobic threshold (AT), which represent the peak VO_2 value when metabolism switches from aerobic to anaerobic because oxygen supply cannot keep up with the increasing metabolic requirements of exercising muscles and lactic acid production significantly increases (14). Also, the oxygen pulse (O_2 pulse) is the ratio of VO_2 and heart rate (HR; mL/beat) provides an estimate of stroke volume and peripheral vascular perfusion/extraction response to exercise, according to the Fick principle (i.e. $VO_2 = Q_C \times [CaO_2 - CvO_2]$ where Q_C = cardiac output [stroke volume x HR]; CaO_2 = arterial oxygen content, CvO_2 = venous oxygen content; ($CaO_2 - CvO_2$) = arteriovenous [a-v] difference in O_2).

Frequently, cardiologists must face CPET results that are not completely decisive for the diagnosis, for example in the case of a patient who presents a reduction in functional capacity due to a reduced peak VO_2 without other significant abnormalities or symptoms of left ventricular dysfunction (10, 11). A reduction in physical capacity, which is frequently reported also in healthy, "couch potatoes" subjects, can occur for muscle deconditioning other than low Q_C or chronotropic/pressure incompetence. Indeed, according to the Fick principle (i.e. $VO_2 = Q_C \times [CaO_2 - CvO_2]$) VO_2 can be reduced both by impaired O_2 delivery (reduced Q_C) or extraction (reduced arteriovenous O_2 content) (15). Table 1 shows the determinants of arteriovenous oxygen content difference.

It must be clearly stated that standard CPET is not capable of discriminating with certainty between these different impairments.

For more precise etiological determination of reduced peak VO_2 (if Q_C or peripheral extraction reduction is involved), "complex" CPET technologies may be useful. Other contexts in which "complex" technologies could be helpful are when the estimated Q_C during exercise can be observed as a variable that continues over time, to highlight its changes during exercise: for example, patients with severe paucisymptomatic aortic stenosis, hypertrophic cardiomyopathy with and without intraventricular gradient at rest, or intramyocardial coronary artery bridge, to highlight the presence of exertional myocardial ischemia linked to a reduction in Q_C (useful for understanding at what HR this occurs if no changes are observed in the electrocardiogram).

Nowadays, several software packages for non-invasive Q_C estimation are available: some of them use recent technologies as inert gas rebreathing (Innocor), morphology impedance cardiography (Physioflow), or light waves that penetrate superficial tissues to calculate the percentage of oxygenated blood (Near-infrared spectroscopy, NIRS) and can be useful for the evaluation of healthy subjects and HF patients (including Left Ventricular Assist Device bearing patients) to stratify prognosis and to guide therapy (16-19).

Cardiac output measurement

The direct Fick method is still considered as the gold standard technique in Q_C measurement, but thermodilution is the most used method for Q_C assessment because it is easier and faster. However, both thermodilution and the direct Fick method require right-sided cardiac catheterization, which is an invasive procedure characterized by rare - albeit possibly life-threatening - complications, significant discomfort and anxiety for patients, and high costs especially if performed during exercise (20).

Moreover, the invasive Q_C measurements above mentioned are often performed while supine, which is not the natural patients' position when performing physical exertion. In the supine position the venous return amount is different than in the sitting position, therefore Q_C and maybe Q_C partition in the lung may be different according to the patient's posture during the assessment.

Non-invasive Q_C measurement during CPET is a meaningful added value with a significant role both for prognosis and for exercise physiology understanding in patients with cardiopulmonary diseases.

Inert gas rebreathing

A non-invasive method for Q_C measurement by inert gas rebreathing (IGR) has been validated in healthy subjects and patients with HF, at rest and during exercise (21). IGR calculates Q_C as the sum of pulmonary blood flow and intrapulmonary shunt, that means the sum of Q_C perfusing well ventilated and not ventilated alveoli, respectively. IGR relies on proper alveolar gas mixing for pulmonary blood flow measurement and estimation of intrapulmonary shunt based on the assumption of a constant oxygen saturation (SO_2) value in the pulmonary capillaries.

Both measurements were initially considered to be challenging in patients with an abnormal ventilatory perfusion match and a significant intrapulmonary shunt conditioning a relevant blood oxygen saturation decrease during exercise, such as in patients affected by pulmonary arterial hypertension (PAH) or parenchymal lung disease which could also be responsible for an incomplete pulmonary gas mixing (22).

Nevertheless, it was subsequently demonstrated that the accuracy of the IGR method is not influenced by either pulmonary obstructive or pulmonary restrictive disease, even when PAH is associated with a

parenchymal disease (23). Particularly it has been shown that IGR is a reliable and accurate method for Q_C assessment also in patients with PAH, except for those with low arterial SO_2 (<90%), mainly due to a wrong shunt flow estimation (24). Moreover, this technique has also been used in advanced HF, left ventricular assist device bearing patients and in the evaluation following percutaneous mitral valvuloplasty or resynchronisation therapy (17, 18, 25-28).

The possibility of measuring Q_C during exercise in PAH patients is relevant because the main goal of all the available treatment strategies for PAH is the reduction of pulmonary vascular resistances and the increase in Q_C (29).

An inadequate increase of Q_C and hyperventilation are a well-known causes of exercise limitation in PAH patients. Indeed, during exercise, PAH patients show an excessive increase in ventilation (VE) compared to carbon dioxide output (VCO_2), determining a high VE/VCO_2 slope associated with a characteristic reduction in the end tidal CO_2 partial pressure ($PetCO_2$) (30-32). In a previous study we demonstrated that exercise hyperventilation and therefore a high VE/VCO_2 slope in PAH patients is associated to high dead space ventilation (VE_{DS}), around 30% of exercise VE, and an enhanced chemoreceptor response to hypoxia and hypercapnia (33).

In this regard, Q_C at rest is a well-known prognostic tool and a marker of response to therapy in PAH patients but the role of the overall Q_C increase during exercise and of the intrapulmonary blood flow partitioning between ventilated and not ventilated lung zones is unknown. This is an important lack of knowledge, as it is not known which of these two components of pulmonary blood flow is mainly affected by treatment. In the past, similar treatment strategies aimed at reduction of pulmonary vascular resistance, applied to PAH in chronic obstructive pulmonary disease patients, showed a negative effect on medium term survival; indeed, an increase of hypoxia, likely resulting from an increase in pulmonary shunt, was observed against a reduction of pulmonary vascular resistance (34, 35).

Thoracic impedance cardiography

Nowadays, total Q_C can be measured non-invasively during exercise by thoracic impedance cardiography, Physioflow, in healthy subjects and in patients with cardiopulmonary diseases (36, 37).

Physioflow measures changes in transthoracic impedance, independent of baseline impedance while administering a high-frequency (75 kHz) and low-amperage (3.8 mA peak to peak) alternating electrical current. Pulsatile variation in impedance is mainly a function of variation in the volume and velocity of the thoracic aortic blood flow. Physioflow software establishes stroke volume index (SVi) and Q_C by the product of HR x SVi x body surface area (38, 39).

A complex CPET with the simultaneous measurement of Q_C by IGR and Physioflow should allow to assess Q_C and Q_C partitioning in the lung during exercise: indeed, while pulmonary blood flow to ventilated lung zones can be measured by IGR, in the absence of intracardiac shunt, non-ventilated lung zones flow can be calculated as the differences between total Q_C and blood flow to ventilated lung zones.

Therefore, we have recently undertaken a study to evaluate the Q_C behaviour during exercise and its partitioning between ventilated and not-ventilated lung areas in a series of PAH patients: our unpublished data showed that, when partitioning Q_C to ventilated and not-ventilated lung zones during exercise, the blood flow to the non-ventilated lung zone was approximately 20% of the total Q_C (a dedicated manuscript is at present under review). We strongly believe that complex CPET could be a useful tool for assessing the response to pulmonary vasodilating drugs in patients with PAH.

Peripheral tissue oxygenation: near infra-red spectroscopy

NIRS is a non-invasive diagnostic technique capable of measuring real time tissue oxygenation using portable instruments. NIRS application in clinical medicine started after the observation that biological tissues are quite transparent to light in the near infrared spectrum (i.e. 700-1,300 nm) (40). The second critical element that enables the use of NIRS is the oxygenation-dependent light absorbing characteristics of haemoglobin. Hence, by applying different light impulse wavelengths, the relative changes in haemoglobin concentration (oxygenated and deoxygenated) can be monitored.

The first clinical applications of the NIRS technique were developed to assess oxygenation status of the two most oxygen-consuming human organs, the brain and skeletal muscle. In particular, NIRS is a well-established method for the evaluation of cerebral oxygenation status in intensive care units and cardiac surgery. In more recent clinical studies, NIRS is used to directly quantify the variation in muscle levels of oxygenated haemoglobin (O_2Hb), deoxygenated haemoglobin (HHb), total haemoglobin (tHb) and, indirectly, venous oxygen saturation (SvO_2%) to study the state of oxygenation and peripheral tissue perfusion. This technique can be applied to the muscle to assess oxygenation status and tissue perfusion, both at rest and during exercise (41-43).

Exercise capacity, expressed as oxygen uptake, is determined by Q_C and peripheral oxygen extraction. The reduction in exercise capacity in patients with HF is partly due to muscle hypoperfusion, partly related to muscle ultrastructural changes and hyperactivation of muscle ergoreflexes: the increase in peripheral oxygen extraction is one of the compensatory mechanisms that the body uses to counteract the reduction of Q_C due to cardiogenic deficit (44-47).

Patients with HF are often limited by muscle fatigue due, at least in part, to peripheral muscle hypoperfusion. NIRS allows non-invasive and repeatable assessment of the severity of muscle perfusion impairment in these patients by showing changes in haemoglobin oxygenation related to changes in muscle perfusion associated with changes in the degree of haemoglobin deoxygenation during exercise.

As regards HF, the NIRS technique has been used to assess muscle oxygenation status during constant workload physical activity (25, 48) with few relevant publications, as the application in this field is just in its early stages. Of note, reliable NIRS measurements of oxygenated and deoxygenated haemoglobin content in the skeletal muscle need steady state conditions, thus it can be applied at rest, during constant workload exercise, during a multi-minute step incremental protocol or a ramp protocol.

In the context of complex CPET, the NIRS allows to study the oxygenation state of the muscle during exercise in healthy subjects and in patients suffering from HF and, in the future, it would be able to be applied to the study of limitation capacity in other pathologies.

Peak oxygen uptake versus cardiac output

Muscle work during exercise requires a complex integration of cardiac, pulmonary, vascular and peripheral mechanisms. Effort limitation in HF is a multifactorial process involving alterations in central hemodynamics, peripheral vasodilatory capacity, intrinsic skeletal muscle alterations, pulmonary factors, iron deficiency, anemia and general conditioning state, all of which can compromise effective oxygen supply and utilization.

As previously stated, according to the Fick's law, Q_C is directly proportional to oxygen consumption (VO_2) and inversely proportional to arteriovenous oxygen difference ($\Delta(a\text{-}v)O_2$), which depends on several factors, including anemia, exercise-induced hemoconcentration, muscle metabolic efficiency, and peripheral blood flow distribution (Table 1). An increase in VO_2 can be achieved by an improvement in Q_C, arteriovenous O_2 difference or both. A healthy, deconditioned subject with normal Q_C but reduced $\Delta(a\text{-}v)O_2$, an HF patient with a reduced Q_C and elevated $\Delta(a\text{-}v)O_2$, or a person with the coexistence of both reduced Q_C and deconditioning, may all have the same VO_2 (Figure 1) (49).

In a previous study it was shown that peak exercise VO_2 is linearly related to peak exercise Q_C in HF patients. However, in the frailer population this correlation seems weaker (26). Notably, in patients with mild and moderate HF, exercise Q_C increase is reduced but $\Delta(a\text{-}v)O_2$ increase is, on the average, preserved. On the other hand, patients with the most compromised exercise performance (peak VO_2 < 50% of predicted) show a lower Q_C and $\Delta(a\text{-}v)O_2$ increase, with both central and peripheral factors responsible for the low peak VO_2 observed. A partial explanation may lie in the fact that these frailer patients are more anemic and have lower iron levels (50). Accordingly, it is essential to evaluate iron profile in more severe HF and perform a correction if the values fall below the recommended standards. Moreover, blood flow distribution to peripheral muscles, mitochondrial O_2 uptake, and capillary density were reported to be more impaired in HF patients with more severe disease (51). A comprehensive assessment of the patient is important to evaluate the different comorbidities and correctly identify the origins of the functional limitation (52).

In advanced HF patients it might be difficult to achieve a maximal effort during CPET. Non-invasive haemodynamic assessment and standard CPET values showed that mid exercise parameters correlate with peak values and therefore with patient's exercise capacity during real life activities (53). The evaluation of complex CPET at submaximal exercise in advanced HF patients is a promising tool to assess patients' well-being and possibly prognosis but more data are definitively needed on this topic.

The assessment of exercise tolerance is also essential in HF with preserved function. The reduction in exercise capacity in these patients may have a multifactorial origin, given the comorbidities usually present in this group of subjects such as obesity, diabetes, anemia, lung disease (52). The identification of this limitation allows better treatment of these patients.

The prognostic relevance of the traditional CPET parameters that are valid for HF with reduced ejection fraction, such as peak VO_2 and the VE/VCO_2 slope relationship, is also confirmed in this class of subjects (54), and the use of complex CPET allows a better phenotyping of these patient for an appropriate tailored therapy.

The research on HF with preserved ejection fraction is still in its early stages and new studies are needed to complete the characterisation of this disease.

Limitations

The non-invasive measures are not able to discriminate an increase in wedge pressure, which can only be inferred from an elevated VE/VCO_2 slope as a rise in pulmonary pressure due to augmented left side pressure (55, 56).

Conclusion

Complex CPET represents a new frontier in the assessment of patients with HF as exercise limitation is multifactorial and its causes can guide a widespread approach to the medical management of severe HF. In particular, non-invasive Q_C measurement techniques have several advantages over invasive Q_C assessment,

including patient comfort, safety, easy reproducibility and lower technical requirements. It is desirable that, in the future, these technologies could be integrated into a single software.

Table 1. Determinants of arteriovenous oxygen content difference

Factors possibly affecting the $C(a–v)O_2$		Effect on $C(a–v)O_2$
Haemoglobin	↑ (Exercise-induced hemoconcentration)	↑
Muscle metabolic efficiency	↑	↑
Peripheral blood distribution toward working muscles	↑	↑
PO_2	↓	↓
pH	↓ (↑p50)	↑
Temperature	↑ (↑p50)	↑

Abbreviations: $C(a–v)O_2$ = arteriovenous oxygen content difference; p50 = O_2 pressure at which haemoglobin is half saturated with O_2.

Vignati C, Cattadori G. Measuring Cardiac Output during Cardiopulmonary Exercise Testing. Ann Am Thorac Soc. 2017;14(Supplement_1):S48-S52.
Annals of the American Thoracic Society Medicine is an official journal of the American Thoracic Society.

Figure legend

Figure 1. Cardiac output, arteriovenous oxygen difference [$C(a–v)O_2$; a = arterial oxygen; v = mixed venous oxygen content], and VO_2 in a healthy deconditioned subject, mild deconditioned patient with heart failure (HF), and normally trained patient with severe HF at peak exercise. Cardiac output is plotted against $C(a–v)O_2$. The solid lines are lines with the same VO_2. $C(a–v)O_2$ can be estimated from measured VO_2 and cardiac output.

Vignati C, Cattadori G. Measuring Cardiac Output during Cardiopulmonary Exercise Testing. Ann Am Thorac Soc. 2017;14(Supplement_1):S48-S52.
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Authors contribution

IM, CV, SF, AA, FDM, DZ and PA drafted the manuscript. PA critically revised the manuscript. All authors gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

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Beyond VO_2: the complex cardiopulmonary exercise test

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ABSTRACT

Cardiopulmonary exercise test (CPET) is a valuable diagnostic tool with a specific application in heart failure (HF) thanks to the strong prognostic value of its parameters. The most important value provided by CPET is the peak oxygen uptake (peak VO_2), the maximum rate of oxygen consumption attainable during physical exertion. According to the Fick principle, VO_2 equals cardiac output (Q_c) times the arteriovenous content difference [$C(a–v)O_2$], where Ca is the arterial oxygen and Cv is the mixed venous oxygen content, respectively; therefore, VO_2 can be reduced both by impaired O_2 delivery (reduced Q_c) or extraction (reduced arteriovenous O_2 content).

However, standard CPET is not capable of discriminating between these different impairments, leading to the need for "complex" CPET technologies. Among non-invasive methods for Q_c measurement during CPET, inert gas rebreathing and thoracic impedance cardiography are the most used techniques, both validated in healthy subjects and patients with HF, at rest and during exercise. On the other hand, the non-invasive assessment of peripheral muscle perfusion is possible with the application of near infra-red spectroscopy, capable of measuring tissue oxygenation. Measuring Q_c allows, by having hemoglobin values available, to discriminate how much any VO_2 deficit depends on muscle, anemia or heart.

Keywords: Heart failure; complex cardiopulmonary exercise test; cardiac output measurement

Introduction

Cardiopulmonary exercise test (CPET) is a valuable tool, capable of complete evaluation of physiological adaptation to exercise, examining metabolic, respiratory, cardiovascular, muscular, and cellular responses (1). CPET is an extremely useful in cases of dyspnea or exercise intolerance of unknown origin, able to discriminate between cardiogenic and pulmonary source. However, thanks to the strong prognostic value of its parameters, it also represents a fundamental instrument in the prognostic stratification and follow-up of patients with heart failure (HF). According to the most recent HF guidelines (2): CPET is recommended as part of the evaluation for heart transplantation and/or mechanical circulatory support, to optimize prescription of exercise training -and to identify the cause of unexplained dyspnea and/or exercise intolerance (2). Performing CPET is also useful in the following cases: evaluation of hypertensive patients (3), patients with chronotropic incompetence (4), patients with congenital heart disease (5), functional characterisation of healthy subjects (6).

The most important value provided by CPET is the peak oxygen uptake (peak VO_2), the maximum rate of oxygen consumption attainable during physical exertion. Peak VO_2 continues to be considered the most useful parameter in assessing prognostic stratification among HF patients (7-11).

The minute ventilation-carbon dioxide production relationship (VE/VCO_2 slope) has recently demonstrated prognostic significance in patients with HF, and in some studies, it has outperformed peak VO_2 (12, 13).

Another critical value is the ventilatory anaerobic threshold (AT), which represent the peak VO_2 value when metabolism switches from aerobic to anaerobic because oxygen supply cannot keep up with the increasing metabolic requirements of exercising muscles and lactic acid production significantly increases (14). Also, the oxygen pulse (O_2 pulse) is the ratio of VO_2 and heart rate (HR; mL/beat) provides an estimate of stroke volume and peripheral vascular perfusion/extraction response to exercise, according to the Fick principle (i.e. $VO_2 = Q_C \times [CaO_2 - CvO_2]$ where Q_C = cardiac output [stroke volume x HR]; CaO_2 = arterial oxygen content, CvO_2 = venous oxygen content; ($CaO_2 - CvO_2$) = arteriovenous [a-v] difference in O_2).

Frequently, cardiologists must face CPET results that are not completely decisive for the diagnosis, for example in the case of a patient who presents a reduction in functional capacity due to a reduced peak VO_2 without other significant abnormalities or symptoms of left ventricular dysfunction (10, 11). A reduction in physical capacity, which is frequently reported also in healthy, "couch potatoes" subjects, can occur for muscle deconditioning other than low Q_C or chronotropic/pressure incompetence. Indeed, according to the Fick principle (i.e. $VO_2 = Q_C \times [CaO_2 - CvO_2]$) VO_2 can be reduced both by impaired O_2 delivery (reduced Q_C) or extraction (reduced arteriovenous O_2 content) (15). Table 1 shows the determinants of arteriovenous oxygen content difference.

It must be clearly stated that standard CPET is not capable of discriminating with certainty between these different impairments.

For more precise etiological determination of reduced peak VO_2 (if Q_C or peripheral extraction reduction is involved), "complex" CPET technologies may be useful. Other contexts in which "complex" technologies could be helpful are when the estimated Q_C during exercise can be observed as a variable that continues over time, to highlight its changes during exercise: for example, patients with severe paucisymptomatic aortic stenosis, hypertrophic cardiomyopathy with and without intraventricular gradient at rest, or intramyocardial coronary artery bridge, to highlight the presence of exertional myocardial ischemia linked to a reduction in Q_C (useful for understanding at what HR this occurs if no changes are observed in the electrocardiogram).

Nowadays, several software packages for non-invasive Q_C estimation are available: some of them use recent technologies as inert gas rebreathing (Innocor), morphology impedance cardiography (Physioflow), or light waves that penetrate superficial tissues to calculate the percentage of oxygenated blood (Near-infrared spectroscopy, NIRS) and can be useful for the evaluation of healthy subjects and HF patients (including Left Ventricular Assist Device bearing patients) to stratify prognosis and to guide therapy (16-19).

Cardiac output measurement

The direct Fick method is still considered as the gold standard technique in Q_C measurement, but thermodilution is the most used method for Q_C assessment because it is easier and faster. However, both thermodilution and the direct Fick method require right-sided cardiac catheterization, which is an invasive procedure characterized by rare - albeit possibly life-threatening - complications, significant discomfort and anxiety for patients, and high costs especially if performed during exercise (20).

Moreover, the invasive Q_C measurements above mentioned are often performed while supine, which is not the natural patients' position when performing physical exertion. In the supine position the venous return amount is different than in the sitting position, therefore Q_C and maybe Q_C partition in the lung may be different according to the patient's posture during the assessment.

Non-invasive Q_C measurement during CPET is a meaningful added value with a significant role both for prognosis and for exercise physiology understanding in patients with cardiopulmonary diseases.

Inert gas rebreathing

A non-invasive method for Q_C measurement by inert gas rebreathing (IGR) has been validated in healthy subjects and patients with HF, at rest and during exercise (21). IGR calculates Q_C as the sum of pulmonary blood flow and intrapulmonary shunt, that means the sum of Q_C perfusing well ventilated and not ventilated alveoli, respectively. IGR relies on proper alveolar gas mixing for pulmonary blood flow measurement and estimation of intrapulmonary shunt based on the assumption of a constant oxygen saturation (SO_2) value in the pulmonary capillaries.

Both measurements were initially considered to be challenging in patients with an abnormal ventilatory perfusion match and a significant intrapulmonary shunt conditioning a relevant blood oxygen saturation decrease during exercise, such as in patients affected by pulmonary arterial hypertension (PAH) or parenchymal lung disease which could also be responsible for an incomplete pulmonary gas mixing (22).

Nevertheless, it was subsequently demonstrated that the accuracy of the IGR method is not influenced by either pulmonary obstructive or pulmonary restrictive disease, even when PAH is associated with a

parenchymal disease (23). Particularly it has been shown that IGR is a reliable and accurate method for Q_C assessment also in patients with PAH, except for those with low arterial SO_2 (<90%), mainly due to a wrong shunt flow estimation (24). Moreover, this technique has also been used in advanced HF, left ventricular assist device bearing patients and in the evaluation following percutaneous mitral valvuloplasty or resynchronisation therapy (17, 18, 25-28).

The possibility of measuring Q_C during exercise in PAH patients is relevant because the main goal of all the available treatment strategies for PAH is the reduction of pulmonary vascular resistances and the increase in Q_C (29).

An inadequate increase of Q_C and hyperventilation are a well-known causes of exercise limitation in PAH patients. Indeed, during exercise, PAH patients show an excessive increase in ventilation (VE) compared to carbon dioxide output (VCO_2), determining a high VE/VCO_2 slope associated with a characteristic reduction in the end tidal CO_2 partial pressure ($PetCO_2$) (30-32). In a previous study we demonstrated that exercise hyperventilation and therefore a high VE/VCO_2 slope in PAH patients is associated to high dead space ventilation (VE_{DS}), around 30% of exercise VE, and an enhanced chemoreceptor response to hypoxia and hypercapnia (33).

In this regard, Q_C at rest is a well-known prognostic tool and a marker of response to therapy in PAH patients but the role of the overall Q_C increase during exercise and of the intrapulmonary blood flow partitioning between ventilated and not ventilated lung zones is unknown. This is an important lack of knowledge, as it is not known which of these two components of pulmonary blood flow is mainly affected by treatment. In the past, similar treatment strategies aimed at reduction of pulmonary vascular resistance, applied to PAH in chronic obstructive pulmonary disease patients, showed a negative effect on medium term survival; indeed, an increase of hypoxia, likely resulting from an increase in pulmonary shunt, was observed against a reduction of pulmonary vascular resistance (34, 35).

Thoracic impedance cardiography

Nowadays, total Q_C can be measured non-invasively during exercise by thoracic impedance cardiography, Physioflow, in healthy subjects and in patients with cardiopulmonary diseases (36, 37).

Physioflow measures changes in transthoracic impedance, independent of baseline impedance while administering a high-frequency (75 kHz) and low-amperage (3.8 mA peak to peak) alternating electrical current. Pulsatile variation in impedance is mainly a function of variation in the volume and velocity of the thoracic aortic blood flow. Physioflow software establishes stroke volume index (SVi) and Q_C by the product of HR x SVi x body surface area (38, 39).

A complex CPET with the simultaneous measurement of Q_C by IGR and Physioflow should allow to assess Q_C and Q_C partitioning in the lung during exercise: indeed, while pulmonary blood flow to ventilated lung zones can be measured by IGR, in the absence of intracardiac shunt, non-ventilated lung zones flow can be calculated as the differences between total Q_C and blood flow to ventilated lung zones.

Therefore, we have recently undertaken a study to evaluate the Q_C behaviour during exercise and its partitioning between ventilated and not-ventilated lung areas in a series of PAH patients: our unpublished data showed that, when partitioning Q_C to ventilated and not-ventilated lung zones during exercise, the blood flow to the non-ventilated lung zone was approximately 20% of the total Q_C (a dedicated manuscript is at present under review). We strongly believe that complex CPET could be a useful tool for assessing the response to pulmonary vasodilating drugs in patients with PAH.

Peripheral tissue oxygenation: near infra-red spectroscopy

NIRS is a non-invasive diagnostic technique capable of measuring real time tissue oxygenation using portable instruments. NIRS application in clinical medicine started after the observation that biological tissues are quite transparent to light in the near infrared spectrum (i.e. 700-1,300 nm) (40). The second critical element that enables the use of NIRS is the oxygenation-dependent light absorbing characteristics of haemoglobin. Hence, by applying different light impulse wavelengths, the relative changes in haemoglobin concentration (oxygenated and deoxygenated) can be monitored.

The first clinical applications of the NIRS technique were developed to assess oxygenation status of the two most oxygen-consuming human organs, the brain and skeletal muscle. In particular, NIRS is a well-established method for the evaluation of cerebral oxygenation status in intensive care units and cardiac surgery. In more recent clinical studies, NIRS is used to directly quantify the variation in muscle levels of oxygenated haemoglobin (O_2Hb), deoxygenated haemoglobin (HHb), total haemoglobin (tHb) and, indirectly, venous oxygen saturation ($SvO_2\%$) to study the state of oxygenation and peripheral tissue perfusion. This technique can be applied to the muscle to assess oxygenation status and tissue perfusion, both at rest and during exercise (41-43).

Exercise capacity, expressed as oxygen uptake, is determined by Q_C and peripheral oxygen extraction. The reduction in exercise capacity in patients with HF is partly due to muscle hypoperfusion, partly related to muscle ultrastructural changes and hyperactivation of muscle ergoreflexes: the increase in peripheral oxygen extraction is one of the compensatory mechanisms that the body uses to counteract the reduction of Q_C due to cardiogenic deficit (44-47).

Patients with HF are often limited by muscle fatigue due, at least in part, to peripheral muscle hypoperfusion. NIRS allows non-invasive and repeatable assessment of the severity of muscle perfusion impairment in these patients by showing changes in haemoglobin oxygenation related to changes in muscle perfusion associated with changes in the degree of haemoglobin deoxygenation during exercise.

As regards HF, the NIRS technique has been used to assess muscle oxygenation status during constant workload physical activity (25, 48) with few relevant publications, as the application in this field is just in its early stages. Of note, reliable NIRS measurements of oxygenated and deoxygenated haemoglobin content in the skeletal muscle need steady state conditions, thus it can be applied at rest, during constant workload exercise, during a multi-minute step incremental protocol or a ramp protocol.

In the context of complex CPET, the NIRS allows to study the oxygenation state of the muscle during exercise in healthy subjects and in patients suffering from HF and, in the future, it would be able to be applied to the study of limitation capacity in other pathologies.

Peak oxygen uptake versus cardiac output

Muscle work during exercise requires a complex integration of cardiac, pulmonary, vascular and peripheral mechanisms. Effort limitation in HF is a multifactorial process involving alterations in central hemodynamics, peripheral vasodilatory capacity, intrinsic skeletal muscle alterations, pulmonary factors, iron deficiency, anemia and general conditioning state, all of which can compromise effective oxygen supply and utilization.

As previously stated, according to the Fick's law, Q_C is directly proportional to oxygen consumption (VO_2) and inversely proportional to arteriovenous oxygen difference ($\Delta(a\text{-}v)O_2$), which depends on several factors, including anemia, exercise-induced hemoconcentration, muscle metabolic efficiency, and peripheral blood flow distribution (Table 1). An increase in VO_2 can be achieved by an improvement in Q_C, arteriovenous O_2 difference or both. A healthy, deconditioned subject with normal Q_C but reduced $\Delta(a\text{-}v)O_2$, an HF patient with a reduced Q_C and elevated $\Delta(a\text{-}v)O_2$, or a person with the coexistence of both reduced Q_C and deconditioning, may all have the same VO_2 (Figure 1) (49).

In a previous study it was shown that peak exercise VO_2 is linearly related to peak exercise Q_C in HF patients. However, in the frailer population this correlation seems weaker (26). Notably, in patients with mild and moderate HF, exercise Q_C increase is reduced but $\Delta(a\text{-}v)O_2$ increase is, on the average, preserved. On the other hand, patients with the most compromised exercise performance (peak VO_2 < 50% of predicted) show a lower Q_C and $\Delta(a\text{-}v)O_2$ increase, with both central and peripheral factors responsible for the low peak VO_2 observed. A partial explanation may lie in the fact that these frailer patients are more anemic and have lower iron levels (50). Accordingly, it is essential to evaluate iron profile in more severe HF and perform a correction if the values fall below the recommended standards. Moreover, blood flow distribution to peripheral muscles, mitochondrial O_2 uptake, and capillary density were reported to be more impaired in HF patients with more severe disease (51). A comprehensive assessment of the patient is

important to evaluate the different comorbidities and correctly identify the origins of the functional limitation (52).

In advanced HF patients it might be difficult to achieve a maximal effort during CPET. Non-invasive haemodynamic assessment and standard CPET values showed that mid exercise parameters correlate with peak values and therefore with patient's exercise capacity during real life activities (53). The evaluation of complex CPET at submaximal exercise in advanced HF patients is a promising tool to assess patients' well-being and possibly prognosis but more data are definitively needed on this topic.

The assessment of exercise tolerance is also essential in HF with preserved function. The reduction in exercise capacity in these patients may have a multifactorial origin, given the comorbidities usually present in this group of subjects such as obesity, diabetes, anemia, lung disease (52). The identification of this limitation allows better treatment of these patients.

The prognostic relevance of the traditional CPET parameters that are valid for HF with reduced ejection fraction, such as peak VO_2 and the VE/VCO_2 slope relationship, is also confirmed in this class of subjects (54), and the use of complex CPET allows a better phenotyping of these patient for an appropriate tailored therapy.

The research on HF with preserved ejection fraction is still in its early stages and new studies are needed to complete the characterisation of this disease.

Limitations

The non-invasive measures are not able to discriminate an increase in wedge pressure, which can only be inferred from an elevated VE/VCO_2 slope as a rise in pulmonary pressure due to augmented left side pressure (55, 56).

Conclusion

Complex CPET represents a new frontier in the assessment of patients with HF as exercise limitation is multifactorial and its causes can guide a widespread approach to the medical management of severe HF. In particular, non-invasive Q_C measurement techniques have several advantages over invasive Q_C assessment, including patient comfort, safety, easy reproducibility and lower technical requirements. It is desirable that, in the future, these technologies could be integrated into a single software.

Table 1. Determinants of arteriovenous oxygen content difference

Factors possibly affecting the $C(a–v)O_2$		Effect on $C(a–v)O_2$
Haemoglobin	↑ (Exercise-induced hemoconcentration)	↑
Muscle metabolic efficiency	↑	↑
Peripheral blood distribution toward working muscles	↑	↑
PO_2	↓	↓
pH	↓ (↑p50)	↑
Temperature	↑ (↑p50)	↑

Abbreviations: $C(a–v)O_2$ = arteriovenous oxygen content difference; p50 = O_2 pressure at which haemoglobin is half saturated with O_2.

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Figure legend

Figure 1. Cardiac output, arteriovenous oxygen difference [$C(a–v)O_2$; a = arterial oxygen; v = mixed venous oxygen content], and VO_2 in a healthy deconditioned subject, mild deconditioned patient with heart failure (HF), and normally trained patient with severe HF at peak exercise. Cardiac output is plotted against $C(a–v)O_2$. The solid lines are lines with the same VO_2. $C(a–v)O_2$ can be estimated from measured VO_2 and cardiac output.

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Authors contribution

~~All authors contributed to the manuscript drafting and revision of the text.~~

IM, CV, SF, AA, FDM, DZ and PA drafted the manuscript. PA critically revised the manuscript. All authors gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

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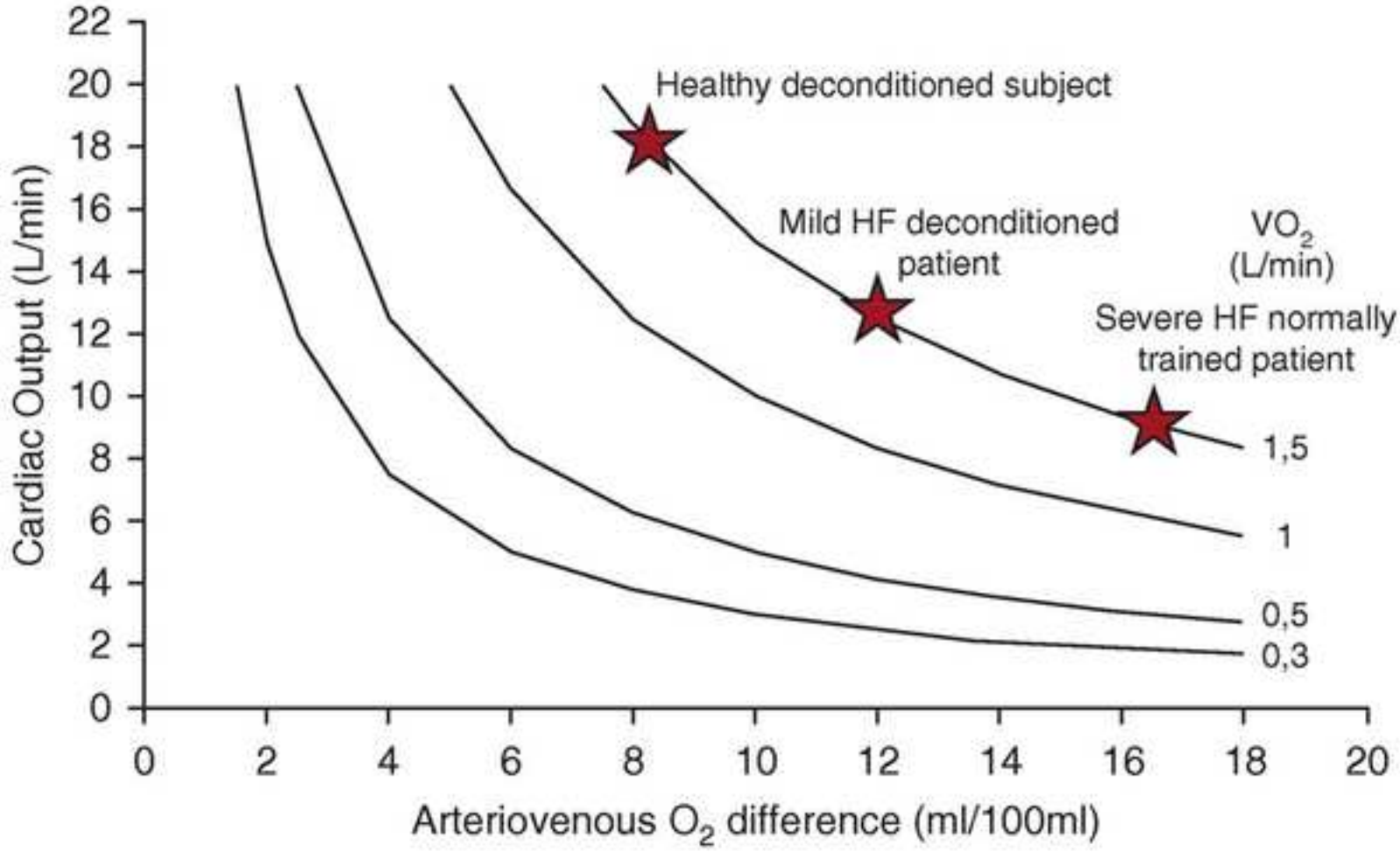
Figure 1



Complex CPET with simultaneous measurement of cardiac output and arteriovenous O_2 difference during exercise

VO_2 = CARDIAC OUTPUT X ARTERIOVENOUS O_2 DIFFERENCE

INERT GAS REBREATHING

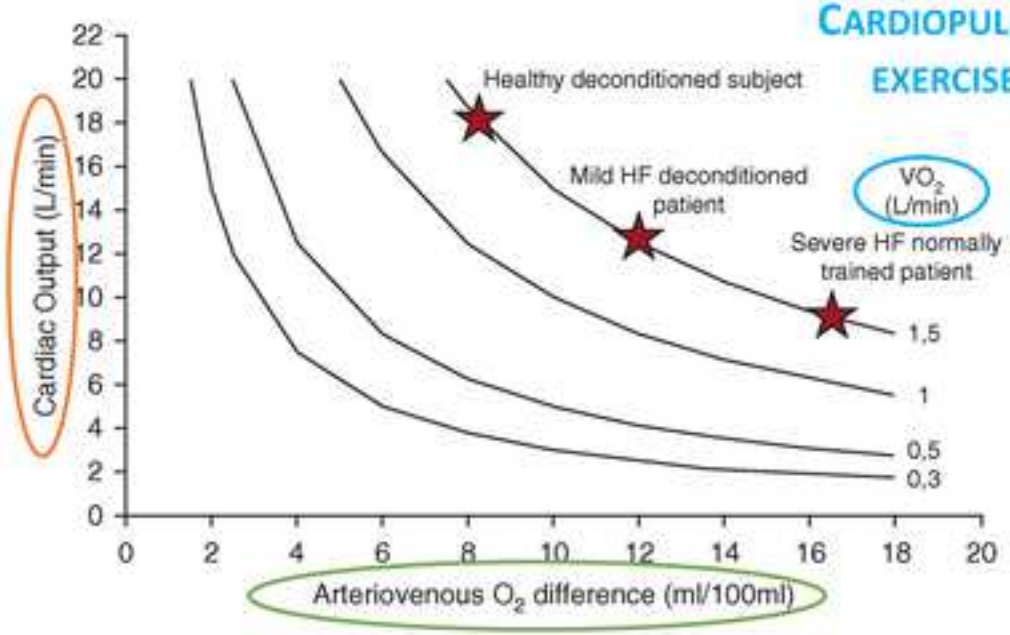
AND/OR

THORACIC IMPEDANCE

CARDIOGRAPHY

CARDIOPULMONARY

EXERCISE TEST



NEAR-INFRARED SPECTROSCOPY

TOTAL Hb, OXYGENATED Hb, DEOXYGENATED Hb