A SYSTEMATIC REVIEW OF THE PROGNOSTIC VALUE OF CARDIOPULMONARY EXERCISE TESTING IN PATIENTS WITH DIVERSE HEART FAILURE ETIOLOGIES

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Abstract

A SYSTEMATIC REVIEW OF THE PROGNOSTIC VALUE OF CARDIOPULMONARY EXERCISE TESTING IN PATIENTS WITH DIVERSE HEART FAILURE ETIOLOGIES

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Heart failure (HF) is a condition with several possible etiologies that influence patient symptomatology, including response to exercise. The purpose of this review was to assess how cardiopulmonary exercise testing (CPET) parameters used for risk stratification differ and are associated with mortality and adverse cardiac events in patients with different HF etiologies. We completed a systematic review of studies that assessed CPET data in adult heart failure patients and reported outcomes of mortality, left ventricular assist device implantation, heart transplantation, or hospitalization. Interestingly, the optimal threshold values derived from CPET were strikingly similar for stratifying risk in patients with different HF etiologies. Even with heterogeneity in the data, the literature suggests that optimal threshold values from CPET can be applied generally without consideration of HF etiology. However, there is a need to consider a broader spectrum of HF etiologies and CPET parameters in larger and more representative study populations.

Keywords: Cardiopulmonary Exercise Testing, Heart Failure, Etiology, Ischemic Cardiomyopathy, Non-Ischemic Cardiomyopathy, Prognosis, $\dot{V}O_2$

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LIST OF ABBREVIATIONS AND SYMBOLS

ACEi – angiotensin converting enzyme inhibitors

ARB – angiotensin receptor blockers

ARNi – angiotensin receptor-neprilysin inhibitors

BB – beta blocker

BNP – B-type natriuretic peptide

CPET – cardiopulmonary exercise test

COPD – chronic obstructive pulmonary disorder

CRT – cardiac resynchronization therapy

EF – ejection fraction

GDMT – guideline directed medical therapy

HF – heart failure

HFpEF – heart failure with preserved ejection fraction

HFrEF – heart failure with reduced ejection fraction

HR – hazard ratio

HTx – heart transplant

ICD – implantable cardioverter defibrillators

LV – left ventricle

LVAD – left ventricular assist device

LVEF – left ventricular ejection fraction

MRA – mineralocorticoid receptor agonist

OUES – oxygen uptake efficiency slope

p$\dot{V}O_2$ – peak oxygen consumption

QOL – quality of life

RAAS – renin-angiotensin-aldosterone system

RER – respiratory exchange ratio

RV – right ventricle

SNS – sympathetic nervous system

SGLT2i – sodium glucose cotransporter 2 inhibitors

VAT – ventilatory anaerobic threshold

$\dot{V}CO_2$ – carbon dioxide output

$\dot{V}$**E** – minute ventilation

6MWT – six-minute walk test

μ – mean

%pp$\dot{V}\mathbf{O_2}$ – percent predicted peak oxygen consumption

GLOSSARY

Aerobic Metabolism – During normal activity, the body uses oxygen and carbohydrates for energy.

Anaerobic Metabolism – During intense exercise, muscle demand for oxygen increases, so the body will switch to making energy without oxygen, thus creating lactic acid.

Cardiopulmonary Exercise Test – a clinical method used to quantify a participants exercise capacity while monitoring cardiovascular and pulmonary response to the stress of exercise.

Ejection Fraction – The percentage amount of blood pumped out of the left ventricle with each beat, relative to the total amount of blood in the ventricle.

Etiology – the cause, or causes, of a disease.

Heart failure – a condition where the heart is no longer able to properly circulate blood throughout the body.

Hemodynamics – how blood flows throughout the blood vessels and the mechanisms that control it

Ischemic Cardiomyopathy – damage to the heart muscle caused by reduced blood supply (i.e., heart attack, stroke, coronary artery disease)

Narrative Synthesis – The practice of summarizing findings or results from several different studies primarily using words.

Non-ischemic Cardiomyopathy – damage to the heart muscle caused by other factors such as genetic mutations or viral infections (i.e., myocarditis)

Prognosis – The practice of forecasting the course or outcome of an illness.

Sympathetic Nervous System – Responsible for the stress response in the body, including increased respiration rate, heart rate, and blood pressure.

CHAPTER 1: INTRODUCTION AND LITERATURE REVIEW

Thesis Organization

This thesis consists of three chapters which will follow a manuscript-based format with a single chapter written as a publishable journal article. The first chapter contains background information on the thesis topic and its constituent parts, including the research question and hypotheses. Chapter 2 contains a scientific article in its publishable form. It is a systematic review that aimed to assess how heart failure (HF) etiology impacts the predictive value of cardiopulmonary exercise testing (CPET). Chapter 3 revisits the key findings of the systematic review and summarizes important takeaways and future directions before concluding the thesis.

Heart Failure Epidemiology

Heart failure is a major global health concern with significant morbidity, mortality, and significant economic costs (Benjamin, 2018). As of 2020, the global prevalence of HF was roughly 64 million cases, with the cost of managing HF at an estimated 350 billion USD, burdening healthcare systems worldwide (Lippi, 2020). In Canada, there are 750 thousand people living with HF, with more than 100 thousand additional cases diagnosed annually. Economically, the Canadian Cardiovascular Society highlights HF as one of the top reasons for hospital admissions with monetary costs expected to exceed $2.8 billion CAD per year by 2030 (CCS, 2024). Even more worrisome is that the hospital readmission rate for HF patients has remained steady over the past decade defying the significant advances in medical therapy.

Several factors may be contributing to the growing problem of HF in Canada. In 2021, the Heart and Stroke Foundation conducted a poll that found approximately 1 in 3 people are impacted by HF in some capacity, whether that be personal, family, or a close friend. Yet, 4 in 10 Canadians do not understand what heart failure is, and 2 in 3 Canadians do not know that there is no cure once diagnosed (Heart and Stroke, 2022). This lack of patient understanding makes an already complex condition even more difficult to treat.

Another serious barrier in HF management is inequities in care. Less than 70% of eligible patients are receiving appropriate medications, while fewer than 30% of Canadian HF patients are achieving their recommended target medication doses (CCS, 2024). Sex, race, and socioeconomic status all influence the availability of healthcare, specifically highly specialized HF care. For example, smaller communities, such as those in the northern regions of Canada, lack access to cardiovascular specialists. Indigenous communities also suffer from disproportionately high rates of HF, and HF related death when compared to other communities in Canada (Heart and Stroke, 2024; Vervoort, 2022).

The current HF care system also falls short in multiple facets of implementing the services and treatments recommended in the Canadian Cardiovascular guidelines for HF management, which makes diagnosing and treating HF increasingly difficult. For example, across all Canadian hospitals, 28.7% of HF patients did not have access to B-type natriuretic peptide testing, a useful marker of HF, and only 48.1% of HF patients had access to onsite echocardiography, both of which are key components of HF diagnosis

(Moghaddam, 2023). Additionally, the complexity of HF necessitates specialized medications and highly trained specialists. However, only 12.2% of HF care from 2020-2021 was provided by centres with specialized resources and expert providers (Heart and Stroke, 2024, Moghaddam, 2023). Accessibility to specialized care makes a huge difference in patient outcomes, with those treated in such settings experiencing much lower rates of rehospitalization (Heart and Stroke, 2024).

Heart Failure Pathophysiology

Contrary to popular belief, HF is not when the heart stops beating; it is a reduction in heart function, caused by structural or functional cardiac abnormalities that reduce the circulation of blood needed to meet the metabolic demands of the body (Greene, 2023; Bozkurt, 2021; CCS, 2024; Heart and Stroke, 2024). The result is debilitating, complex, and progressive symptoms including shortness of breath, fatigue, fluid retention, exercise intolerance, and ultimately, organ failure (Greene, 2023; Bozkurt, 2021; Yancy, 2017). Heart failure often occurs along with, or because of, the effects of several other serious health conditions such as kidney disease, diabetes, chronic obstructive pulmonary disorder, coronary artery disease, hypertension, valvular disease, or genetic predispositions that lead to impaired ventricular filling (diastolic dysfunction) or decreased contractility (systolic dysfunction; Ponikowski, 2016, heart and stroke, 2024).

Classifying by Ejection Fraction

There are several different classifications of HF based on the structural and functional abnormalities a patient presents with. Heart failure with reduced ejection fraction (HFrEF), or systolic heart failure, occurs when the left ventricle (LV) struggles

to contract and properly empty blood from the heart into the vasculature of the body. This leads to a backlog of fluid, increasing diastolic volume and pressure (Fine, 2022). Individuals who have a left ventricular ejection fraction (LVEF) ≤ 40%, are considered to have HFrEF. The most common causes of HFrEF include uncontrolled hypertension, myocardial infarction, myocarditis, or dilated cardiomyopathy (Fine, 2022; Schwinger, 2021). As such, HFrEF patients typically present with remodelling of the heart in the form of chamber dilation, which contributes to the volume overload and decreased contractility needed to eject blood from the LV, often referred to as forward HF (Schwinger, 2021).

Patients can have heart failure with preserved ejection fraction (HFpEF), or diastolic heart failure, which is when the filling, rather than the emptying, of the LV is impaired. This also leads to a backlog of fluid and increased diastolic pressure; however, diastolic volume typically remains normal because the LV maintains its contractility and ability to produce a normal LVEF ≥ 50% (Fine, 2022). The most common causes of HFpEF are active processes that prevent ventricular relaxation such as valvular disease, constrictive pericarditis, and hypertrophic cardiomyopathy (Fine, 2022). Patients with HFpEF more commonly present with chamber constriction due to ventricular stiffness, making it more difficult for blood to enter the LV, which is why it is often referred to as backward HF (Schwinger, 2021).

Lastly, those patients with a LVEF from 41-49%, are classified as having HF with mildly reduced ejection fraction (HFmrEF), and can be seen as a distinct population, or a combination of those with HFpEF and HFrEF (Fine, 2022).

Classifying by Location

Heart failure affects the entire heart, but it can also be classified based on the side of the heart containing the pathology responsible for the overall dysfunction. In left-sided HF, the LV fails to eject a sufficient volume of blood to the body causing a volume and pressure overload. This leads to increase pulmonary pressure and congestion that makes it increasingly difficult to breath, leading to dyspnea or tachypnoea (Fine, 2022; Schwinger, 2021). Additionally, this backlogged fluid leaks into the capillaries, interstitial space, and alveoli accumulating over time and causing pulmonary edema, or fluid in the lungs, further increasing the work required to breathe (Fine, 2022). Left HF is usually the result of ischemic heart disease, or damaged heart muscle from injuries like heart attack, hypertension, aortic stenosis, cardiomyopathies, or birth defects.

On the other side, right HF is most commonly the product of chronic LV dysfunction. In this case, the right ventricle (RV) is unable to pump blood to the lungs causing increased intravenous pressure and consequent peripheral and abdominal edema (Fine, 2022; Konstam, 2018). Failure in the RV often leads to liver dysfunction, which means the breakdown of aldosterone is reduced, intensifying fluid accumulation, and leading to chronic venous congestion (Fine, 2022). This can be especially problematic in the viscera, or abdominal organs, as it can hinder the digestive system leading to malabsorption of nutrients, anorexia, and other related ailments (Fine, 2022). The most common causes of right HF are pulmonary hypertension, valvular dysfunction, and pericardial diseases (Ibrahim, 2016).

The Body's Response to Heart Failure Progression

Interestingly, part of the pathophysiology driving the progressive nature of HF are the body's own compensatory mechanisms aimed at maintaining cardiac output and tissue perfusion. For example, the stress of HF triggers the activation of neurohumoral systems, such as the renin-angiotensin-aldosterone system (RAAS) and vasopressin pathway, which work to maintain a healthy blood pressure (BP) and to deliver oxygen to the periphery. However, chronic activation of these systems can cause hormonal imbalances that enhance myocardial damage (Fine, 2022). The RAAS and Vasopressin systems decrease renal excretion of water, increasing fluid retention in response to low BP, increasing the workload on the heart and worsening symptoms (Fine, 2022; Pharm, 2024).

The sympathetic nervous system (SNS), responsible for the body's stress response, is another compensatory mechanism in patients with heart failure; however, its hyperactivation further hinders cardiac function (Pharm, 2024). In patients with physically strenuous diseases such as HF, the SNS can become hyperactive in its role of increasing contractility and vasoconstriction, which causes an imbalance in the body's ability to regulate the heart, amplifying the effects of HF (Pharm, 2024). Although these innate responses by the body are an attempt to compensate for HF, they often exacerbate deterioration and disease progression (Schwinger, 2021).

Diagnosing Heart Failure

Diagnosing heart failure is a multi-step process involving patient history, physical examination, cardiac imaging (e.g., echocardiography, cardiac magnetic resonance

imaging), and assessment of hemodynamic biomarkers (e.g., B-type natriuretic peptide) (Yancy, 2017).

Patient History

First, when diagnosing HF, it is important to collect a detailed patient history to better understand underlying medical conditions, symptoms, and patient functional capacity (Malik, 2023). For example, physicians frequently ask patients about previous chest pain or heart attack because this is indicative of coronary artery disease, which is responsible for roughly 75% of HFrEF cases (Shamsham, 2000). Further, taking a thorough history of patients that present with acute heart failure, or sudden weakening of the heart, is essential to identify the triggers of acute decompensation such as recent infection, medication noncompliance or increased sodium consumption (Malik, 2022).

Physical Examination

At the physical examination stage, findings will vary depending on the severity of the condition. Chest examination classically reveals pulmonary rales, which are clicking or rattling sounds in the lungs with inhalation. Another classical finding in patients with HF is jugular venous distention (Malik, 2023; Thibodeau, 2018). In this assessment, the patient lays supine at a 45-degree angle with their head tilted back; in patients with HF, there will be visible bulging of the external jugular vein 4-5cm from the top of the sternum, as blood is unable to flow through the heart as it should, causing elevated blood pressure (Shamsham, 2000; Malik, 2023; Thibodeau, 2018). In a similar fashion, hepatojugular reflux is assessed through a clinician applying pressure over the liver for 30-60 seconds with the patient laying in the same 45-degree supine position. If the height

of the neck veins increases by 3-4cm for the duration of the compression period, it is indicative of hepatic congestion and failure of the RV to accommodate the increased venous return, hallmark signs of HF (Malik, 2023, Shamsham, 2000; Omar, 2017). There are also audible queues that inform physicians about the presence and cause of heart disease. The presence of murmurs, which are abnormal heart sounds due to turbulent blood flow in the heart, are often found in patients with HF (Shamsham, 2000; Malik, 2023)

Cardiac Imaging

Another key component to making a HF diagnosis, or understanding the severity of the condition, is through non-invasive cardiac imaging techniques. An electrocardiogram (ECG) is an extremely useful tool for visualizing atrial and ventricular arrhythmias (Shamsham, 2000). Although no part of an ECG can specifically indicate HF, it is able to show signs of prior infarction, enlarged chambers, and electrical conduction delays, which help better understand the condition and guide future HF therapy decisions (Malik, 2023). Chest radiography on the other hand, can be directly applied to a HF diagnosis. Findings such as an enlarged cardiac silhouette, fluid in the lungs, and vascular congestion are indicative of HF (Malik, 2023; Shamsham, 2000). Often the go-to mode of cardiac imaging in suspected HF patients is echocardiography (Echo) due to its accessibility and useful information (Malik, 2023). Echo studies provide insight into the structural integrity of the heart's chambers and valves, while quantifying left and right ventricular function (Malik, 2023; Shamsham, 2000). The Echo is how clinicians determine information such as valve regurgitation and LVEF, which can be used to classify HF patients and guide future therapies.

Hemodynamics

Hemodynamic biomarkers can also provide key details that may lead clinicians to a HF diagnosis. For example, elevated serum B-type natriuretic peptide (BNP) or N-terminal pro-BNP (NT-ProBNP) can help differentiate between cardiac and non-cardiac causes of dyspnea (Malik, 2023). BNP is mainly synthesized by myocytes in the LV in response to ventricular stretching caused by pressure overload or volume expansion, which are common in patients with HF (Cao, 2019). Therefore, the worse the HF, the more chronic the stretching, and the higher one's BNP levels will be. Similarly, NT-ProBNP is the chemically inactive form of BNP, which gives it more stability and a longer half-life making it more reliable in diagnosing and monitoring HF (Ponikowski, 2016). It is worth noting that both BNP and NT-ProBNP levels can be abnormal in patients with other conditions. For example, in patients with kidney disease, blood filtration is impaired allowing BNP levels to continue circulating in the body, compounding its concentration (Takase, 2014). Conversely, in patients with obesity, glomerular filtration rates are significantly elevated, meaning these people are simply clearing BNP levels at a much higher rate (Malik, 2023; Madamanchi, 2014).

Managing Heart Failure

Once diagnosed with HF, clinical interventions include pharmacological prescriptions, device therapies, such as implantable defibrillators, left ventricular assist devices (LVAD), cardiac resynchronization therapies, and in extreme cases heart transplantation (Yancy, 2017). There are also exercise-based rehabilitation programs for deconditioned HF patients that help improve cardiorespiratory fitness. The overarching

goal of these HF therapies is to improve symptoms and quality of life (QOL), while decreasing hospitalizations and risk of mortality (Malik, 2023).

Medications

Guideline-directed medical therapy (GDMT), is the foundation for pharmacological management of HF. The American College of Cardiology (ACC), American Heart Association (AHA), Heart Failure Society of America (HFSA), and the European Society of Cardiology (ESC), are the primary organizations referred to for guidelines around managing HF (van der Meer, 2019; Severino, 2023; Patel, 2023; Heidenreich, 2022). Current GDMT guidelines for HF include four main drug classes that have been shown to improve survival and reduce the risk of HF related hospitalizations (Severino, 2023; Patel, 2023).

The first class is beta blockers (BB), which reverse the neurohumoral effects of the SNS. Through competitive binding to beta-adrenergic receptors that otherwise trigger activation of the RAAS, BB reduce heart rate and blood pressure, while widening the vasculature leading to improved blood flow and alleviation of HF symptoms (Masarone, 2021; Patel, 2023). In randomized control trials, BB have been consistently shown to reduce mortality, prevent arrhythmia, and improve LVEF in patients with HF (Bristow, 2011).

Second are mineralocorticoid receptor agonists (MRA), which block the effects of mineralocorticoids, such as aldosterone, in the RAAS (Patel, 2023). Aldosterone plays a key role in HF pathophysiology by promoting kidney damage by promoting sodium reabsorption, leading to myocardial hypertrophy and reduced myocardial perfusion

(Jadhav, 2023). Therefore, MRA help regulate sodium excretion, blood volume, and thus blood pressure, decreasing the risk of cardiovascular events (Jadhav, 2023; Patel, 2023).

Third, there are sodium glucose cotransporter 2 inhibitors (SGLT2i), which were initially intended to be used as oral hypoglycemics in the treatment of diabetes (Patel, 2023). However, they have been found to have cardiovascular benefits, especially in those with HF. Interestingly, cardiac muscles are not believed to have SGLT2i receptors, so the exact mechanism for HF patients experiencing cardioprotective benefits is not entirely understood (Sharath, 2024). Despite this, several studies assessing cardiovascular events, have almost unanimously shown that SGLT2i can improve outcomes across all HF phenotypes, irrespective of diabetes status (McMurray, 2019; Packer, 2021; Sharath, 2024; Patel, 2024).

Lastly, are the direct inhibitors of the RAAS, which effectively work to control blood pressure. The RAAS system plays a significant role in HF as it is responsible for sodium retention and hypertension (Signhania, 2020). The RAAS drug class can be further divided into angiotensin receptor-neprilysin inhibitors (ARNi), angiotensin receptor blockers (ARB), and angiotensin converting enzyme inhibitors (ACEi; Patel, 2023).

Neprilysin is an enzyme that breaks down natriuretic peptides leading to vasoconstrictive effects (Singhania, 2020; Patel, 2023). The PARADIGM-HF trial reshaped the landscape of HF GDMT when they showed that combining an ARNi with an ARB led to a significant reduction in the risk of death and rehospitalizations (McMurray, 2014; Singhania, 2020, Patel, 2023). Since then, ACC/AHA/HFSA

guidelines have included ARNi as a first-line agent in the management of HF (Heidenreich, 2022; Patel 2023).

The hormone angiotensin II has long been understood as a key substrate in the neurohormonal pathway of chronic HF (Patel, 2023). After ACEi and BB were long used as a therapeutic agent for HF, the Val-HeFT trial demonstrated that ARBs significantly reduced the incidence of the morbidity and mortality due to cardiac related events (Cohn, 2001). Additional research has shown that ARBs reverse LV hypertrophy associated with HF by blocking the AT1 receptors that bind angiotensin II and cause vasoconstriction (Singhania 2020). As such, ARBs have also become a 1A recommended therapy for managing HF (Heidenreich, 2022).

Finally, ACEis were developed as a targeted treatment for hypertension, however they were also found to have a positive effect on the hemodynamics and symptoms of HF (Brown, 1998; Patel, 2023). Through cleaving the C-terminal dipeptide from Angiotensin I and bradykinin, key peptides in the RAAS pathway, ACEi can disrupt and regulate Angiotensin II and aldosterone levels, leading to reduced blood pressure and vasodilation, alleviating HF symptoms (Brown, 1998). Further, major clinical trials, such as the SOLVD and CONSENSUS trials, have collectively established that using ACEi in the management of HF significantly reduces the risk of hospitalization and mortality (SOLVD investigators, 1991; CONSENSUS trial group, 1987; Patel, 2023).

Assistive Devices

In more severe cases of HF, patients may receive assistive devices to help support heart function. As aforementioned, device therapies such as implantable cardioverter

defibrillators (ICD), left ventricular assist devices (LVAD), and cardiac resynchronization therapies (CRT), are the most used devices to help manage patients with HF (Muthumala, 2017; Gustafsson, 2017).

ICD therapy is primarily used to prevent sudden cardiac death in HFrEF patients, as the risk of fatal arrhythmia and cardiac cessation is much greater in this population (Butler, 2022; Muthimala, 2017; Iqbal, 2023). These devices have become progressively smaller with time, with the generator now placed subcutaneously in the chest and endocardial patches attached to the venous system (Muthumala, 2017). The ICD is then able to detect life threatening arrhythmia's, at which point a shock is delivered, resynchronizing and normalizing the rhythm of the heart (Iqbal, 2023).

LVADs have become increasingly capable of acting as both a bridge-to-transplant and a long-term therapy (Gustafsson, 2017). For decades LVADs have been used as short-term solution (< 2 years) to preserve HF patients while they waited for a heart transplant (Gustafsson, 2017). However, there is a notable discrepancy between the number of hearts needed and suitable donors available. Therefore, technological advancements in recent years have allowed LVADs to be used more broadly and for extended periods of time (> 10 years) in HF patients (Gustafsson, 2017). As the name suggests, LVADs alleviate the physiological stress of HF by helping the LV provide a continuous flow of blood to the rest of the body (Capriotti, 2019).

Cardiac resynchronization therapy pacemakers (CRT-P) and cardiac resynchronization therapy defibrillators (CRT-D) are the two main types of CRT devices. In general, CRT is used in patients with abnormal electrical, and thus physical, cardiac

activation. These devices work by providing synchronized pacing of the RV and LV, correcting any cardiac desynchrony, and improving cardiac function. When comparing a CRT-P to a CRT-D there is no established guidelines distinguishing between when one should receive one device over the other. Both devices have been shown to reduce all-cause mortality, while equally improving patient symptoms and cardiac function when compared in randomized control trials (Canterbury, 2021; Muthumala, 2017).

Heart Transplantation

Heart Transplant (HTx) is the gold standard of established therapies for patients with end-stage HF (Masarone, 2023). However, with limited hearts available, only a few patients will receive a HTx, which means meticulously selecting recipients is important to ensure the best use of the limited resources (Masarone, 2023). “I NEED HELP” is a common mnemonic used in the field of HF to indicate which patients should be referred for a HTx assessment (Baumwol, 2017). This translates to:

I: Inotropes or Inodilators required by the patient.

N: NYHA class III-IV or Natriuretic plasma levels are elevated.

E: End organ dysfunction (kidney or liver dysfunction due to heart failure).

E: Ejection fraction <20% (HFrEF).

D: Defibrillator shocks (appropriate and chronic).

H: Hospitalizations (2 or more HF related hospital visits).

E: Edema (increased fluid retention or increasing diuretic dosages).

L: Low blood pressure (systolic < 90–100 mmHg).

P: Prognostic medications (GDMT intolerance).

Each of these clinical traits is a red flag when it comes to HF prognostication and need for HTx assessment (Masarone, 2023; Baumwol, 2017). Patients that are selected for and successfully receive a HTx, report a better QOL and significant symptom relief when compared to their non-transplanted counterparts (Carvalaho, 2021; Jalowiec, 1997).

Exercise Rehabilitation

Traditionally, rest was recommended for patients with HF (O'Connor, 2009). However, over the past two decades research has shown deconditioning to be a major contributor to HF progression (O'Connor, 2009). Today, exercise-based rehabilitation is widely used in patients with both chronic and acute HF as it has been shown to improve cardiac functional capacity and QOL, while decreasing risk for cardiac events (O'Connor, 2009; Molloy, 2024; Liang, 2024). Since patients with HF have a limited exercise capacity, common rehabilitation activities include a combination of light aerobic exercise with strength, balance, and flexibility training (Liang, 2024). The world's largest multicentre randomized control trial of exercise in HF, called HF-Action, has been used to show that after adjusting for prognostic factors exercise training significantly reduced all-cause mortality and all-cause hospitalization, while improving health-related QOL (O'Connor, 2009). Essentially, the HF-Action trial helped solidify prescribed exercise training as a therapeutic approach to managing HF.

Exercise tests used to track patient progress in cardiac rehabilitation programs, such as the six minute walk test (6MWT) and CPET, are also frequently used to prognosticate risk for cardiac events and play a considerable role in determining HTx eligibility in the clinical setting. The 6MWT is the most readily used exercise test based

on its ease of use, low cost, and tolerability to patients (Giannitsi, 2019). The 6MWT is a submaximal assessment in which the participant walks as far as they can on a flat surface in six minutes (Giannitsi, 2019). While a poor 6MWT performance has been consistently shown to predict varying outcomes of mortality, hospitalization, and poor QOL, there is little information available about what is driving the exercise intolerance (Forman, 2012; Giannitsi, 2019). As such, the CPET, which provides a far more comprehensive look into patient functional capacity is considered the gold standard of exercise testing in patients with HF (Forman, 2012).

Cardiopulmonary Exercise Testing

Cardiopulmonary exercise testing is a clinical tool used to comprehensively assess the function of the cardiovascular, respiratory, and musculoskeletal systems during exercise (Albouaini, 2007). This mode of patient assessment provides comprehensive insight into an individual's physiological responses to exertion, offering clinicians a nuanced understanding of a patient's exercise capacity and cardiorespiratory fitness through hemodynamics, ventilatory gas exchange data, and the responses of various organ systems to stress (Malhotra, 2016; Myers, 2009). This information is tremendously advantageous for making cardiovascular and pulmonary diagnoses, prognostication, and tracking disease progression (Dores, 2024; Balady, 2010). As such, CPET is considered the gold standard across the globe when it comes to assessing cardiorespiratory fitness (Zannoni, 2023; Malhotra, 2016). The unanimous valuing of CPET implies that it should be one of, if not the first, test used when it comes to identifying sources of exercise intolerance (Glaab, 2022). While CPET is widely used and recommended by several scientific societies across an array of fields, it is still underused primarily due to the lack

of trained personnel equipped with the skills to interpret its complexities, and practicing clinicians being unaware of its utility and availability (Balady, 2010; Guazzi, 2016).

Prior to a CPET, patients should continue taking their normal medications and wear comfortable clothing appropriate for exercise. The early stages of a CPET includes patients being attached to a metabolic cart, a 12-lead ECG that monitors HR and BP, and a pulse oximeter that collects oxygen saturation at rest. Once the patient is deemed fit to proceed, the test begins with a 2-minute warm-up period of unloaded cycling, or treadmill walking, that helps control for any confounding premature hyperventilation caused by nerves or initial discomfort. Patients then begin exercise, on a cycle ergometer or treadmill, against a standardized protocol that increases workload with time. While there are several different protocols that can be used interchangeably based on the patients' abilities, the most common protocols used are the ramp protocol of 10W per minute on the cycle ergometer (Glaab, 2022), or by treadmill following the standardized or modified Bruce protocol (Takken, 2009). All standardized CPET protocols follow some pattern of increasing work rate over time, whether it be continuous or incrementally, the goal is to push the patient to a symptom-limited maximal effort.

The metabolic cart collects breath-by-breath gas exchange data to derive three key parameters: O_2 uptake ($\dot{V}O_2$), CO_2 Output ($\dot{V}CO_2$), and minute ventilation ($\dot{V}E$). Peak $\dot{V}O_2$ ($p\dot{V}O_2$) is widely considered to be the most objective measure of patient functional capacity and is calculated as $HRmax \bullet SV_{max} (CaO_2 - C\dot{V}O_2)_{max}$, where SV is stroke volume and ($CaO_2 - C\dot{V}O_2$) is the oxygen extraction of the peripheral tissues, or arterial oxygen content minus venous oxygen content (Lala, 2021). From these three parameters,

several other parameters are mathematically derived, as presented in the appendix (Table A; Malhotra, 2016). For example, the ventilatory efficiency is a submaximal parameter derived from a ratio of minute ventilation ($\dot{V}$E) to work rate ($\dot{V}CO_2$) during exercise ($\dot{V}E/\dot{V}CO_2$), whereas the respiratory exchange ratio (RER) is a ratio of CO_2 being produced to O_2 consumed during exercise. At most clinical institutions, a patient's maximal effort is quantified by reaching an RER > 1.05 or 1.10. Achieving an RER > 1 indicates a switch from aerobic to anaerobic metabolism, resulting in the non-metabolic buffering of CO_2 and lactic acid build-up, indicating maximal effort (Lala, 2021). Additional parameters include the ventilatory anaerobic threshold (VAT), VAT @ $\dot{V}E/\dot{V}CO_2$, and oxygen uptake efficiency slope (OUES). The ventilatory anaerobic threshold is the earliest timepoint at which a patient's skeletal muscle switches from aerobic to anaerobic metabolism during exercise, leading to the production of lactic acid that requires bicarbonate buffering, causing a disproportionate increase in $\dot{V}$E relative to $\dot{V}O_2$ and, thus a divergence detectable by the V-slope method (Malhotra, 2016). Oxygen uptake efficiency slope is based on the relation between $\dot{V}O_2$ (ml/min) and minute ventilation ($\dot{V}$E; L/min) and is calculated as follows, $\dot{V}O_2$ = OUES • log $\dot{V}$E + b (Baba, 1996).

By measuring these hemodynamic and ventilatory parameters throughout graded exercise, and at peak exertion, CPET enables the precise identification of limitations within the cardiovascular or pulmonary systems (Malhotra, 2016). From there, clinicians and other practitioners can assess treatment efficacy, stratify risk, and guide clinical decision-making, such as formulating personalized exercise prescriptions for rehabilitation. In more extreme cases, CPET plays a pivotal role in determining which

patients are eligible for, and needing of, advanced therapies such as defibrillator implantation, left ventricular assist device, or heart transplantation (Malhotra, 2016).

Cardiopulmonary Exercise Testing in Heart Failure

Cardiopulmonary exercise testing has evolved into one of the most valuable diagnostic and prognostic tools across many clinical specialties; however, it is particularly useful in assessing the underlying pathophysiology of HF (Leclerc, 2017). CPET-derived parameters, such as $p\dot{V}O_2$, are robust predictors of adverse outcomes in HF (Malhotra, 2016). $p\dot{V}O_2$ is an objective measure used to help determine HF patient prognosis. It has been repeatedly shown that lower $p\dot{V}O_2$ correlates with increased mortality, hospitalizations, and poorer quality of life (Malhotra, 2016; Chaudhry, 2023; Swank, 2012; Myers, 2013). As such, $p\dot{V}O_2$ and other CPET-derived parameters help guide risk stratification and decisions about treatment of HF patients (Corra, 2018; Lewis, 2021). For example, CPET indicates which individuals appear clinically disabled, but would greatly benefit from rehabilitation in the form of exercise prescriptions versus those who are truly limited due to the heart function and needing of advanced therapies. As technology continues to advance, CPET is increasingly valuable in establishing clinical guidelines for HF management, playing a key role in comprehensive cardiovascular assessment and risk stratification (Yancy, 2017). American College of Cardiology and American Heart Association guidelines (Heidenreich, 2022) classify CPET as a valuable tool for defining unexplained dyspnea, assessing functional capacity before or after cardiac surgery or transplantation, and therapy optimization (Balady et al, 2010).

Ongoing research exploring novel biomarkers (Costache, 2022) and integrating CPET data with digital health platforms and artificial intelligence algorithms (Inbar, 2021) is showing promising results. Interestingly, a preliminary study showed an AI algorithm can correctly classify patients as having chronic obstructive pulmonary disorder (COPD), HF, or being healthy solely from CPET data to a high degree of accuracy and precision with a predictive power of 96-100% and a sensitivity and specificity of 99% (Inbar, 2021). Future CPET related research may include larger and more complex populations with various pathologies and exercise limitations with the goal of further enhancing the predictive value, and clinical utility, of CPET in tailoring treatment strategies and improving outcomes for HF patients.

Heart Failure Etiologies

The etiology of HF refers to the comorbidities or injuries that lead to its development, such as congenital or acquired structural changes in the heart, lifestyle choices, coronary artery disease, heart attack, hypertension, valvular disease, or various cardiomyopathies (ischemic, idiopathic, hypertrophic, restrictive, etc.) (Cubero, 2004). Ischemic cardiomyopathy, which is damage to the heart muscle due to reduce blood supply, is the most common cause of HF; with COPD, hypertension and rheumatic heart disease also contributing significantly to the HF population (Malik, 2023). These four etiologies make up two-thirds of all HF cases (Malik, 2023). Damage and inflammation of the airways are associated with COPD, leading to poor gas exchange and low oxygen levels causing a chronic rise in BP and eventually HF (Khalid, 2021). Hypertension, or high blood pressure, induces mechanical stress on the heart muscle that eventually causes the heart to fail (Malik, 2022). As the name indicates, rheumatic heart disease arises from

rheumatic fever, which is an autoimmune response to a strain of streptococci infection that is also the leading cause of cardiovascular mortality in young individuals (Liu, 2015). Inflammation associated with rheumatic fever most commonly leads to valvular disease that eventually translates to HF due to the inability of the heart to properly circulate blood (Malik, 2023).

Impact of Etiology on Heart Failure Response to Exercise

It is well documented that the etiology of heart failure can uniquely influence the functionality of the myocardium and nervous system skewing hemodynamics, ventricular filling, and contractility (Notarius 2007, Pina 2003). Understanding how these etiological factors influence the heart's response to exercise is crucial for interpreting CPETs accurately and to help ensure optimal patient outcomes. For example, one study demonstrated that HF patients with ischemic cardiomyopathy have greater sympathetic outflow at rest, which means these people are more likely to experience hypertension and vasoconstriction of their blood vessels than those with non-ischemic dilated cardiomyopathy (Notarius, 2007). Another study comparing HF patients with a similar level of cardiac dysfunction explained that patients with ischemic HF are more likely to have peripheral vascular disease that could be limiting to exercise capacity whereas non-ischemic HF patients may have skeletal muscle myopathy hindering exercise performance (Clark, 1997). As such, etiology specific symptoms may hinder exercise performance independent of HF. Further, p$\dot{V}O_2$ has consistently been shown to be lower in patients with ischemic vs non-ischemic cardiomyopathy (Notarius, 2007; Arena, 2005). In a case-controlled study of HF patients with similar LV dysfunction, p$\dot{V}O_2$ was more severely reduced in patients with ischemic versus non-ischemic HF, while other

measures of exercise capacity followed a similar pattern (Juillière, 2000). A proposed reason behind the poorer exercise response of ischemic HF patients is that the left ventricle might have a worse preserved adaptation to excessive wall stress during exercise in ischemic than in non-ischemic HF (De Feo, 2005). In terms of outcomes in HF patients with different etiologies, ischemic HF has also been consistently shown to be associated with an increased risk of mortality compared to patients with non-ischemic HF (Likoff, 1987, Juillière, 2000). Given the pathophysiological variability of HF, patient response to exercise, and thus clinical prognosis, may be dependent on the etiology of the HF (Arena, 2005; Juilièrre, 2000).

Since the 1980s-90s, it has been repeatedly shown that careful measurement of CPET parameters in HF patients can indicate disease severity, patient prognosis, and the combination of factors which are driving exercise intolerance (Malhotra, 2016). However, many of the modern-day thresholds used to determine risk were established in the general HF population, independent of subgroup analyses. For example, the pioneering study by Mancini et al. (1991) found that patients with a $p\dot{V}O_2 > 14.0$ ml/kg/min have significantly higher survival rates at 1- and 2-years with 94% and 84% respectively. A notable limitation of this study, which was acknowledged by the authors, was the homogeneity across their 122 study participants (Mancini, 1991). The entire sample consisted of HF patients with reduced ejection fraction (EF < 40%) and an etiology of either coronary artery disease or dilated cardiomyopathy. Heart failure is a far more complex condition with a plethora of possible etiologies that affect disease mechanics and patient symptomatology (Malhotra, 2016, Arena, 2005).

Current Reviews

There is ample evidence supporting the use of CPET in the diagnosis and management of HF. However, there are relatively few systematic reviews and meta-analyses available in which the importance of CPET in the prognostication of the HF population is assessed. While the support for CPET in HF is consistent, there is a lack of standardization in how the evidence is reported. As such, completing qualitative and quantitative syntheses where possible is a useful way to consolidate and exemplify the robust evidence available.

One systematic review and meta-analysis was particularly applicable to my thesis. In said review, the authors investigated the prognostic value of a variety of CPET derived variables for the outcome of cardiovascular events (mortality, HTx, LVAD) in patients with HF (Cahalin, 2020). Through standard literature searching methods, the authors identified 30 articles aimed at determining the prognostic value of index CPET variables in patients with systolic HF (HFrEF), thus meeting their inclusion criteria (Cahalin, 2020). Separate analyses were completed for each of the CPET variables of interest as not every study included results for the same CPET variables. Ultimately, p$\dot{V}O_2$, $\dot{V}E/\dot{V}CO_2$ slope, OUES, and exercise oscillatory ventilation (EOV) were significant prognostic markers for cardiovascular events (Cahalin, 2020). This investigation appears to be the largest systematic review and meta-analysis on the prognostic value of CPET variables in patients with HF, with the results strongly in favour of CPET in HF.

Another systematic review and meta-analysis followed a similar methodology to compare the ability of $\dot{V}E/\dot{V}CO_2$ and p$\dot{V}O_2$ to predict cardiovascular events in systolic HF (Poggio, 2010). The authors searched the available literature and identified 12 articles

that involved systolic HF (HFrEF) patients and sufficiently detailed $\dot{V}E/\dot{V}CO_2$ data in relation to the outcome of cardiovascular events (mortality, HTx, LVAD), thus meeting their inclusion criteria. Of these 12 articles, 6 provided sufficient $p\dot{V}O_2$ data for comparison to $\dot{V}E/\dot{V}CO_2$ in which both variables performed similarly in predicting cardiac events in HFrEF patients, although $\dot{V}E/\dot{V}CO_2$ appeared to be slightly more effective (Poggio, 2010). Essentially, this systematic review and meta-analysis reaffirmed the value of two key CPET derived variables, $\dot{V}E/\dot{V}CO_2$ and $p\dot{V}O_2$, in predicting adverse cardiac events in HF patients.

While these meta-analyses provide support for the use of CPET in the general HF population, for reasons discussed earlier, there is reason to believe that when assessing separate groups of HF patients based on etiology, these findings may vary. There is literature available comparing subgroups of HF patients, yet there do not appear to be any published reviews or meta-analyses assessing the prognostic value of CPET in HF patients with different etiologies. Additionally, with novel CPET parameters continuing to be discovered, such as the $\dot{V}E/\dot{V}CO_2$ nadir and hemodynamic gain index (HGI), this is an opportune time to reassess if and how the predictive value of CPET for various outcomes differs based on HF etiology.

Research Question and Hypothesis

Researchers have clearly defined the clinical importance of CPET for risk stratification in patients with HF (Malhotra, 2016). However, with several possible HF etiologies that have been shown to alter the physiological response to exercise, it is worth exploring how this information may be used clinically for more individualized risk stratification of HF patients (Arena, 2005; Notarius, 2007; Clark, 1997; Juillière, 2000).

The impetus for this thesis was to summarize the current state of knowledge in the field and to identify whether there is a need for more research on the relationship between HF etiology and risk stratification in HF patients using CPET. As such, the primary objective of this research was to determine if and how the CPET thresholds used to stratify risk vary in HF patients with different etiologies. Given the variability in HF symptomatology in different etiologies, it was hypothesized that the CPET thresholds used to stratify risk will predict outcomes differently based on etiology. As such, this novel review may help clinicians determine if there are more appropriate ways to treat or classify HF patients based on CPET results, further optimizing patient care and outcomes.

CHAPTER 2: MANUSCRIPT

ABSTRACT

The aim of this review was to determine how cardiopulmonary exercise test (CPET) parameters, and prognostic threshold values, differ and are associated with mortality and adverse cardiac events in patients with diverse heart failure etiologies. Studies that assessed adult heart failure patients and reported outcomes of all-cause mortality, left ventricular assist device (LVAD) implantation, heart transplantation, or hospitalization were eligible for inclusion. Study quality and risk of bias was assessed using the Joanna Briggs Institute checklist for cohort studies. A total of 491 ischemic and 218 non-ischemic heart failure patients were identified across 4 studies. The only unanimously measured CPET variable was peak oxygen consumption ($p\dot{V}O_2$), with a mean optimal threshold value of ≤ 13.33 (± 2.28) ml/kg/min in ischemic patients and ≤ 14.3 (± 0.42) ml/kg/min in non-ischemic patients. Although there was heterogeneity in the data, the optimal threshold values for predicting outcomes were strikingly similar across HF etiologies. Ultimately, the current state of the literature suggests optimal threshold values from CPET can be applied generally without consideration of etiology. However, there is a clear need to consider additional HF etiologies and CPET parameters in future investigations.

INTRODUCTION

Heart failure (HF) is a significant and costly medical condition characterized by inadequate cardiac output, reduced oxygenation of the periphery, and poor quality of life (Savarese, 2023). Heart failure arises from several possible causes, including various ischemic and non-ischemic cardiomyopathies. Ischemic cardiomyopathy primarily arises from coronary artery disease, whereas non-ischemic cardiomyopathy may include a gamut of familial, hypertrophic, or inflammatory cardiomyopathies. Among the more than 64 million patients with HF worldwide, exercise intolerance is a trademark symptom, irrespective of etiology, and is driven by several levels of impaired metabolic efficiency (Savarese, 2023; Chua, 1997; Malhotra, 2016). Cardiopulmonary exercise testing (CPET) is the gold standard for assessing exercise capacity as it allows clinicians to objectively quantify effort, identify sources of exercise intolerance, monitor disease progression, and determine risk of mortality and need for advanced therapies (Malhotra, 2016).

Currently, there is a gap in understanding how various subgroups of HF etiologies respond to CPET. Patients with ischemic HF have been shown to exhibit a lower exercise capacity and higher risk of exercise or training related complications than those with nonischemic cardiomyopathy (Webb-Peploe, 2000). In one study, the authors reported that etiology of HF influences the extent to which the sympathetic nervous system is activated, which leads to HF patients with ischemic cardiomyopathy experiencing decreased exercise capacity in comparison to their nonischemic counterparts (Notarius, 2007). As such, there is a need to reassess CPET parameters in patients with different HF etiologies to determine if the associated thresholds used for risk stratification need to be

adjusted for more accurate prognostication of HF patients. Other reviews have assessed and summarized the prognostic value of CPET parameters in the general HF population (Cahalin, 2013); however, to our knowledge, there are no published systematic reviews comparing the prognostic value of CPET parameters in patients with different HF etiologies, underscoring the need for an updated review and differential triggers for advanced HF therapies.

The aim of this systematic review was to consolidate and assess the published evidence on the prognostic value of CPET parameters in HF patients with different etiologies. The primary objective of this study was to determine how CPET parameters, and the associated threshold values for risk stratification, differ and are associated with all-cause mortality and other adverse cardiac events in patients with different HF etiologies.

METHODS

This study was registered in PROSPERO (CRD42023472445) and reported according to the preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Data was primarily synthesized qualitatively, via narrative synthesis.

Eligibility Criteria

Studies eligible for inclusion were those involving adult (18+) human participants with a diagnosis of HF and who underwent CPET. Prospective and retrospective cohort and cross-sectional (prevalence) studies were considered for inclusion, while grey literature and conference abstracts were excluded. No restrictions

on publication date or language were imposed in the search. Studies reporting independent or composite outcomes of all-cause mortality, left ventricular device (LVAD) implantation, heart transplantation, or hospitalization were eligible for inclusion.

Search Strategy and Registration

A comprehensive search strategy was developed in partnership with an information specialist (AO), using a combination of database-specific subject headings and text words for the main concepts and protocols of cardiopulmonary exercise testing (CPET, CPX, Bruce protocol, Naughton protocol, etc.), synonymous exercise testing terminology (spiroergometry, cardiopulmonary performance testing, cardiopulmonary function testing, etc.) and heart failure (heart disease, cardiomyopathy, etc.). A sensitive filter for prognostic studies was applied (Hedges Project, 2022) We searched the following databases on October 19, 2023: Ovid MEDLINE; Ovid Embase; Cochrane Database of Systematic Reviews (Ovid); and Cochrane Central Register of Controlled Trials (Ovid); a full example search strategy can be found in the appendix. The reference lists of included publications were searched, and relevant articles were considered for inclusion.

Study Selection Process

After obtaining results from our search, articles were imported for management in the software, Covidence. Pairs of authors (HL, KW, BK, MS, JRA) independently screened the titles and abstracts of records for the inclusion criteria. Conflicts were resolved through discussion with other co-authors (IB, SW). The remaining full-text articles were screened for inclusion by a single author (HL), while a second reviewer

(KW, BK, MS) screened all excluded articles. Any articles classified as “maybe” were included or excluded after discussion with other co-authors (IB, SW).

Data Extraction and Quality Assessment

Data was extracted by a single reviewer (HL), with a biostatistician (KW) cross-checking the values collected from each article to ensure accurate and reliable information. Extracted data included patient demographics, HF etiologies, relevant CPET parameters, and independent or composite outcomes of left ventricular assist device implantation, heart transplantation, all-cause mortality, and hospitalization. We opted not to collect information regarding medications due to the continuous nature of titration and the plethora of HF medication classes, given that our other cardiac events of interest were binary. We collected patient demographics, continuous data as mean and standard deviation for all available CPET parameters, optimal threshold values, and associated effect measures for each etiology.

Study Risk of Bias Assessment

The quality of included articles was assessed in Covidence following the JBI critical appraisal guidelines and checklist for cohort studies (JBI, 2024) Two authors independently assessed each included article (HL, IB, MS) with discrepancies being resolved through discussion between authors.

RESULTS

Study Selection

Our comprehensive literature search identified 15,907 records, with 9 additional studies identified through manual citation searching, from which 2746 duplicates were

removed. Most of records were removed at the title and abstract screening stage (13,170), leaving 234 full text articles for review. The majority of the full-text articles (n = 189) were removed because there was no analysis, or sub-analysis considering HF patient etiology. The second most common cause for exclusion was “wrong study design” (n = 21), as these studies often compared CPET values between HF etiologies; however, they did not report the potential differences to outcomes, failing to address our research question, and thus the inclusion criteria. A total of 4 retrospective cohort studies met the inclusion criteria, with no additional studies identified through manual review of the reference lists (Figure 1).

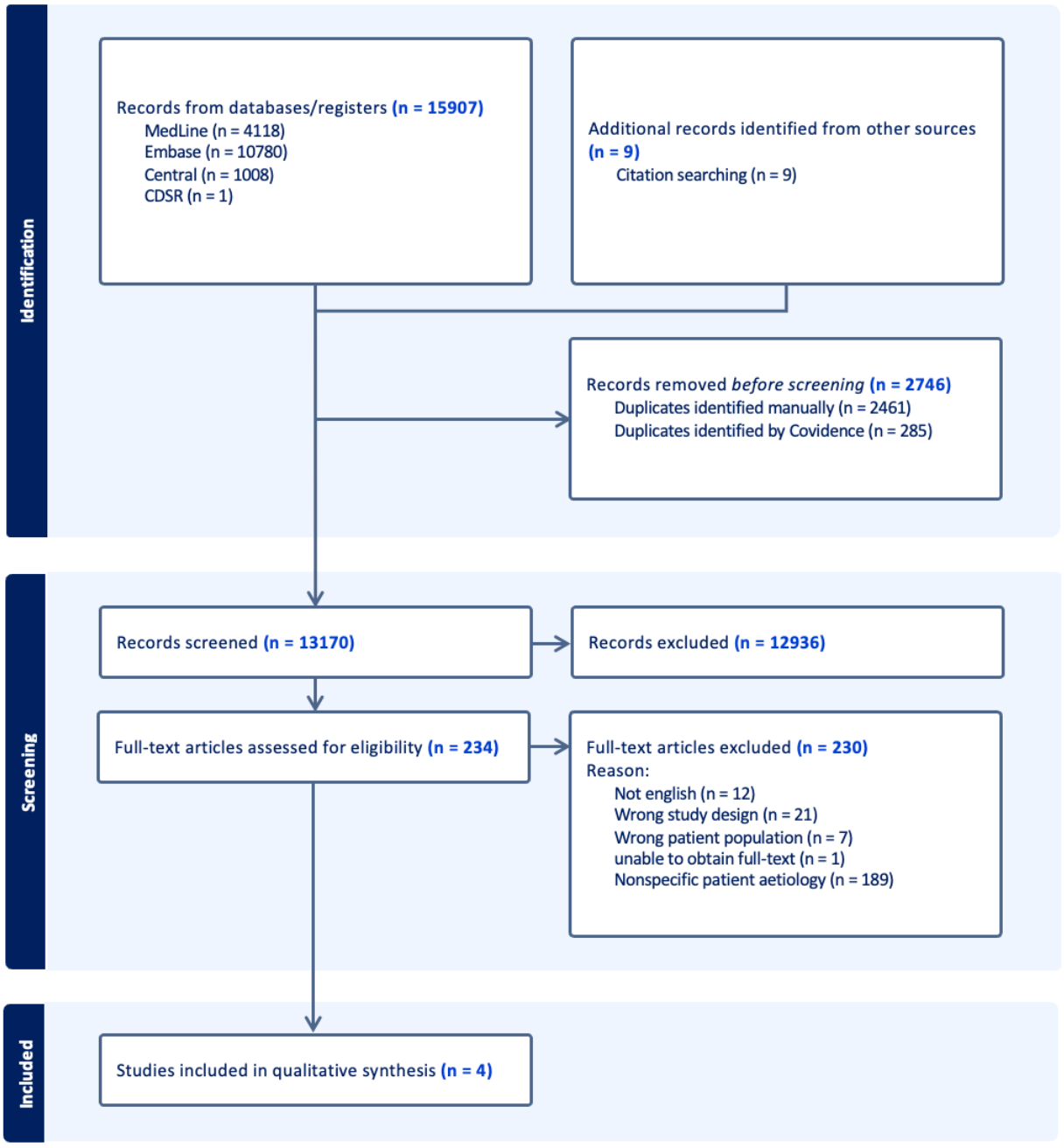

Figure 1. PRISMA Flow Diagram

Table 1. Methodologies and patient characteristics for CPET testing in different HF aetiologies (n = 4).

Source	CPET Protocol (Modality)	CPET Variables Used	Ischemic HF			Non-Ischemic HF		
			Sample Size (M/F)	Mean Age (yrs.) (±SD)	Mean LVEF (%) (±SD)	Sample Size (M/F)	Mean Age (yrs.) (±SD)	Mean LVEF (%) (±SD)
Arena 2005[12]	Standard Ramping protocol (cycle ergometer or treadmill)	$\dot{V}E/\dot{V}CO_2$ $p\dot{V}O_2$	137 (115/22)	61.1 (±10)	32.6 (±11.9)	131 (108/23)	50.3 (±16.2)	31.4 (±13)
Honold 2013[13]	Modified Bruce or modified Naughton protocol	OUES $\dot{V}E/\dot{V}CO_2$ $p\dot{V}O_2$	157 (136/21)	60.0 (±12)	39.0 (±11)	Not Assessed		
Stelken 1996[14]	Modified Bruce or modified Naughton protocol	$\%pp\dot{V}O_2$ $p\dot{V}O_2$	94 (85/9)	53.0 (±8)	23.0 (±8)	87 (44/11)	57.0 (±11)	23.0 (±10)
Honold 2008[15]	Standard Ramping protocol (cycle ergometer)	$p\dot{V}O_2$	103 (89/14)	57.0 (±11)	41.0 (±10)	Not Assessed		

Note: $\mathbf{p\dot{V}O_2}$ (peak oxygen uptake – maximum rate of oxygen intake during exercise); $\mathbf{\%pp\dot{V}O_2}$ (percent predicted peak oxygen uptake – percentile rank based on normative values); $\mathbf{\dot{V}E/\dot{V}CO_2}$ (ventilatory Efficiency - Amount of minute ventilation it requires to remove 1 L of CO2); **OUES** (Oxygen Uptake Efficiency Slope Relation between oxygen intake and minute ventilation in response to exercise). Mean = $\mu \pm$ standard deviation.

Table 2. Association of CPET parameter thresholds with HF clinical outcomes stratified by aetiology.

Source	Mean Follow-up	Results in Patients WITH an Outcome		
		Ischemic **CPET Variable: (threshold)**	**Non-Ischemic** **CPET Variable: (threshold)**	**Conclusions**
***Outcome**: cardiac events (mortality or hospitalization) (n = 2)*				
Arena 2005[12]	1 year	$n_{outcome}$ = 53 $\dot{V}E/\dot{V}CO_2$ slope: (≥ 34.2) HR 4.3 (2.4-7.8) Sensitivity: 78% Specificity: 72% μ = 39.8 ± 11.9 $p\dot{V}O_2$: (≤ 14.1ml/kg/min) HR 3.3 (1.9-5.8) Sensitivity: 71% Specificity: 67% μ = 12.3 ± 4.5	$n_{outcome}$ = 36 $\dot{V}E/\dot{V}CO_2$ slope: (≥ 34.5) HR 8.2 (3.9-77.8) Sensitivity: 78% Specificity: 72% μ = 39.9 ± 8 $p\dot{V}O_2$: (≤ 14.6ml/kg/min) HR 4.3 (2.1-8.9) Sensitivity: 71% Specificity: 67% μ = 13.4 ± 4.6	Ischemic group demonstrated a worse prognosis during the 1-year tracking period. CPET characteristics of patients with a cardiac related event were similar, irrespective of HF etiology.
Honold 2008[15]	2 years	$n_{outcome}$ = 14/103 $p\dot{V}O_2$: (≤ 10ml/kg/min) HR 0.76 (0.59-0.98) Sensitivity: 0.69 Specificity: 0.96	Not Applicable	Supports the notion that lower $p\dot{V}O_2$ thresholds are more predictive in patients on beta-blockers.

Note: $\mathbf{p\dot{V}O_2}$ (peak oxygen uptake – maximum rate of oxygen intake during exercise); $\mathbf{\%pp\dot{V}O_2}$ (percent predicted peak oxygen uptake – percentile rank based on normative values); $\mathbf{\dot{V}E/\dot{V}CO_2}$ (ventilatory Efficiency - Amount of minute ventilation it requires to remove 1 L of CO2); **OUES** (Oxygen Uptake Efficiency Slope Relation between oxygen intake and minute ventilation in response to exercise). Mean = μ ± standard deviation.

Table 3. Association of CPET parameter thresholds with HF clinical outcomes stratified by aetiology.

Source	Mean Follow-up	Results in Patients WITH an Outcome		
		Ischemic **CPET Variable: (threshold)**	**Non-Ischemic** **CPET Variable: (threshold)**	**Conclusions**
***Outcome**: all-cause mortality (n = 1)*				
Honold 2013[13]	4 years	$n_{outcome}$ = 24 OUES: (≤ 1466.6) μ = 1246.6 ± 727.2 Sensitivity: 70.6% Specificity: 75% $\dot{V}E/\dot{V}CO_2$ slope: (≥ 32.1) μ = 43.9 ± 15 Sensitivity: 79.2% Specificity: 54.9% $p\dot{V}O_2$: (≤ 15.2ml/kg/min) μ = 14.8 ± 3.1 Sensitivity: 76.5% Specificity: 61.7%	Not Applicable	CPET with $p\dot{V}O_2$: > 15.2ml/kg/min, OUES > 1466.6, and $VE/\dot{V}CO_2$ slope ≥ 32.1 demonstrate at least moderately predict mortality in these patients with ischemic HF.

Note: $p\dot{V}O_2$ (peak oxygen uptake – maximum rate of oxygen intake during exercise); **%pp**$\dot{V}O_2$ (percent predicted peak oxygen uptake – percentile rank based on normative values); $\dot{V}E/\dot{V}CO_2$ (ventilatory Efficiency - Amount of minute ventilation it requires to remove 1 L of CO2); **OUES** (Oxygen Uptake Efficiency Slope Relation between oxygen intake and minute ventilation in response to exercise). Mean = μ ± standard deviation.

Table 4. Association of CPET parameter thresholds with HF clinical outcomes stratified by aetiology.

Source	Mean Follow-up	Results in Patients WITH an Outcome		
		Ischemic **CPET Variable: (threshold)**	**Non-Ischemic** **CPET Variable: (threshold)**	**Conclusions**
Outcome: *cardiac death or status 1 heart transplant listing (n = 1)*				
Stelken 1996[14]	1 year	$n_{outcome}$ = 20 %pp$\dot{V}O_2$: (≤ 50%) Sensitivity = 92% Specificity = 58% μ = 38 ± 10 p$\dot{V}O_2$: (≤ 14ml/kg/min) Sensitivity = 77% Specificity = 68% μ = 12 ± 4.3	$n_{outcome}$ = 6 %pp$\dot{V}O_2$:(≤ 50%) Sensitivity = 92% Specificity = 58% μ = 36 ± 9 p$\dot{V}O_2$: (≤ 14ml/kg/min) Sensitivity = 77% Specificity = 68% μ = 12.5 ± 1.9	≤ 50% predicted p$\dot{V}O_2$: and p$\dot{V}O_2$: ≤ 14ml/kg/min were significant univariate predictors of outcomes irrespective of etiology.

Note: p$\dot{V}O_2$ (peak oxygen uptake – maximum rate of oxygen intake during exercise); **%pp$\dot{V}O_2$** (percent predicted peak oxygen uptake – percentile rank based on normative values); **$\dot{V}E/\dot{V}CO_2$** (ventilatory Efficiency - Amount of minute ventilation it requires to remove 1 L of CO2); **OUES** (Oxygen Uptake Efficiency Slope Relation between oxygen intake and minute ventilation in response to exercise). Mean = μ ± standard deviation.

Study Characteristics

As outlined in Table 1, two of the studies focused solely on patients with ischemic HF (Honold, 2013; Honold 2008), while the two remaining studies compared ischemic versus non-ischemic patients in their analysis (Arena, 2005; Stelken, 1996). The proportion of female patients was strikingly low with only 16% (Arena, 2005), 13.4% (Honold, 2013), 9.6% (Stelken, 1996), and 13.6% (Honold, 2008) across studies. All studies consisted of patients with a reduced EF (< 50%), or systolic HF, while there was no data available for patients with preserved EF, or diastolic HF. There was variability in the CPET protocols used across studies with some using a single protocol for all patients and others following multiple protocols. Two studies followed a standard ramp protocol on a cycle ergometer (Arena, 2005; Honold, 2008), with one of these studies also including patients ramped on a treadmill (Arena, 2005) The two remaining studies all included patients who underwent a modified Bruce protocol or a modified Naughton protocol (Stelken, 1996; Honold 2013). All included studies collected etiology specific demographics and CPET parameters and used receiver operating curve analysis to identify optimal threshold values for their outcome of interest. After converting all time to follow-up measures to years, the range of median follow-up time was between 1 to 4 years (Table 2).

Patient Characteristics

Ischemic Heart Failure Characteristics

In the studies that defined their subgroups, patients were classified as having ischemic HF if they had a history of chronic coronary artery disease or acute myocardial infarction (Arena, 2005; Stelken, 1996) A total of 491 ischemic HF patients were

assessed across studies, 66 of whom were women (13.44%). The mean age of ischemic patients across studies was 57.78 (± 3.62) years, and the mean ejection fraction (EF) was 33.9 (± 8.10)%. Studies consisted of patients with reduced ejection fraction (< 40%; Arena, 2005; Honold, 2013; Stelken 1996), with one study averaging a mildly reduced ejection fraction (40-49%) of 41% (Honold, 2008). The only unanimously reported CPET variable was $p\dot{V}O_2$, with mean of 15.85 (± 1.58) ml/kg/min across ischemic HF patients with and without an outcome. The mean RER was maximal (>1.10) in the three studies that measured it (Arena, 2005; Stelken, 1996; Honold, 2008).

Non-Ischemic Heart Failure Characteristics

In the two studies assessing non-ischemic HF, patients were classified as non-ischemic if they were diagnosed with an idiopathic cardiomyopathy, a dilated cardiomyopathy, or did not have a history of coronary artery disease (Arena, 2005; Stelken, 1996) A total of 218 non-ischemic patients were assessed, 49 of whom were female (22.5%). The mean age of non-ischemic patients across studies was 47.15 (± 3.68) years, and the mean ejection fraction was 27 (± 2.11)%. All studies consisted of patients with a reduced ejection fraction (< 40%). $p\dot{V}O_2$ and RER were the only consistently reported CPET parameters, with a mean $p\dot{V}O_2$ of 17.95 (± 0.64) ml/kg/min. One study reported a mean RER of 1.14 from their participants (Stelken, 1996), indicating a maximal effort, while the second study reported a mean RER of 1.07, which may be considered maximal at some institutions and submaximal in others.

Outcomes

Ischemic Heart Failure Outcomes

The most common outcome measure across studies was mortality, as either all-cause (n = 3; Arena, 2005; Honold, 2013; Honold, 2008), or cardiac death (n = 1; Stelken, 1996). Two studies that assessed all-cause mortality also included a secondary outcome of hospitalization (Arena, 2005; Honold, 2008), while the single study assessing cardiac death was part of a composite outcome in addition to transplant listing (Table 2). In patients with any outcome listed above, the mean p$\dot{V}O_2$ across studies was 12.78 (± 1.36) ml/kg/min, compared to 16.83 (± 1.48) ml/kg/min in patients without an outcome. Three of the four studies assessed $\dot{V}E/\dot{V}CO_2$ slope with a mean value of 40.23 (± 11.6) in patients with an outcome, versus 32.23 (± 1.22) in patients without an outcome. The mean RER was maximal (>1.10) in patients with the outcome (Arena, 2005; Stelken, 1996; Honold, 2008).

All studies used the area under receiver operating characteristic curve (AUROC) to predict optimal CPET threshold values for risk stratification in their patient population. Peak $\dot{V}O_2$ was the only CPET parameter to have an optimal threshold value calculated in every study, although effect measures were inconsistently reported. The mean p$\dot{V}O_2$ threshold across studies was ≤ 13.33 (± 2.28) ml/kg/min, which is consistent with the current guideline threshold value of 14 ml/kg/min. The mean p$\dot{V}O_2$ was likely lower due to one study establishing a p$\dot{V}O_2$ ≤ 10 ml/kg/min to be prognostically superior. However, 86% of patients with an outcome were on beta-blockers, reaffirming the notion that a lower p$\dot{V}O_2$ threshold is more predictive in beta-blocked patients. Beta-blockers are widely prescribed in patients with cardiovascular diseases because they combat the stress

on the heart by reducing HR and BP, which also inherently limits exercise capacity. Only one study assessed the current percent predicted p$\dot{V}O_2$ threshold of ≤ 50% and found it to be a significant univariate predictor of an outcome (Stelken, 1996). Another study assessing the optimal threshold for oxygen uptake efficiency slope determined a threshold of < 1.47 to be prognostic, which is consistent with the current guideline threshold of < 1.40 (Honold, 2013). Lastly, two studies assessed the optimal threshold for $\dot{V}E/\dot{V}CO_2$ slope, with the mean threshold being < 33.15 (± 1.5), similar to the current guideline of < 34 (Arena, 2005; Honold, 2013).

Non-Ischemic Heart Failure Outcomes

The primary outcomes measured in the non-ischemic population was all-cause mortality, with a secondary outcome of either hospitalization (Arena, 2005), or transplant listing. In patients with at least one of the previous outcomes, the mean p$\dot{V}O_2$ across studies was 12.95 (± 0.64) ml/kg/min, compared to 19.0 (± 0.14) ml/kg/min in patients without an outcome. One of the two studies assessed $\dot{V}E/\dot{V}CO_2$ slope with a mean value of 39.9 (± 8.0) in patients with an outcome, versus 30.0 (± 6.5) in patients without an outcome. The mean RER was submaximal (< 1.10) in patients with, and without, an outcome (Arena, 2005; Stelken, 1996).

Authors similarly used AUROC analysis to identify optimal threshold values for stratifying risk in non-ischemic patients. Peak $\dot{V}O_2$ was the only CPET parameter to have an optimal threshold value calculated in each study, while effect measures were inconsistently reported. The mean p$\dot{V}O_2$ threshold across studies was ≤ 14.3 (± 0.42) ml/kg/min (Arena, 2005; Stelken, 1996), which is consistent with both the ischemic threshold (≤ 13.33), and the current guideline of 14ml/kg/min. The only other CPET

variable for which an optimal threshold value was identified was for $\dot{V}E/\dot{V}CO_2$ slope. A single study identified a $\dot{V}E/\dot{V}CO_2 < 34.5$ (HR 8.2 (3.9-17.2; Arena, 2005) to be prognostically significant, which is consistent with the ischemic population (< 33.15), and the current guideline of < 34.

Risk of Bias Assessment

Risk of bias was assessed using the Joanna Briggs Institute critical appraisal checklist for cohort studies. Three of the included articles were considered to have a "low risk" of bias achieving 8 or 9 of a possible 11 points (Arena, 2005; Honold, 2013; Honold, 2008). The remaining study was classified as having "some concerns" achieving a score of 7 of a possible 11 points (Stelken, 1996). The most common source of bias across these 4 studies was failing to describe the strategies used, if any, to deal with confounding factors (Figure 2). Some studies listed strategies to control for confounders however, few or none of the well documented confounders in cardiopulmonary exercise testing, such as obesity, anxiety, anemia, or acid-base disorders were controlled for (Glaab, 2022). Another repeating source of bias was the potential for patients to have experienced an outcome of hospitalization prior to undergoing CPET. Multiple studies assessed hospitalization as an outcome of interest (Arena, 2005; Honold, 2008); however, the way hospitalizations were defined was unclear. Heart failure patients have extremely high rates of hospitalization, and authors did not specify whether patients were hospitalized and then underwent CPET, or if they underwent CPET, and then were hospitalized.

Table 5. Risk of bias assessment using the Joanna Briggs Institute checklist for cohort studies.

Subgroup or Study	1	2	3	4	5	6	7	8	9	10	11
Low risk of Bias											
Arena 2005	+	+	+	+	−	?	+	+	+	?	+
Honold 2013	+	+	?	+	?	+	+	+	+	+	+
Honold 2008	+	+	+	+	?	?	+	+	+	+	+
Some Concerns											
Stelken 1996	+	+	?	+	?	?	+	+	+	?	+

Note: Green (+) Icon = low risk of bias. Yellow (?) Icon = some risk of bias or missing information. Red (-) Icon = High risk of bias. Questions: 1. Were the two groups similar and recruited from the same population? 2. Were the exposures measured similarly to assign people to both exposed and unexposed groups? 3. Was the exposure measured in a valid and reliable way? 4. Were confounding factors identified? 5. Were strategies to deal with confounding factors stated? 6. Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)? 7. Were the outcomes measured in a valid and reliable way? 8. Was the follow up time reported and sufficient to be long enough for outcomes to occur? 9. Was follow up complete, and if not, were the reasons to loss to follow up described and explored? 10. Were strategies to address incomplete follow up utilized? 11. Was appropriate statistical analysis used?

DISCUSSION

The findings of this systematic review can be summarized as follows: first, we found a limited number of studies (4) that specifically analyzed the prognostic value of CPET parameters in patients with ischemic or non-ischemic cardiomyopathy. There was also a significant level of heterogeneity in the type of data collected, and the way findings were reported. Second, we identified several different outcomes of interest; most commonly was all-cause mortality (Arena, 2005; Honold, 2013; Honold, 2008), including cardiac death (Stelken, 1996), and secondary outcomes of cardiac events, such as hospitalization (Arena, 2005; Honold, 2008) or heart transplant listing (Stelken, 1996).

Third, at baseline, and during exercise, patient characteristics were often significantly different between ischemic and non-ischemic HF patients, with ischemic heart failure patients consistently demonstrating a worse prognosis than their non-ischemic counterparts (Arena, 2005; Stelken, 1996). However, the CPET characteristics in patients with an outcome were strikingly similar irrespective of etiology in the included cohort.

Taken together, these studies do not demonstrate significant differences in CPET thresholds for diverse etiologies of HF. As we expand our understanding of genetic, inflammatory and 'idiopathic' cardiomyopathy, tailored parameters for assessment of advanced HF therapies will be needed expanding beyond dilated cardiomyopathies.

Among articles that have assessed risk in HF patients with different etiologies independent of CPET, ischemic HF has been shown to independently predict increased risk of mortality compared to patients with non-ischemic HF (Likoff, 1987). In this population, the left ventricle might have a worse preserved adaptation to excessive wall stress during exercise in ischemic than in non-ischemic HF (De Feo, 2005). Exercise testing responses and prognostic characteristics, such risk of mortality and need for advanced therapies, differ significantly between groups with ischemic and non-ischemic HF (Arena, 2005 IJC) Given this etiological variability in HF mechanics and patient response to exercise, one may hypothesize that the predictive thresholds derived from a CPET could be different based on etiology. While this systematic review reaffirms the notion that ischemic HF patients are clinically worse off, there is no indication that the optimal threshold values use to risk stratify HF patients differ, or need to be adjusted, based on etiology for more accurate prognostication of HF patients.

Limitations of the evidence

We planned to conduct a meta-analysis but, the available data was highly heterogeneous in terms of CPET parameters assessed and measures of effect reported, hindering our ability to run quantitative analyses. We found considerable heterogeneity in the patient populations, CPET protocols used, CPET parameters analyzed, and the effect measures reported. Further, the studies reviewed included very few women in their sample, only 13.44% in the ischemic population and 22.45% in the non-ischemic population, hindering the generalizability of these findings to the female patient, which is significant as HF has been noted to affected individuals differently based on sex. For example, non-ischemic HF factors such as obesity, diabetes, and infection are more common in women, whereas men are more likely to experience ischemic HF due to things like heart attack and stroke (Lala, 2022). Additionally, few studies sufficiently adjusted for potential confounding factors. Lastly, the included studies had small sample sizes, ranging from 14-53 ischemic patients, and 87-131 non-ischemic HF patients, highlighting the need for a more comprehensive investigation.

Limitations of this review

We were only able to report on ischemic versus non-ischemic patient populations as those were the only populations assessed in the studies that met our inclusion criteria. While we did not impose any etiological exclusions, there are several diverse etiologies specifically worth exploring in the future, such as hypertrophic and Chagasic cardiomyopathies. Additionally, optimal threshold values were only derived for a select few CPET parameters across the included studies; namely, p$\dot{V}O_2$, %pp$\dot{V}O_2$, $\dot{V}E/\dot{V}CO_2$ slope, and OUES. While these are strong identifiers of risk, there are several other

established CPET parameters, such as the ventilatory anaerobic threshold (VAT), $\dot{V}E/\dot{V}CO_2$ @ VAT, exercise oscillatory ventilation, and more novel parameters such as the $\dot{V}E/\dot{V}CO_2$ nadir, and hemodynamic gain index, that are clinically relevant and worth considering in patients with different etiologies (Malhotra, 2016; Nayor, 2020; Morales-Oyaryide, 2023; Chaikijurajai, 2024). We were also only able to assess observational studies, specifically retrospective cohort studies, in this review.

CONCLUSION

Patients with ischemic HF generally have a higher risk of death than patients with non-ischemic HF (Morales-Oyaryide, 2023) However, the optimal threshold values derived from CPET are strikingly similar for predicting outcomes in patients with different HF etiologies. Although there is still a clear need to consider other HF etiologies and additional CPET parameters in larger study populations, the current state of the literature suggests optimal threshold values from CPET can be applied generally without consideration of etiology. Moving forward, it would be beneficial for future studies to list more granular details about patient etiology, while including additional CPET parameters when assessing prognosis as a CPET is much more than a p$\dot{V}O_2$.

CHAPTER 3: GENERAL DISCUSSION

Thesis Overview

In this thesis, we investigated the prognostic value of CPET for various clinical outcomes in HF patients with different etiologies. The goal was to determine whether the optimal threshold values for CPET derived variables, that are used to risk stratify for these outcomes, vary between etiologies. The pathophysiological differences and variable symptoms experienced by etiologically different groups of HF patients fueled the hypothesis that these predictive threshold values would be different based on etiology. This systematic review is to our knowledge the first synthesis of the literature assessing the prognostic value of CPET in different HF etiologies.

Summary of Findings

After an extremely comprehensive literature search, only 4 studies were found which specifically assessed the prognostic value of CPET parameters in patients with different heart failure etiologies. However, these were limited to patient populations with ischemic or non-ischemic cardiomyopathy. There is plenty of research showing that CPET is an effective tool for prognostication in the general HF population, which I believe has limited the urgency to conduct etiology specific subgroup analyses of CPET in HF. There is also a relatively limited understanding of the pathophysiology of these different etiologies, or at least competing views on their pathophysiological mechanisms (Malik, 2023). As we come to better understand lesser known inflammatory, infiltrative, and stress-induced cardiomyopathies, the capacity for comparing the exercise response of several different HF groups will develop far beyond the current ischemic vs non-ischemic HF studies that we identified through this investigation.

There was also a significant level of heterogeneity between the 4 studies in the type of data collected and the way findings were reported. The available outcomes of interest included, most commonly, all-cause mortality (Arena, 2005; Honold, 2013; Honold, 2008) including cardiac death (Stelken, 1996), and secondary outcomes of cardiac events, such as hospitalization (Arena 2005; Honold, 2008) or heart transplant listing (Stelken, 1996). The primary conclusion is that at baseline, and during exercise testing, patient CPET characteristics were often significantly different between ischemic and non-ischemic HF patients, with ischemic heart failure patients consistently demonstrating a worse prognosis than their non-ischemic counterparts (Arena, 2005; Stelken, 1996). However, the actual CPET derived data, and predictive thresholds, in patients with any outcome were strikingly similar irrespective of etiology (ischemic vs non-ischemic cardiomyopathy), refuting our hypothesis.

When looking more closely at the results of the included studies, ischemic patients had worse prognosis, in one study, during follow-up (Arena, 2005). Myocardial infarction and CAD are among the main causes of ischemic heart disease; these ailments are extremely damaging to the body and are thus expectedly correlated with worse prognosis. Interestingly, two of the studies reported optimal predictive thresholds for $p\dot{V}O_2$ to be slightly higher than the current established threshold of ≤ 14 ml/kg/min (Arena, 2005; Honold, 2013; Malhotra, 2016). While these differences are not significant, the average age of patients included in these studies was relatively young, which likely accounts for the slightly elevated $p\dot{V}O_2$ threshold values. It is well documented that $p\dot{V}O_2$ decreases with age (Malhotra, 2016). Lastly, one study that included a heavily beta-blocked ischemic HF patient population identified a markedly lower optimal $p\dot{V}O_2$

threshold of ≤ 10 ml/min/kg (Honold, 2008). Since beta-blockers reduce HR, patients are unable to achieve their true p$\dot{V}O_2$. Current guidelines on CPET in HF support this notion with the optimal threshold value for p$\dot{V}O_2$ of beta-blocked patients being ≤ 12 ml/min/kg, which is 2 ml/kg/min lower than the standard value (Malhotra, 2016).

Strengths

This thesis provides a novel synthesis of the use of CPET to predict outcomes in HF patients with different etiologies, contributing valuable insight into what's known, while highlighting current knowledge gaps in the field. The literature search and design of this systematic review were comprehensive and rigorous with 13157 titles and abstracts screened by two persons for inclusion. Full-text reviews and data extraction were also completed by multiple authors to ensure accurate and reliable information was being retained and presented.

Our inclusion criteria were also well defined with specific interest in studies that included the following:

1) Assessment of adult heart failure patients through CPET.
2) Results specifically separated based on HF etiology.
3) Linking of CPET results, and ideally predictive thresholds, to clinical outcomes.

Several studies narrowly failed to meet the inclusion criteria for a few different reasons. The first is that studies would assess how CPET differed based on HF etiologies. However, these differences were then not linked to patient outcomes (Clark, 1997; Juillière, 2000; Kakutani, 2018; Wanderley Braga, 2006). In other cases, authors would provide information on how CPET predicted outcomes in HF patients and go as far as to

indicate the etiological composition of their study population, but never provided etiology specific sub-analyses leading to their exclusion (Chua, 1997; van den Broek, 1992; Scrutinio, 1998). The last type of study commonly excluded was those that compared outcomes in etiologically different HF groups but failed to report the associated CPET data (Arena, 2005, Likoff, 1987, Guimaraes, 2010).

Limitations

Demographics

The studies included in this review all had relatively small sample sizes with the largest subgroup being 137 ischemic HF patients (Arena, 2005). Additionally, the age of patients was relatively young, with average age of participants in each study being less than 62 years. HF is a disease that widely affects elderly patients, and they should also be represented in these studies. Lastly, every study reviewed included patients with HFrEF. As discussed in the introduction, there are different classes of HF that may affect patient phenotype when it comes to exercise. Another significant concern was the lack of female representation in these study populations, which has long been a flaw in cardiovascular research (Lala, 2022). In studies that have assessed sex-based differences in HF patients, there have been significant differences in the way men and women experience this condition, highlighting the need for more equitable and representative study populations.

Etiologies

There are ample possible causes of heart failure with more diverse etiologies than we were able to assess. From the 4 studies that met the inclusion criteria, we were only able to derive data for ischemic or non-ischemic patient populations.

CPET Parameters

There was only data for a select few CPET parameters across the included studies, namely, p$\dot{V}O_2$, %pp$\dot{V}O_2$, $\dot{V}E/\dot{V}CO_2$ slope, and OUES. While these parameters have been shown to be strong identifiers of risk in HF patients, there are several other established and novel CPET parameters worth exploring.

Data Reporting

There was also considerable heterogeneity in the way the data was reported. Some authors included hazard ratios, 95% confidence intervals, area under the curve, sensitivity, and specificity measures, while others only reported some combination of these. We had the intention of doing a meta-analysis, but given the heterogeneity in the data, and the way it was reported, we were not able to do so. Another specific limitation was the possibility of sample overlap in the Honold 2008 and 2013 studies, respectively. While we attempted to contact the authors about this possibility, I did not receive a response. We opted to include both studies as they looked at two different versions of p$\dot{V}O_2$, with the 2013 study assessing the general threshold of 14 ml/kg/min, and the earlier 2008 study focusing on the lower p$\dot{V}O_2$ threshold of 12ml/kg/min in the beta-blocked patient population. One should acknowledge the possibility of reused patient data when interpreting these results.

Future Directions

Upon consolidating the results of these applicable studies. We have identified a significant knowledge gap pertaining to how CPET could be used to risk stratify HF patients with different HF etiologies. Given the multitude of limitations and lack of

investigation, I would encourage future researchers assessing CPET in HF patients to take the next step in their analysis and include etiology specific sub-analyses.

Within this future research, there is a need to incorporate additional CPET parameters in larger samples, and more diverse patient populations. With additional well established CPET parameters such as ventilatory anaerobic threshold (VAT), $\dot{V}E/\dot{V}CO_2$ at VAT, exercise oscillatory ventilation (EOV), and more novel parameters such as the $\dot{V}E/\dot{V}CO_2$ nadir, and hemodynamic gain index, there is a clear need to conduct more intense investigations into how these parameters differ when predicting outcomes in HF patients with different etiologies (Malhotra, 2016; Braga, 2006; Nayor, 2020; Morales-Oyarvide, 2023)

Future research should also include other relatively common and uncommon etiologies, such as dilated, hypertrophic, Chagasic, peripartum, alcohol cardiomyopathy, among others. While this review increases knowledge surrounding ischemic and non-ischemic heart failure, it is necessary to include additional etiologies to ensure optimal care is available to each patient. A warranted next step is to conduct a similar review of how CPET predicts outcomes in patients with reduced ejection fraction (HFrEF) and preserved ejection fraction (HFpEF). Patients with HFrEF typically exhibit reduced VO2 peak due to impaired cardiac contractility, whereas HFpEF patients often show abnormal ventilatory responses and impaired exercise tolerance despite preserved ejection fraction (Schwinger, 2021). Another component not discussed in this thesis is cardiac cachexia, or muscle wasting, in patients with heart failure. Research suggests that cachexia is associated with severity of heart failure and ventilatory inefficiency (Mantegazza, 2017).

Investigating how this relationship correlates with CPET parameters, may be a useful way to further understand and improve care for patients experiencing cardiac cachexia.

Further research is also warranted to understand the specific mechanisms and differences in the pathophysiology of various HF etiologies. Investigating how specific etiologies influence patient response to exercise could refine our understanding of HF heterogeneity and guide the development of novel therapeutic approaches. Ongoing advancements in CPET technology, such as enhanced invasive CPETs, gas exchange analyzers, and non-invasive hemodynamic monitoring, present opportunities to also expand the scope of parameters assessed during CPET. Further, incorporating biomarkers (i.e., NT-proBNP) and artificial intelligence-driven analytics may enhance the predictive accuracy and diagnostic utility of CPET in diverse HF populations.

Conclusion

In summary, while the current evidence synthesized in this thesis supports the generalizability of certain CPET-derived thresholds across HF etiologies, continued research efforts are essential to deepen our understanding of exercise physiology in HF and refine prognostic models. By incorporating larger study populations, exploring additional CPET parameters, and including more intricate etiological analyses, clinicians and researchers can advance towards more individualized, effective, and patient-centered management of heart failure.

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APPENDIX

Table A. Common CPET variables and associated thresholds used for risk stratification in HF patients.[5]

CPET Parameter	High Risk (>20% 1-year Mortality)	Low Risk (>95% 1-year Event-free Survival)
p$\dot{V}O_2$	<14 ml/kg/min	>20 ml/kg/min
HRR	< 6 bpm	>>6 bpm
sBP	<120 mmHg	>120 mmHg
VE/VCO2 slope	>36	<30
$\dot{V}O_2$ @ VAT	<9 ml/kg/min	>11 ml/kg/min
(OUES)	<1.4	>1.4

p$\dot{V}O_2$ (Peak Oxygen Uptake - Maximum rate of oxygen intake during exercise); **HRR (**Heart Rate Recovery - Difference between peak HR during exercise and HR 1 min after resting); **Peak sBP** (Peak Systolic Blood Pressure - Maximum systolic blood pressure during exercise); **VE/VCO2** (Ventilatory Efficiency - Amount of minute ventilation it requires to remove 1 L of CO2); **$\dot{V}$O2 @ VAT** (Oxygen Uptake at Ventilatory Anaerobic Threshold - the point during exercise the body switches from aerobic to anaerobic metabolism); **OUES** (Oxygen Uptake Efficiency Slope Relation between oxygen intake and minute ventilation in response to exercise).

Literature Search Strategies

Embase <1974 to 2023 October 18>

#	Searches	Results	Type
1	exp exercise test/	116966	Advanced
2	(Bicycle adj2 ergometer*).mp.	10766	Advanced
3	(Bicycle adj2 ergometre*).mp.	2	Advanced
4	(Bruce adj2 Protocol).mp.	2357	Advanced
5	(cardiopulmonary adj2 function test*).mp.	220	Advanced
6	(cardio-pulmonary adj2 function test*).mp.	9	Advanced
7	(cardiopulmonary adj2 performance test*).mp.	4	Advanced
8	(cardio-pulmonary adj2 performance test*).mp.	0	Advanced
9	CHF Protocol.mp.	5	Advanced
10	CPET.mp.	5895	Advanced
11	CPEX.mp.	151	Advanced
12	CPX.mp.	3469	Advanced

13 (Cycle adj2 Ergometer*).mp.	8335	Advanced
14 (Cycle adj2 ergometre*).mp.	4	Advanced
15 (ergometry adj2 test*).mp.	677	Advanced
16 Ergospirometry.mp.	483	Advanced
17 (Eurofit adj2 test*).mp.	156	Advanced
18 european fitness testing battery.mp.	0	Advanced
19 (Exercise adj2 test*).mp.	93282	Advanced
20 Exercise-induced cardiopulmonary evaluation*.mp.	0	Advanced
21 (fitness adj2 test*).mp.	4717	Advanced
22 (Naughton adj2 Protocol*).mp.	142	Advanced
23 (Ramp adj2 Protocol*).mp.	928	Advanced
24 Spiroergometry.mp.	671	Advanced
25 (Step adj2 test*).mp.	6698	Advanced
26 (stress adj2 test*).mp.	35168	Advanced
27 (Treadmill adj2 test*).mp.	13161	Advanced
28 VO2 max test*.mp.	129	Advanced
29 (Walk* adj2 test*).mp.	43428	Advanced
30 or/1-29	191954	Advanced
31 exp heart failure/	643589	Advanced
32 (heart adj2 fail*).mp.	510952	Advanced
33 (cardiac adj2 fail*).mp.	26216	Advanced
34 cardio-renal syndrome*.mp.	655	Advanced
35 cardiorenal syndrome*.mp.	3564	Advanced
36 reno cardiac syndrome*.mp.	26	Advanced
37 renocardiac syndrome*.mp.	66	Advanced
38 cardiac asthma.mp.	132	Advanced
39 (paroxysmal adj2 dyspnea*).mp.	1550	Advanced
40 (cardiac adj2 decompensat*).mp.	2179	Advanced
41 (cardiac adj2 incompetence).mp.	64	Advanced
42 (cardiac adj2 insufficiency).mp.	4648	Advanced
43 (cardiac adj2 stand-still).mp.	5	Advanced
44 (cardial adj2 decompensat*).mp.	26	Advanced
45 (cardial adj2 insufficiency).mp.	46	Advanced
46 (heart* adj2 decompensat*).mp.	11236	Advanced
47 (heart* adj2 incompetence).mp.	63	Advanced
48 (heart* adj2 insufficiency).mp.	1341	Advanced
49 (myocardial adj2 failure*).mp.	5727	Advanced
50 (myocardial adj2 insufficiency).mp.	509	Advanced

51	cardiopulmonary insufficiency.mp.	6433	Advanced
52	cardio-pulmonary insufficiency.mp.	32	Advanced
53	pulmonocardiac insufficiency.mp.	0	Advanced
54	or/31-53	718263	Advanced
55	30 and 54	23115	Advanced
56	exp disease course/	4280926	Advanced
57	risk:.mp.	5144744	Advanced
58	diagnos:.mp.	7676219	Advanced
59	follow-up.mp.	2583717	Advanced
60	ep.fs.	1181248	Advanced
61	outcome.tw.	1870545	Advanced
62	prognos:.tw.	1203014	Advanced
63	survival.tw.	1762253	Advanced
64	or/56-63	15774162	Advanced
65	55 and 64	16708	Advanced
66	limit 65 to (conference abstract or conference paper or "conference review" or conference proceeding)	5823	Advanced
67	65 not 66	10885	Advanced
68	(exp animals/ or exp animal experimentation/ or nonhuman/) not ((exp animals/ or exp animal experimentation/ or nonhuman/) and exp human/)	7279341	Advanced
69	67 not 68	10780	Advanced

Ovid MEDLINE(R) ALL <1946 to October 18, 2023>

#	**Searches**	**Results**	**Type**
1	exp Exercise Test/	71235	Advanced
2	(Bicycle adj2 ergometer*).mp.	3435	Advanced
3	(Bicycle adj2 ergometre*).mp.	3	Advanced
4	(Bruce adj2 Protocol).mp.	1218	Advanced
5	(cardiopulmonary adj2 function test*).mp.	152	Advanced
6	(cardio-pulmonary adj2 function test*).mp.	5	Advanced
7	(cardiopulmonary adj2 performance test*).mp.	3	Advanced
8	(cardio-pulmonary adj2 performance test*).mp.	0	Advanced
9	CHF Protocol.mp.	6	Advanced
10	CPET.mp.	2441	Advanced
11	CPEX.mp.	25	Advanced
12	CPX.mp.	1678	Advanced
13	(Cycle adj2 Ergometer*).mp.	6385	Advanced
14	(Cycle adj2 ergometre*).mp.	2	Advanced

15 (ergometry adj2 test*).mp.	509	Advanced
16 Ergospirometry.mp.	265	Advanced
17 (Eurofit adj2 test*).mp.	108	Advanced
18 european fitness testing battery.mp.	0	Advanced
19 (Exercise adj2 test*).mp.	84105	Advanced
20 Exercise-induced cardiopulmonary evaluation*.mp.	0	Advanced
21 (fitness adj2 test*).mp.	4008	Advanced
22 (Naughton adj2 Protocol*).mp.	84	Advanced
23 (Ramp adj2 Protocol*).mp.	487	Advanced
24 Spiroergometry.mp.	336	Advanced
25 (Step adj2 test*).mp.	4679	Advanced
26 (stress adj2 test*).mp.	21056	Advanced
27 (Treadmill adj2 test*).mp.	8143	Advanced
28 VO2 max test*.mp.	79	Advanced
29 (Walk* adj2 test*).mp.	18501	Advanced
30 or/1-29	126751	Advanced
31 exp Heart Failure/	148847	Advanced
32 (heart adj2 fail*).mp.	259801	Advanced
33 (cardiac adj2 fail*).mp.	17217	Advanced
34 cardio-renal syndrome*.mp.	1120	Advanced
35 cardiorenal syndrome*.mp.	1454	Advanced
36 reno cardiac syndrome*.mp.	14	Advanced
37 renocardiac syndrome*.mp.	44	Advanced
38 cardiac asthma.mp.	147	Advanced
39 (paroxysmal adj2 dyspnea*).mp.	556	Advanced
40 (cardiac adj2 decompensat*).mp.	1492	Advanced
41 (cardiac adj2 incompetence).mp.	40	Advanced
42 (cardiac adj2 insufficiency).mp.	4622	Advanced
43 (cardiac adj2 stand-still).mp.	1	Advanced
44 (cardial adj2 decompensat*).mp.	16	Advanced
45 (cardial adj2 insufficiency).mp.	57	Advanced
46 (heart* adj2 decompensat*).mp.	5520	Advanced
47 (heart* adj2 incompetence).mp.	43	Advanced
48 (heart* adj2 insufficiency).mp.	1454	Advanced
49 (myocardial adj2 failure*).mp.	3822	Advanced
50 (myocardial adj2 insufficiency).mp.	495	Advanced
51 cardiopulmonary insufficiency.mp.	188	Advanced
52 cardio-pulmonary insufficiency.mp.	47	Advanced

53	pulmonocardiac insufficiency.mp.	0	Advanced
54	or/31-53	274971	Advanced
55	30 and 54	8699	Advanced
56	incidence/	302455	Advanced
57	exp Mortality/	424469	Advanced
58	Follow-Up Studies/	693533	Advanced
59	prognos*.mp.	1104376	Advanced
60	predict*.mp.	2183054	Advanced
61	course*.tw.	712389	Advanced
62	56 or 57 or 58 or 59 or 60 or 61	4523984	Advanced
63	55 and 62	4130	Advanced
64	animals/ not (animals/ and humans/)	5126674	Advanced
65	63 not 64	4119	Advanced
66	remove duplicates from 65	4118	Advanced

EBM Reviews - Cochrane Central Register of Controlled Trials

#	**Searches**	**Results**	**Type**
1	exp Exercise Test/	10414	Advanced
2	(Bicycle adj2 ergometer*).mp.	1734	Advanced
3	(Bicycle adj2 ergometre*).mp.	2	Advanced
4	(Bruce adj2 Protocol).mp.	406	Advanced
5	(cardiopulmonary adj2 function test*).mp.	41	Advanced
6	(cardio-pulmonary adj2 function test*).mp.	1	Advanced
7	(cardiopulmonary adj2 performance test*).mp.	1	Advanced
8	(cardio-pulmonary adj2 performance test*).mp.	0	Advanced
9	CHF Protocol.mp.	1	Advanced
10	CPET.mp.	794	Advanced
11	CPEX.mp.	9	Advanced
12	CPX.mp.	324	Advanced
13	(Cycle adj2 Ergometer*).mp.	2618	Advanced
14	(Cycle adj2 ergometre*).mp.	0	Advanced
15	(ergometry adj2 test*).mp.	194	Advanced
16	Ergospirometry.mp.	121	Advanced
17	(Eurofit adj2 test*).mp.	27	Advanced
18	european fitness testing battery.mp.	0	Advanced
19	(Exercise adj2 test*).mp.	18471	Advanced
20	Exercise-induced cardiopulmonary evaluation*.mp.	0	Advanced
21	(fitness adj2 test*).mp.	1120	Advanced

22 (Naughton adj2 Protocol*).mp.	39	Advanced
23 (Ramp adj2 Protocol*).mp.	131	Advanced
24 Spiroergometry.mp.	158	Advanced
25 (Step adj2 test*).mp.	1264	Advanced
26 (stress adj2 test*).mp.	3767	Advanced
27 (Treadmill adj2 test*).mp.	2603	Advanced
28 VO2 max test*.mp.	66	Advanced
29 (Walk* adj2 test*).mp.	13087	Advanced
30 or/1-29	37087	Advanced
31 exp Heart Failure/	14489	Advanced
32 (heart adj2 fail*).mp.	36007	Advanced
33 (cardiac adj2 fail*).mp.	1538	Advanced
34 cardio-renal syndrome*.mp.	71	Advanced
35 cardiorenal syndrome*.mp.	118	Advanced
36 reno cardiac syndrome*.mp.	0	Advanced
37 renocardiac syndrome*.mp.	1	Advanced
38 cardiac asthma.mp.	13	Advanced
39 (paroxysmal adj2 dyspnea*).mp.	43	Advanced
40 (cardiac adj2 decompensat*).mp.	127	Advanced
41 (cardiac adj2 incompetence).mp.	1	Advanced
42 (cardiac adj2 insufficiency).mp.	367	Advanced
43 (cardiac adj2 stand-still).mp.	1	Advanced
44 (cardial adj2 decompensat*).mp.	1	Advanced
45 (cardial adj2 insufficiency).mp.	2	Advanced
46 (heart* adj2 decompensat*).mp.	1339	Advanced
47 (heart* adj2 incompetence).mp.	7	Advanced
48 (heart* adj2 insufficiency).mp.	98	Advanced
49 (myocardial adj2 failure*).mp.	444	Advanced
50 (myocardial adj2 insufficiency).mp.	31	Advanced
51 cardiopulmonary insufficiency.mp.	155	Advanced
52 cardio-pulmonary insufficiency.mp.	0	Advanced
53 pulmonocardiac insufficiency.mp.	0	Advanced
54 or/31-53	37190	Advanced
55 30 and 54	3772	Advanced
56 incidence/	15025	Advanced
57 exp Mortality/	21520	Advanced
58 Follow-Up Studies/	67405	Advanced
59 prognos*.mp.	54421	Advanced

60	predict*.mp.	117512	Advanced
61	course*.tw.	68273	Advanced
62	56 or 57 or 58 or 59 or 60 or 61	290747	Advanced
63	55 and 62	1012	Advanced
64	remove duplicates from 63	1008	Advanced

EBM Reviews - Cochrane Database of Systematic Reviews <2005 to October 18, 2023>

#	**Searches**	**Results**	**Type**
1	(Bicycle adj2 ergometer*).ti,ab.	0	Advanced
2	(Bicycle adj2 ergometre*).ti,ab.	0	Advanced
3	(Bruce adj2 Protocol).ti,ab.	0	Advanced
4	(cardiopulmonary adj2 function test*).ti,ab.	0	Advanced
5	(cardio-pulmonary adj2 function test*).ti,ab.	0	Advanced
6	(cardiopulmonary adj2 performance test*).ti,ab.	0	Advanced
7	(cardio-pulmonary adj2 performance test*).ti,ab.	0	Advanced
8	CHF Protocol.ti,ab.	0	Advanced
9	CPET.ti,ab.	1	Advanced
10	CPEX.ti,ab.	0	Advanced
11	CPX.ti,ab.	1	Advanced
12	(Cycle adj2 Ergometer*).ti,ab.	1	Advanced
13	(Cycle adj2 ergometre*).ti,ab.	0	Advanced
14	(ergometry adj2 test*).ti,ab.	0	Advanced
15	Ergospirometry.ti,ab.	1	Advanced
16	(Eurofit adj2 test*).ti,ab.	0	Advanced
17	european fitness testing battery.ti,ab.	0	Advanced
18	(Exercise adj2 test*).ti,ab.	19	Advanced
19	Exercise-induced cardiopulmonary evaluation*.ti,ab.	0	Advanced
20	(fitness adj2 test*).ti,ab.	0	Advanced
21	(Naughton adj2 Protocol*).ti,ab.	0	Advanced
22	(Ramp adj2 Protocol*).ti,ab.	0	Advanced
23	Spiroergometry.ti,ab.	0	Advanced
24	(Step adj2 test*).ti,ab.	2	Advanced
25	(stress adj2 test*).ti,ab.	0	Advanced
26	(Treadmill adj2 test*).ti,ab.	7	Advanced
27	VO2 max test*.ti,ab.	0	Advanced
28	(Walk* adj2 test*).ti,ab.	33	Advanced
29	or/1-28	54	Advanced
30	(heart adj2 fail*).ti,ab.	145	Advanced

31 (cardiac adj2 fail*).ti,ab.	11	Advanced
32 cardio-renal syndrome*.ti,ab.	0	Advanced
33 cardiorenal syndrome*.ti,ab.	0	Advanced
34 reno cardiac syndrome*.ti,ab.	0	Advanced
35 renocardiac syndrome*.ti,ab.	0	Advanced
36 cardiac asthma.ti,ab.	0	Advanced
37 (paroxysmal adj2 dyspnea*).ti,ab.	0	Advanced
38 (cardiac adj2 decompensat*).ti,ab.	0	Advanced
39 (cardiac adj2 incompetence).ti,ab.	0	Advanced
40 (cardiac adj2 insufficiency).ti,ab.	0	Advanced
41 (cardiac adj2 stand-still).ti,ab.	0	Advanced
42 (cardial adj2 decompensat*).ti,ab.	0	Advanced
43 (cardial adj2 insufficiency).ti,ab.	0	Advanced
44 (heart* adj2 decompensat*).ti,ab.	6	Advanced
45 (heart* adj2 incompetence).ti,ab.	0	Advanced
46 (heart* adj2 insufficiency).ti,ab.	0	Advanced
47 (myocardial adj2 failure*).ti,ab.	3	Advanced
48 (myocardial adj2 insufficiency).ti,ab.	0	Advanced
49 cardiopulmonary insufficiency.ti,ab.	0	Advanced
50 cardio-pulmonary insufficiency.ti,ab.	0	Advanced
51 pulmonocardiac insufficiency.ti,ab.	0	Advanced
52 or/30-51	151	Advanced
53 29 and 52	1	Advanced