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Early recovery of oxygen kinetics in heart failure: A systematic review of oxygen kinetics during the 1stminute of recovery after cardiopulmonary exercise test in heart failure

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ADMINISTRATIVE INFORMATION

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INTRODUCTION

Review question / Objective Cardiopulmonary exercise test (CPET) is the gold standard assessment tool for the evaluation of functional capacity in heart failure (HF). Specifically, Oxygen kinetics behavior obtained during early recovery phase of CPET, are linked with the pathophysiological mechanisms involved in HF. In particular, oxygen kinetics during 1st minute of recovery, defined as the linear slope of the oxygen uptake reduction during 1st minute of recovery (VO2/t-slope), after maximal or submaximal CPET, are delayed in HF. In recent published clinical trials, there are evidence revealing correlation between VO2/t-slope and highest oxygen uptake (VO2peak) in HF population and also parallel variation of VO2/t-slope and of VO2peak (another ergospirometric parameters obtain also during CPT) in HF, after implementing a predefined period of physical exercise program. During the first minutes of exercise, metabolic demands are resulting oxygen deficit which is increased in HF, effecting the variability of both VO2peak and VO2/t-slope, suggesting them as promising indicators for HF diagnosis, classification and prognosis. Since both VO2/t-slope and VO2peak are proportionally improving after implementation of exercise program in HF, the existence of a common pathophysiological pathway between the two indicators its possible. However, during CPET, advance stage HF patients present exercise intolerance, and so limiting the ability to measure VO2peak. In contrast evaluation of VO2/t-slope is independent of the duration and of the intensity of CPET, revealing a clinical advantage in respect of VO2peak. Thus, the correlation between VO2/t-slope and the VO2peak during CPET in HF and the subsequently hypothesis of using VO2/t-slope as a diagnostic and prognostic indicator similarly and/or additionally to VO2peak in health individuals and in HF population, but also in HF before and after training interventions needs to be examined.

Rationale Cardiopulmonary exercise testing (CPET) has been established as the gold standard assessment tool for the evaluation of cardiovascular physiology and exercise capacity [1]. Ergospirometric indicators obtained during CPET, are commonly used for the prognosis and the diagnosis of cardiovascular disease, revealing the adaptation of cardiometabolic physiology to aerobic exercise in heart failure (HF). The most common representative indicator is the peak oxygen uptake (VO2peak) which is a critical marker of cardiovascular and respiratory capacity and a reliable parameter of the severity of heart failure. Even though previous studies highlighted the role of VO2peak as a significant indicator of exercise capacity and overall cardiovascular health, the necessity of alternative novel markers, due to the complexity of HF pathophysiology, is noticeable.

Among other suggested metabolic and cardiorespiratory parameters for HF assessments, measurement of oxygen kinetics during and after CPET can quantify the severity and prognosis of HF. Specifically, recent clinical trials emphasize the significant role of oxygen kinetics obtained during the recovery phase of CPET, in the assessment of clinical prognosis, evaluation and functional capacity in HF. In particular, metabolic parameters obtained during the recovery phase of CPET and related to oxygen kinetics, such as the oxygen uptake slope (VO2/t-slope) has been considered strong indicators of cardiorespiratory function. Research evidence from the literature suggest that VO2/t-slope during the 1st minute of recovery, which is expressed by the corresponding slope of the exponential decrease curve of oxygen consumption (calculated by the first-degree slope of the decrease in VO2 during recovery) can possibly consist of a surrogate marker to estimate functional capacity and exercise tolerance.

VO2/t-slope evaluates how efficiently the body is utilizing oxygen during exercise, which can be particularly useful in identifying early signs of patients' functional decline or improvement and therefore appears prolonged in HF in respect of healthy subjects. In healthy population during initial phases of exercise, metabolic demands are resulting oxygen deficit, which is expressed as the energy bonds, consumed by the primary energy-released molecules: phosphocreatine and adenosine triphosphate. In HF population oxygen deficit is significant increased, effecting the value of VO2/t-slope. Exercise improves oxygen consumption, prevents vascular diseases and promotes cardiovascular health and both VO2/t-slope and VO2peak are proportionally improving after implementation of exercise program in HF, revealing common pathophysiological pathway between the two indicators. However, during CPET, advance stage HF patients present exercise intolerance, and so limiting the ability to measure VO2peak. In contrast evaluation of VO2/t-slope is independent of the duration and of the intensity of CPET, revealing a clinical advantage in respect of VO2peak. Thus, the hypothesis of using VO2/t-slope as a diagnostic and prognostic indicator similarly and/or additionally to VO2peak in health individuals and in HF population, but also in HF before and after training interventions needs to be examined.

Condition being studied Heart failure is the state of any heart disease in which, despite adequate ventricular filling, the heart's output is decreased or in which the heart is unable to pump blood at a rate adequate for satisfying the requirements of the tissues with function parameters remaining within normal limits. Heart failure is not a disease but a syndrome . It's a combination of signs and symptoms caused by the failure of the heart to pump blood to support the circulatory system at rest or during activity. It develops when the heart fails to properly fill with blood during diastole, resulting in a decrease in intracardiac pressures or in ejection during systole, reducing cardiac output to the rest of the body. The filling failure and high intracardiac pressure can lead to fluid accumulation in ventricles of heart. This manifests as water retention and swelling due to fluid accumulation (edema) called congestion. Impaired ejection can lead to inadequate blood flow to the body tissues, resulting in ischemia. Symptoms of heart failure are traditionally divided into left-sided and right-sided because the left and right ventricles supply different parts of the circulation. In biventricular heart failure, both sides of the heart are affected. Left-sided heart failure is the more common. Since heart failure is a syndrome and not a disease, establishing the underlying cause is vital to diagnosis and treatment. In heart failure, the structure or the function of the heart or in some cases both are altered. Heart failure is the potential end stage of all heart diseases. Common causes of heart failure include coronary artery disease, including a previous myocardial infarction, high blood pressure, atrial fibrillation, valvular heart disease, excess alcohol use, infection, and cardiomyopathy of an unknown cause. In addition, viral infection and subsequent inflammation of the heart's myocardial tissue (termed myocarditis) can similarly contribute to the development of heart failure. Genetic predisposition plays an important role. If more than one cause is present, progression is more likely and prognosis is worse .Heart failure is caused by any condition that reduces the efficiency of the heart muscle, through damage or overloading. Over time, these increases

in workload, which are mediated by long-term activation of neurohormonal systems such as the renin–angiotensin system and the sympathoadrenal system, lead to fibrosis, dilation, and structural changes in the shape of the left ventricle from elliptical to spherical. The most common classification of heart failure type is made by measuring ejection fraction, or the proportion of blood pumped out of the heart during a single contraction. Ejection fraction is given as a percentage with the normal range being between 50 and 60% The types are: Heart failure with reduced ejection fraction (HFrEF): Synonyms no longer recommended are "heart failure due to left ventricular systolic dysfunction" and "systolic heart failure".HFrEF is associated with an ejection fraction less than 40%.

Heart failure with mildly reduced ejection fraction (HFmrEF), previously called "heart failure with mid-range ejection fraction",is defined by an ejection fraction of 41–49%.

Heart failure with preserved ejection fraction (HFpEF): Synonyms no longer recommended include "diastolic heart failure" and "heart failure with normal ejection fraction." HFpEF occurs when the left ventricle contracts normally during systole, but the ventricle is stiff and does not relax normally during diastole, which impairs filling.

Heart failure with recovered ejection fraction (HFrecovEF or HFrecEF): patients previously with HFrEF with complete normalization of left ventricular ejection (≥50%).

Heart failure may also be classified as acute or chronic. The goals of the treatment for people with chronic heart failure are the prolongation of life, prevention of acute decompensation, and reduction of symptoms, allowing for greater activity.

METHODS

Search strategy This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA), which consists if a check list with 27 items and a four-step flowchart to assist the construction of systematic reviews and meta-analyses.In this study, articles that were abstracts, oral or poster presentations in conferences, non-peer-reviewed manuscripts, letters to the editor, book chapters as well as unpublished papers, were excluded. We had also excluded animal studies, reviews, case reports and editorials; however, we screened the reference lists of such publications and of the retrieved articles for relevant papers. Studies without any clinical and/or the mathematical correlation between VO2/t-slope and VO2peak, indicating only the correlation of these markers with other metabolic or respiratory indices were excluded.The literature review used databases in which all studies reporting clinical and/or the mathematical correlation of VO2/t-slope and VO2peak between HF patients and/or between HF and healthy population, with or without following a specific training period program. The following descriptors were used: “VO2/t-slope”, “oxygen kinetics”, “recovery”, “cardiopulmonary test”, “VO2peak” and “heart failure”. The articles used are indexed in the Medical Literature Analysis and Retrieval System Online (Medline) databases, consulted in PubMed, Scientific Electronic Library Online (SciELO), Cochrane (CENTRAL) and Science Direct.The screening of the articles included in this manuscript was performed based on the analysis of whether the title and abstract met the eligibility criteria, which were elected by fulfilling the inclusion criteria and not meeting any of the exclusion criteria. Articles that met the inclusion criteria were read in full, while the articles that met any of the exclusion criteria were excluded from the selection of this review.Data extraction was performed independently by two investigators (MP & GM). For eligible studies, were extracted the authors’ name, year of publication, design of the studies, participants’ characteristics by group (number of participants by group, heart failure classification, diagnostic strategies, tests performed, treatment strategies) and the outcomes. Specifically, were extracted the main and the secondary outcomes on the correlation of VO2/t-slope and VO2peak during CPET and before and after exercise training, including results from statistical analyses.

Eligibility Criteria

Inclusion Criteria

Only manuscripts concerning measurements of oxygen kinetics during the recovery phase of CPET between HF patients and/or between HF and healthy population, with or without following a specific training period program, were chosen for this study. Specifically, the direct (mathematical) and/or the indirect (clinical) correlation between VO2/t-slope and VO2peak was the main target in each study. Eligible studies for the systematic review were considered randomized controlled trials (RCTs), observational studies (controlled, prospective, cohort and single group studies), cross-sectional and longitudinal studies and only full papers without restrictions on country of origin, language, publication date, or gender of the participants.

Exclusion Criteria

In this study, articles that were abstracts, oral or poster presentations in conferences, non-peer-reviewed manuscripts, letters to the editor, book chapters as well as unpublished papers, were

excluded. We had also excluded animal studies, reviews, case reports and editorials; however, we screened the reference lists of such publications and of the retrieved articles for relevant papers. Studies without any clinical and/or the mathematical correlation between VO2/t-slope and VO2peak, indicating only the correlation of these markers with other metabolic or respiratory indices were excluded.
Study Selection
Four databases were consulted to find 548 articles and of these 458 duplicated articles were excluded from more than one database, resulting in 90 articles. In addition, 69 articles were not included in the analysis because of the non-correlation direct or indirect between VO2peak and VO2/t-slope. Thus, out of a total of 542 articles, 10 were selected, according to the eligibility criteria for the study, which represents 0.018% of all the articles found.. The articles were in English.

Participant or population Patients profile and clinical manifestation
The patients of the selected articles in the systematic reviews presented an age between 30 and75 years old, Body mass index between 21-35, HF of all possible NYHA and Weber classification levels, ejection fraction>15%, they were males and females (more males rather than females) and they were under optimum HF treatment.
Groups and Diagnostic tests
Five of the selected articles had control groups (5% of the selected articles), 3 examined groups based of HF classification (3% of the selected articles) and 1 subgroups of HF classification (1% of the selected articles). In one of the selected articles (1% of the selected articles) the outcomes were validated after submaximal and after maximal CPET, in the rest 9 articles (9% of the selected articles) only after maximal CPET.

Intervention Direct-mathematical (Pearson correlation) and indirect-clinical (Proportional increase of both VO2peak and VO2/t-slope after maximal but also after submaximal CPET correlation between healthy and HF patients, between HF groups and in HF groups before and after implanting of exersice program) correlation between VO2peak and VO2/t-slope.
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Comparator Direct-mathematical (Pearson correlation) and indirect-clinical (Proportional increase of both VO2peak and VO2/t-slope after maximal but also after submaximal CPET correlation between healthy and HF patients, between HF groups and in HF groups before and after implanting of exersice program) correlation between VO2peak and VO2/t-slope.Five of the eligibility selected articles validated the outcome before and after the application of an exercise program (5% of the selected articles) and the other five validated the outcome without any exercise program.
Two of the selected articles in the systematic review (2% of the selected articles) revealed direct (mathematical and clinical) correlation between VO2peak and VO2/t-slope and nine (9% of the selected articles) indirect (clinical).

Study designs to be included Of the 10 articles selected, all are randomized controlled trials, 1 published in 1999, 1 in 2001, 1 in 2003, 1 in 2005, 3 in 2006, 1 in 2009 and 2 in 2014.The number of participants in the studies ranged from 6 to 92 patients and all articles were peer-reviewed. Nine studies were conducted in the Greece and one in Brazil.

Eligibility criteria Eligibility Criteria
Inclusion Criteria
Only manuscripts concerning measurements of oxygen kinetics during the recovery phase of CPET between HF patients and/or between HF and healthy population, with or without following a specific training period program, were chosen for this study. Specifically, the direct (mathematical) and/or the indirect (clinical) correlation between VO2/t-slope and VO2peak was the main target in each study. Eligible studies for the systematic review were considered randomized controlled trials (RCTs), observational studies (controlled, prospective, cohort and single group studies), cross-sectional and longitudinal studies and only full papers without restrictions on country of origin, language, publication date, or gender of the participants.
Exclusion Criteria
In this study, articles that were abstracts, oral or poster presentations in conferences, non-peer-reviewed manuscripts, letters to the editor, book chapters as well as unpublished papers, were excluded. We had also excluded animal studies, reviews, case reports and editorials; however, we screened the reference lists of such publications and of the retrieved articles for relevant papers. Studies without any clinical and/or the mathematical correlation between VO2/t-slope and VO2peak, indicating only the correlation of these

markers with other metabolic or respiratory indices were excluded.

Information sources The literature review used databases in which all studies reporting clinical and/or the mathematical correlation of VO2/t-slope and VO2peak between HF patients and/or between HF and healthy population, with or without following a specific training period program. The following descriptors were used: "VO2/t-slope", "oxygen kinetics", "recovery", "cardiopulmonary test", "VO2peak" and "heart failure". The articles used are indexed in the Medical Literature Analysis and Retrieval System Online (Medline) databases, consulted in PubMed, Scientific Electronic Library Online (SciELO), Cochrane (CENTRAL) and Science Direct.

Main outcome(s) Direct-mathematical (Pearson correlation) and indirect-clinical (Proportional increase of both VO2peak and VO2/t-slope after maximal but also after submaximal CPET correlation between healthy and HF patients, between HF groups and in HF groups before and after implanting of exersice program) correlation between VO2peak and VO2/t-slope.

Additional outcome(s) Respiratory and skeletal muscles histological and biochemical alterations due to HF, could explain the delayed VO2/t-slope in HF population. Clinical superiority of VO2/t-slope in diagnosis and prognosis of HF, especially in advance stages of the disease, since is independent from the duration and the intensity of the CPET.

Data management The results of the data extraction procedure are shown in Table I. Data extraction was performed independently by two investigators (MP & GM). For eligible studies, were extracted the authors' name, year of publication, design of the studies, participants' characteristics by group (number of participants by group, heart failure classification, diagnostic strategies, tests performed, treatment strategies) and the outcomes. Specifically, were extracted the main and the secondary outcomes on the correlation of VO2/t-slope and VO2peak during CPET and before and after exercise training, including results from statistical analyses.

Quality assessment / Risk of bias analysis To reduce the risk of bias, all studies included in this manuscript underwent peer review. To assess the quality in each study, the PEDro scale from the Physiotherapy Evidence Database was adopted. The PEDro scale is a valid measure of the methodological quality of clinical trials, particularly when evaluation of internal validity is needed. The scale consists of 11 items (maximum score=10) and the assessment of the quality in each study was independently estimated by two-investigators authors. Conflicts in the risk of bias assessment were resolved by a third reviewer to reach a consensus.
Since all the selected studies were randomized control clinical trials with high level of evidence and methods structure, the average score on the PEDro scale regarding the selected manuscripts was 8/10, representing satisfied quality.

Strategy of data synthesis Data extraction was performed independently by two investigators (MP & GM). For eligible studies, were extracted the authors' name, year of publication, design of the studies, participants' characteristics by group (number of participants by group, heart failure classification, diagnostic strategies, tests performed, treatment strategies) and the outcomes. Specifically, were extracted the main and the secondary outcomes on the correlation of VO2/t-slope and VO2peak during CPET and before and after exercise training, including results from statistical analyses.
Study Selection
Four databases were consulted to find 548 articles and of these 458 duplicated articles were excluded from more than one database, resulting in 90 articles. In addition, 69 articles were not included in the analysis because of the non-correlation direct or indirect between VO2peak and VO2/t-slope. Thus, out of a total of 542 articles, 10 were selected, according to the eligibility criteria for the study, which represents 0.018% of all the articles found. The articles were in English.
Study Characteristics
Of the 10 articles selected, all are randomized controlled trials, 1 published in 1999, 1 in 2001, 1 in 2003, 1 in 2005, 3 in 2006, 1 in 2009 and 2 in 2014.The number of participants in the studies ranged from 6 to 92 patients and all articles were peer-reviewed. Nine studies were conducted in the Greece and one in Brazil.
Risk of Bias within the studies
The results of the quality assessment are presented in Table II. Since all the selected studies were randomized control clinical trials with high level of evidence and methods structure, the average score on the PEDro scale regarding the selected manuscripts was 8/10, representing satisfied quality.
Patients profile and clinical manifestation
The patients of the selected articles in the systematic reviews presented an age between 30 and75 years old, Body mass index between 21-35, HF of all possible NYHA and Weber classification

levels, ejection fraction>15%, they were males and females (more males rather than females) and they were under optimum HF treatment.
Groups and Diagnostic tests
Five of the selected articles had control groups (5% of the selected articles), 3 examined groups based of HF classification (3% of the selected articles) and 1 subgroups of HF classification (1% of the selected articles). In one of the selected articles (1% of the selected articles) the outcomes were validated after submaximal and after maximal CPET, in the rest 9 articles (9% of the selected articles) only after maximal CPET.
Clinical Outcomes
Five of the eligibility selected articles validated the outcome before and after the application of an exercise program (5% of the selected articles) and the other five validated the outcome without any exercise program.
Two of the selected articles in the systematic review (2% of the selected articles) revealed direct (mathematical and clinical) correlation between VO2peak and VO2/t-slope and nine (9% of the selected articles) indirect (clinical).

Subgroup analysis Five of the 10 selected articles in order to form the systematic review, had control groups (5% of the selected articles), 3 examined groups based of HF classification (3% of the selected articles) and 1 subgroups of HF classification (1% of the selected articles). In one of the selected articles (1% of the selected articles) the outcomes were validated after submaximal and after maximal CPET, in the rest 9 articles (9% of the selected articles) only after maximal CPET.

Sensitivity analysis N/A.

Language restriction No restriction in languages.

Country(ies) involved Greece.

Keywords VO2/t-slope, oxygen kinetics, recovery, cardiopulmonary test, VO2peak and heart failure.

Dissemination plans N.A.

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