ΕΛΛΗΝΙΚΗ ΔΗΜΟΚΡΑΤΙΑ
Εθνικόν και Καποδιστριακόν Πανεπιστήμιον Αθηνών
ΙΔΡΥΘΕΝ ΤΟ 1837

Ιατρική Σχολή

Πρόγραμμα Μεταπτυχιακών Σπουδών

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Ερευνητική Διπλωματική Εργασία

«Comparing Circulatory Power (CircP) index and central haemodynamic factors during cardiopulmonary exercise testing between normotensive and hypertensive patients»

Σπυριδούλα Φιλίππου

Α.Μ.: 7450202100022

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Αθανάσιος Πρωτογέρου

Αθήνα, 2024

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Αθήνα, 2024

Στη μικρή

ΠΕΡΙΕΧΟΜΕΝΑ

ΑΝΑΛΥΤΙΚΑ ΠΕΡΙΕΧΟΜΕΝΑ

ΕΚΦΡΑΣΗ ΕΥΧΑΡΙΣΤΙΩΝ

Η παρούσα διπλωματική εργασία εκπονήθηκε στα πλαίσια του Προγράμματος Μεταπτυχιακών Σπουδών «Μοριακή και Εφαρμοσμένη Φυσιολογία» της Ιατρικής Σχολής του Εθνικού και Καποδιστριακού Πανεπιστημίου Αθηνών. Με την ολοκλήρωση του προγράμματος θέλω να ευχαριστήσω όλους όσους συνέβαλαν στη διεκπεραίωση της παρούσας μελέτης. Αρχικά, θέλω να εκφράσω τις βαθύτατες και εγκάρδιες ευχαριστίες μου στον Καθηγητή κ. Αθανάσιο Πρωτογέρου για την εμπιστοσύνη, την υποστήριξη και την καθοδήγηση σε μονοπάτια γνώσης της Παθοφυσιολογίας. Είχα την τιμή να έχω σαν επιβλέποντα, έναν καθηγητή πρότυπο για όλους τους φοιτητές, ο οποίος δίνει συνεχώς ερεθίσματα και κίνητρο για ουσιαστική έρευνα.

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ΠΕΡΙΛΗΨΗ

Εισαγωγή: Ο δείκτης κυκλοφορικής ισχύος (CircP) ενισχύει την προγνωστική αξία της καρδιοαναπνευστικής δοκιμασίας κοπώσεως σε ένα μεγάλο εύρος καρδιαγγειακών παθήσεων και παθήσεων του πνεύμονα. Ωστόσο, ο συγκεκριμένος δείκτης έχει μελετηθεί σε περιορισμένο εύρος κλινικού πληθυσμού. Οι διαφορές στις τιμές του CircP ανάμεσα σε νορμοτασικούς και υπερτασικούς ασθενείς, καθώς και η συσχέτισή του με την αορτική δυσκαμψία (ταχύτητα καρωτιδο-μηριαίου σφυγμικού κύματος, cfPWV), τις ανακλάσεις των κυμάτων πίεσης (δείκτης επαύξησης κυμάτων, AIx) και την αναδιαμόρφωση των καρωτίδων (πάχος έσω χιτώνα, IMT), δεν έχει διερευνηθεί μέχρι στιγμής. Σκοπός της παρούσας μελέτης είναι να ελεγχθούν οι υποθέσεις ότι ο CircP είναι υψηλότερη στα νορμοτασικά από ό,τι στα υπερτασικά άτομα και, ότι ο CircP θα σχετίζεται σημαντικά με τους κεντρικούς αιμοδυναμικούς δείκτες και την καρωτιδική αναδιαμόρφωση.

Μέθοδος: Σε σταθερές εργαστηριακές συνθήκες μετρήθηκαν οι τιμές των δεικτών cfPWV και AIx με τη χρήση της συσκευής Sphygmocor AtCor που διαθέτει ενσωματωμένο αλγόριθμο για την ανάλυση των σφυγμικών κυμάτων. Ο δείκτης IMT της αριστερής και δεξιάς κοινής καρωτίδας μετρήθηκε με υπερηχογράφημα. Σε ξεχωριστή μέρα, πραγματοποιήθηκε καρδιοαναπνευστική δοκιμασία κοπώσεως. Ο δείκτης CircP υπολογίστηκε ως το γινόμενο της μέγιστης κατανάλωσης οξυγόνου (VO2peak; ml O2-kg-1 -min-1), που προέκυψε από την ανάλυση αερίων, και της μέγιστης συστολικής αρτηριακής πίεσης (peak SBP; mmHg), που προέκυψε από άλλη συσκευή καταγραφής ενσωματωμένη στο κυκλοεργόμετρο. Όλα τα άτομα διεξήγαγαν εξατομικευμένο, σταδιακά αυξανόμενο, πρωτόκολλο breath-by-breath σε ποδηλατικό εργόμετρο. Πραγματοποιήθηκε ανάλυση γραμμικής παλινδρόμησης και t-test σε 2 ανεξάρτητα δείγματα.

Αποτελέσματα: Η ανάλυση πραγματοποιήθηκε σε 34 συμμετέχοντες (ηλικίας 54,63±12,7 ετών, 67% άνδρες, 79% υπερτασικοί, 88% δυσλιπιδαιμικοί, 18% με διαβήτη τύπου 1 και 3% ασθενείς με διαβήτη τύπου 2). Βρέθηκε ότι οι νορμοτασικοί είχαν υψηλότερες τιμές του CircP από τους υπερτασικούς (4333±1920 έναντι 3193±797). Επιπλέον, ο CircP βρέθηκε να εξαρτάται σημαντικά από την ηλικία (0,004, $p<0,01$) και τον δείκτη μάζας σώματος (0,028, $p<0,05$). Ο δείκτης AIx (-0,005, $p<0,01$), το αριστερό και το δεξιό IMT (-0,015, $p<0,05$; -0,004, $p<0,01$) βρέθηκαν να έχουν σημαντική συσχέτιση με τον CircP.

Συμπέρασμα: Ο δείκτης CircP ήταν υψηλότερος στους νορμοτασικούς συμμετέχοντες και σχετίζεται σημαντικά με την ανάκλαση των κυμάτων πίεσης και την αναδιαμόρφωση των καρωτίδων.

Λέξεις κλειδιά: Κυκλοφορική ισχύς, Καρδιοαναπνευστική δοκιμασία κοπώσεως, Υπέρταση, Ανάλυση κυμάτων πίεσης, Αναδιαμόρφωση καρωτίδων

ABSTRACT

Background: Circulatory Power (CircP) enhances the prognostic value of cardiopulmonary exercise test (CPET) in a wide range of cardiovascular and pulmonary diseases; however, it has been investigated only in specific ones. The differences in CircP between normotensive and hypertensive individuals, as well as its association with aortic stiffness (carotid-femoral pulse wave velocity, cfPWV), pressure wave reflections (augmentation index, AIx) and carotid remodeling (intima-media thickness, IMT), has not been investigated so far. To test the hypotheses that CircP is higher in normotensive than in hypertensive individuals and, that CircP will be significantly associated with carotid remodeling.

Method: Under standardized laboratory conditions using the Sphygmocor AtCor device having a built-in algorithm for pulse wave analysis, cfPWV and AIx were measured; left/ right common carotid IMT were measured by ultrasound. A separated day CPET was performed and CircP was calculated as the product of peak oxygen consumption (VO2peak; mL O2·kg−1 ·min−1), derived from gas analyzer, and peak systolic blood pressure (peak SBP; mmHg), derived from another cuff-based recording device. All individuals conducted an individualized incremental breath-by-breath protocol on cycle ergometer. Linear regression analysis and 2 independent samples t-test were performed.

Results: Analysis was performed in 34 consecutive individuals (aged 54,63±12,7; 67% men; 79%hypertensive; 88% dyslipidemic; 18% with type 1 diabetes; 3% patients with type 2 diabetes); normotensive had higher units of CircP than hypertensive (4333±1920 versus 3193±797). CircP was found to depend considerably on age (0.004, $p<0.01$), body mass index (0.028, $p<0.05$). AIx (-0.005, $p<0,01$), left and right IMT (-0.015, $p<0.05$; -0.004, $p<0.01$) were found to have significant correlation with CircP.

Conclusion: CircP is higher in normotensive than in hypertensive individuals, and it is significantly associated with pressure wave reflections and carotid remodeling.

Keywords: circulatory power; cardiopulmonary exercise test; hypertension; pulse wave analysis; carotid remodeling

ABBREVIATIONS

AHA: American Heart Association

AIx: Augmentation Index

AP: Arterial Pressure

AT: Anaerobic Threshold

baPWV: brachial- ankle Pulse Wave Velocity

BP: Blood Pressure

BR: Breathing Reserve

CAD: Coronary Artery Disease

cfPWV: carotid- femoral Pulse Wave Velocity

CircP: Circulatory Power

COPD: Chronic Obstructive Pulmonary Disease

CPET: Cardiopulmonary Exercise Test

CV: Cardiovascular

CVD: Cardiovascular Disease

DBP: Diastolic Blood Pressure

ECG: Electrocardiogram

HR: Heart Rate

HRQoL: Health- Related Quality of Life

PP: Pulse Pressure

PWV: Pulse Wave Velocity

RER: Respiratory Exchange Ratio

SBP: Systolic Blood Pressure

SpO2: Oxygen Saturation

T2DM: Type 2 Diabetes Mellitus

VE: Ventilatory Efficiency

VO2: Oxygen Uptake

VO2peak: Peak Oxygen Uptake

1. INTRODUCTION

The cardiorespiratory fitness (CRF), as assessed by detailed Cardiopulmonary Exercise Test (CPET) methodology (Ross et. al 2016 (AHA scientific statement)) has strong association with the health-related quality of life (HRQoL) (Appelqvist-Schmidlechner et al., 2020) and an inverse, independent and graded association between all-cause mortality across the age spectrum (Kokkinos et al., 2022). CRF is now recognized as an important marker of cardiovascular health and it is currently a major risk factor not routinely assessed in clinical practice (Ross et al.,2016). In fact, the majority of individuals in the United States who are defined as apparently healthy have less-than-ideal cardiovascular health, as a result of unhealthy lifestyle characteristics largely due to physical inactivity in a addition to other unhealthy life style factors (poor diet, excess body weight, smoking) (Mozaffarian, et.al. 2015).

A large body of epidemiological and clinical evidence demonstrate that CRF, particularly exercise intolerance, as assessed by detailed CPET methodology is a potentially stronger predictor of mortality than established risk factors (including as smoking, hypertension, high cholesterol, and type 2 diabetes mellitus (T2DM)). So, the addition of CRF to traditional risk factors may significantly improve the reclassification of risk for adverse outcomes (Ross et al., 2016).

There are different methods to assess CRF, but CPET is considered the safest and most reliable method, since data that derive from cardiorespiratory tests at rest have little clinical relevance (Myers et al., 2009). Moreover, through the assessment of cardiorespiratory fitness, it is easier to determine the presence of pathology and to apply clinical guidelines and lifestyle changes (Guazi et al., 2012). Assessing the physiological response to aerobic exertion provides a wealth of information on potential underlying abnormalities that, if detected, might be addressed before the subject develops a noncommunicable disease or suffers an initial adverse event (Guazi, et.al. 2016).

CRF has been proven that improves arterial health through physical exercise training either with aerobic or resistance training (Carcone et al., 2020, Lopes et al., 2021). CPET provides numerous indicators of CRF. Circulatory Power (CircP) seems to be the strongest independent predictor of mortality among other CPET parameters (Giardini et al., 2007),) and characterizes the association between cardiac-generated blood flow and peripheral perfusion pressure (Forman et al., 2012). CircP as a CPET metric can enhance risk stratification and classification of diseases in patients with a wide range of cardiovascular and pulmonary conditions (Busque 2022).

Hypertension is one of the prevailing risk factors for the development of several cardiovascular diseases such as coronary artery disease, congestive heart failure, atrial fibrillation, peripheral arterial disease, aortic aneurysm, and chronic kidney disease (Tackling and Borhade, 2023). Age-adjusted increase of arterial stiffness is accelerated by uncontrolled hypertension (Benetos et al., 2022). However, increased arterial stiffness is now days considered to be a precursor and predictor of the hypertension incidence (Agbaje et al., 2022, Najjar et al., 2008). Arterial stiffness results from a degenerative process affecting mainly the extracellular matrix of elastic arteries under the effect of aging and risk factors. There are many methods and indices to assess

arterial stiffening; among them pulse wave velocity (PWV), the speed of an arterial pulsation through the arterial tree, is the most widely applied and clinically relevant, especially between carotid and femoral arteries (Vlachopoulos et al., 2015). Other indices, indirectly and only partly relevant to arterial stiffness, that derive also by central pulse wave analysis, are the augmentation pressure (AP) or augmentation index (AIx). AIx is a percentage of AP on aortic pulse pressure (Nichols et al., 2011, Vlachopoulos et al., 2015) quantifying of pressure wave reflections (Safar et al., 2008). Changes in extracellular matrix proteins and in the mechanical properties of the vessel wall related to arterial stiffening may activate number of mechanisms involved also in the process of atherosclerosis (Palombo et al., 2015). Intima-media thickness (IMT) is a marker of atherosclerosis, associated with CAD and has a positive linear correlation between carotid IMT and cfPWV in general population, hypertensive, and diabetic patients (Kim H-L et al., 2019). It has been demonstrated that CIMT values at baseline strongly predicted incident hypertension after 4 years of follow-up (Dutra et al., 2024). The aim of this study is to fill the gap in the available data about CircP values and to provide further information about central haemodyamic factors and their association with CPET indicators of CRF.

2. GENERAL SECTION

2.1 Cardiopulmonary Exercise Testing (CPET)

Over the years, the abundance of research around the test has led to the establishment of its importance and a considerable amount of valuable information. From the original trial tests, we have reached the point of applying it to a clinical study population, thus enhancing its use in daily clinical practice. “It is likely that no test in medicine is as informative and cost-effective as cardiopulmonary exercise testing for distinguishing among the broad spectrum of disorders causing symptoms of exercise intolerance. Without it, the evaluation of patients with exercise intolerance maybe too narrowly focused by the physician’s particular subspecialty.” (Sietsema et.al. 2021). The cardiorespiratory stress test is an essential tool for the proper assessment of a healthy person or patient participating in an exercise or rehabilitation program (Νανάς, 2006). Within UK respiratory departments, the number of CPET increased by 81% between 2005 and 2015 with an estimated annual increase of 8% per year (Bucknall et.al. 2018). CPET is routinely performed on both adult and pediatric patients, in respiratory or cardiology laboratories, and is increasingly being performed in anesthetic departments or presurgical assessment units (Pritchard et.al. 2021). The AHA states that early exercise stress testing in emergency departments and chest pain units is safe, accurate, and cost-effective because of fewer hospital admissions (Fletcher et.al. 2013).

CPET is a relatively non-invasive objective test which provides a direct objective measurement of the global exercise responses of the respiratory, cardiovascular, and skeletal muscle systems during incremental exercise (Pritchard et.al. 2021). Experts recommend that deconditioned patients with diabetes mellitus, men older than 45 years or women older than 55 years, and those with two or more risk factors for CAD undergo exercise stress testing before starting a vigorous exercise program (Garner et.al. 2017). Through the test, basic mechanisms of pathophysiology are detected, factors limiting exercise are quantified and the progression of the disease and response to treatment is assessed. CPET can be particularly valuable in identifying the source of exercise intolerance, monitoring disease progression, evaluating treatment responsiveness and providing information about prognosis (Glaab et.al. 2022). Also, offers to the clinician the ability to obtain a wealth of information beyond standard exercise testing that, when appropriately applied and interpreted, can assist in the management of complex cardiovascular and pulmonary disease (Balady et.al. 2010). CPET test supervision, monitoring, and interpretation should be performed by competent personnel as recommended in established exercise testing guidelines (Rodgers et.al. 2000). Assessment of ventilatory efficiency provides insight into cardiopulmonary coupling and function and, when abnormal, is related to lower levels of aerobic capacity (Loe et.al. 2014) and may indicate subclinical pathophysiology that warrants further investigation (Guazi et.al. 2016).

Deficiencies in CPET-derived variables specifically ventilatory anaerobic threshold (AT), peak O2 consumption (VO2peak), and ventilatory efficiency for carbon dioxide (VE/VCO2) are associated with poor postoperative outcomes (mortality, morbidity, admission to intensive care, and length of hospital stay) after intra-abdominal surgery (Older et. al. 1999, Moran et.al. 2016, Hartley et.al. 2012, Wilson et.al. 2010). Preoperative exercise stress testing is not indicated for risk stratification before non-cardiac surgery in patients who are able to achieve a minimum of 4 METs (e.g., walking up one flight of stairs) without cardiac symptoms, even if they have a history of CAD

(Wolk et.al. 2014, Scott et.al. 2014). Exercise stress testing is helpful for risk stratification in patients undergoing vascular surgery and in those who have active cardiac symptoms before undergoing nonemergent noncardiac surgery (Wolk et.al. 2014, Scott et.al. 2014). The physiologic factors that determine maximal exercise capacity have long attracted the attention of exercise scientists, and a great deal of effort continues in this area. Clearly, the most influential factors are age, gender, and genetic endowment. Although these factors are rather intuitive, the question more often concerns what limits subjects who are relatively homogeneous (Myers et.al. 2001). Major factors that influence maximal exercise capacity are age, gender, genetics, physical training, environmental conditions (heat, cold), and the presence or not of a heart disease (Myers et.al. 2001).

Physiology of exercise testing

A single bout of exhaustive exercise, such as that required by a graded exercise test, requires the coordinated interaction of virtually all the body's physiologic and metabolic systems. The cardiopulmonary system has a particularly crucial role in the acute response to exercise. The cardiovascular system responds to acute exercise with a series of adjustments that ensure active muscles receive a blood supply that is appropriate to their metabolic needs, that heat generated by the muscles is dissipated, and that blood supply to the brain and heart is maintained. This requires a major redistribution of cardiac output along with several local metabolic changes. Because the demands placed on the heart muscle during acute exercise can be severe and may result in abnormalities that are not present at rest, the exercise test has long been recognized as a valuable tool to evaluate cardiac perfusion and function under controlled conditions. Maximal work relies virtually entirely on carbohydrates. At higher levels of exercise, total body oxygen demand may exceed the capacity of the cardiovascular system to deliver oxygen. Oxygen uptake increases linearly with increasing work. Traditionally, oxygen uptake has been termed maximal when it no longer increases with increasing work (i.e., it levels off) (Myers et.al. 2001).

Cardiac output must closely match ventilation in the lung to deliver oxygenated blood to the working muscle. The physiologic response to exercise requires the integration of cardiac, pulmonary, and peripheral components. To perform large amounts of work, an individual must take a large amount of air into the lung. The amount of air moving into and out of the lung is usually measured in exhaled liters per minute, expressed as minute ventilation (VE), and can easily be quantified with automated techniques. Maximal VE is an important concept in terms of cardiopulmonary performance; for the skeletal muscle to consume oxygen, blood must be delivered to the lungs by the heart, ventilation must match cardiac output in the lung, and efficient gas exchange must occur. Inefficient ventilation, even in the absence of clinically apparent pulmonary disease, contributes to abnormal exercise responses in certain disease states (Myers et.al. 2001).

Indications

The cardiorespiratory stress test is an important tool for the entire scientific team of clinicians related to rehabilitation and health. The use of exercise testing procedures, including CPET, is still not common in apparently healthy individuals receiving health care (e.g., as part of an annual checkup with a primary care physician (Guazi et.al. 2016.) CPET can be particularly valuable in identifying the source of exercise

intolerance (pathophysiology of exercise limitation), monitoring disease progression, evaluating treatment responsiveness and providing information about prognosis (Glaab et.al. 2022). The results of the test can contribute either to diagnosis or to treatment planning when it comes to a specific condition.

The test can provide many values that will help to draw conclusions and therefore there are several indications for referring to a test. The most common ones are summarized below (Glaab et.al. 2022):

(a) determining the cause(s) and severity of exertional dyspnea, exercise intolerance or exercise-induced hypoxaemia;

For patients with unexplained dyspnea and for whom initial test results are nondiagnostic, the weight of evidence suggests that CPET is a useful tool in identifying the following: cardiac and/ or pulmonary causes (ATS, 2003), mitochondrial myopathy (e.g., ragged red fiber disease and McArdle's syndrome) (Hooper et.al. 1995, Elliot et.al. 1989, Flaherty et.al. 2001, Dandurand et.al. 1995), and psychological factors (hyperventilation, panic, anxiety syndromes, etc.) or deconditioning (Pratter et.al. 1989, Martinez et.al. 1999, Weisman et.al. 1996, Taivassalo et.al. 1998). the weight of evidence suggests that the global assessment provided by comprehensive CPET in the evaluation of exercise intolerance permits a unique and objective determination of functional capacity. Also, impairment, quantification of factors limiting exercise, definition of the underlying pathophysiologic mechanisms such as the contribution of respiratory versus cardiac etiology in the setting of coexisting illness, timely detection of early (occult) disease (e.g., ischemia), (Weisman et.al. 1994, Sue et.al. 1991, Weber et.al. 1986, ATS 2003).

(b) assessing exercise capacity and estimating prognosis in various disease states (including chronic heart failure).

Strong evidence exists to support the value of CPET in the assessment of exercise capacity and response to therapy of patients with heart failure who are being considered for heart transplantation (Mancini et.al. 1991, Stevenson et.al. 1995). A study has reported that abnormally high minute ventilation for a given level of metabolism (high slope of VE–VCO2 relationship), was found to be an independent prognostic marker in patients with severe heart failure (Chua et.al. 1997).

(c) assessing perisurgical and postsurgical complication risk (e.g., for thoracic, heart and visceral surgery; surgical and bronchoscopic lung volume reduction);

The National Institutes of Health-sponsored multicenter National Emphysema Treatment Trial, evaluating the efficacy of LVRS, has chosen the maximal work rate derived from CPET as its primary physiologic outcome parameter, because it was considered to be the best objective measure of functional status (ATS/ ACCP, 2003). CPET is useful in assessing disease progression before transplantation, and in assessing functional capacity, quantitating causes of exercise limitation, and providing exercise prescription for pulmonary rehabilitation before and after transplantation (Howard et.al. 1994, ATS/ACCP 2003).

(d) measuring the response to treatment (e.g., drugs, rehabilitation)

(e) guiding and monitoring individual physical training in rehabilitation (e.g., cardiac, pulmonary), and in preventive and sports medicine

(f) evaluating the limitations/impairments of individual maximum and continuous exercise capacity in occupational medicine

Consensus opinion from the ACCF/AHA is that exercise stress testing can be used for exercise prescriptions, but data on patient-oriented outcomes are lacking (Garner et.al. 2017).

Contraindications to exercise testing

For certain individuals the risks of exercise testing outweigh the potential benefits. For these patients it is important to carefully assess risk versus benefit when deciding whether the exercise test should be performed (ACSM Guidelines, 2000). There are absolute and relative contraindications to exercise testing (ACSM Guidelines 2000).

Absolute contraindications	**Relative contraindications**
Active endocarditis	Acquired complete heart block (left bundle branch block)
Acute aortic dissection	Hypertrophic obstructive cardiomyopathy with severe resting gradient
Acute myocarditis/pericarditis	Known left main coronary artery disease
Decompensated heart failure inability to exercise	Recent stroke or transient ischemic attack
Myocardial infraction in previous two days	Resting systolic blood pressure >200mg or diastolic blood pressure >110 mg Hg
Ongoing unstable angina	Tachyarrythmia with uncontrolled ventricular rate
Symptomatic severe aortic stenosis	
Uncontrolled cardiac arrhythmia with hemodynamic compromise	

Table 1. Contraindications to Exercise Testing (Garner et al.2017)

Important electrolyte imbalance, and hyperthyroidism. It is essential before preforming the test to have a complete check-up and medical history to identify these contraindications. Patients with absolute contraindications should not perform exercise tests until such conditions are stabilized or adequately treated. Patients with relative contraindications may be tested only after careful evaluation of the risk/benefit ratio (ACSM Guidelines, 2000) and whether the clinical benefit will outweigh the potential risks (Ναναζ, 2006). Although absolute contraindications are clear, in selected cases with relative contraindications to high level exercise, even submaximal testing can provide valuable information about functional capacity and prognosis (Fletcher et.al. 2013). Patients who are unable to exercise because of neurological or orthopedic

problems are not candidates for exercise testing (ATS/ACCP, 2003). Those patients whose disability is limited to the lower extremities may be candidates for arm-cranking ergometry, although the peak VO2 (and thus the stress to the cardiac and pulmonary systems) for arm exercise averages only roughly 70% of peak Vo2 for leg exercise in healthy subjects (Casaburi et.al. 1992, Martin et.al. 1991).

Calibration- Procedure

Calibration is a major point for the test. The validity of the results depends for a large part in the quality of daily calibration of the ergo spirometry system (Cohen-Solal, Carré 2012). The first stage is a warm-up period for the device of at least 20 minutes which is essential for the analyzers. Calibration of the flow sensor and the gas analyzers of the metabolic cart are usually performed just prior to starting the CPET (Radtke et.al. 2019). Gas analyzers must be calibrated at least daily and repeatedly in the case of very high use of the system if there are any changes in the composition of ambient gases and/or if outliers observed. (Cohen-Solal, Carré 2012). The calibration data must be recorded. The quality of acquisition of the other parameters including ECG, BP, SaO2 must also be checked before exercise testing. Ergometers must be calibrated at least annually. Cardiopulmonary exercise testing, especially when it features breath-by-breath gas exchange analysis, requires meticulous attention to calibration procedures to assure accurate and reproducible measurements (ATS/ACCP, 2003).

The cardiorespiratory exercise test involves 10-15 minutes of continuous exercise until exhaustion and requires the cooperation of the respiratory, cardiovascular and muscular systems to achieve it. The cooperation of these systems can provide information on the function of the respiratory cardiovascular, microcirculatory and musculoskeletal systems in response to exercise to exhaustion conditions. From the data obtained it will be possible to identify dysfunction in a specific target organ. Thus, it could be said that the cardiorespiratory stress test records the body's response to acute exercise by using data from metabolic measurement systems in addition to the electrocardiogram (Νανάς, 2006). The purpose of the test is to check the systems involved in exercise under conditions of increased metabolic demands.

CPET provides a global assessment of the integrative exercise responses involving the pulmonary, cardiovascular, hematopoietic, neuropsychological, and skeletal muscle systems, which are not adequately reflected through the measurement of individual organ system function. This relatively noninvasive, dynamic physiologic overview permits the evaluation of both submaximal and peak exercise responses, providing the physician with relevant information for clinical decision making (ATS/ACCP, 2003). Two modes of exercise are commonly employed in cardiopulmonary exercise tests: treadmill and cycle ergometer. In most clinical circumstances, cycle ergometry is the preferable mode of exercise; however, depending on the reason(s) for which CPET was requested and equipment availability, a treadmill may be an acceptable alternative (ATS/ACCP, 2003) According to current recommendations (Sietsema et.al. 2021, Guazzi et.al. 2012, Arena et.al. 2011, Kroidl et.al. 2015, Radtke et.al. 2019) the CPET procedure is divided into four parts:

1. Resting phase (2–3 min): adaptation of respiration to the mask or mouthpiece including measurements of capillary BGA, ECG and blood pressure.

2. Unloaded phase ("active baseline"; 2–3 min): unloaded cycling with no added resistance (internal work rate depending on equipment: 0–15 watts), cadence 55–70 revolutions per min (rpm)VO2 normally doubles during this warm-up phase.

3. Incremental exercice phase (10 ± 2 min): cadence ± 55–70 rpm.

4. Recovery phase (cool down period; 3–5 min): unloaded pedaling

(Glaab et.al 2022)

Consent

Any patient attending for CPET should therefore be provided with all relevant information about the test process, the risks, and benefits of completing the investigation, and implications of not performing the test. This information should be presented in lay terms. If the subjects change their mind at any point before the test commences or even during the test, the test must be stopped. Patients attending for a CPET should receive clear information ahead of the appointment, which clearly outlines the test procedure and provides a rationale for why the test is required (Pritchard et.al. 2021).

Preparation

Before, during and after CPET, the practitioner must consider all aspects involved with the patient's test. Practitioners should always remain professional, answer any patient questions honestly and avoid asking leading questions. Consideration for the patient's dignity when undressing and during ECG preparation should be paramount. (Pritchard et.al. 2021). It is very important that the test taker follows the instructions given to him/her regarding what to do before the test. These are given below (Pritchard et.al. 2021):

- Refrain from exercise on the day of the test and be well rested
- Eat a light meal or breakfast no less than 2 hours before the test
- Maintain hydration by drinking water
- Avoid caffeine and alcohol prior to the test
- Take all routine/normal medication and bring along a medication list (unless otherwise clearly indicated, e.g., beta-blockers for the diagnosis of myocardial ischemia)
- Bring along all rescue medications, for example, inhalers or nitrolingual sprays
- Wear light comfortable clothing and shoes suitable to exercise
- Abstain from smoking for at least 8 hours hours prior to the test
- Refrain from wearing any nail varnish or false nails.

A brief history and physical examination are required to rule out contraindications to testing and to detect important clinical signs, such as cardiac murmur, gallop sounds, pulmonary wheezing, or rales. Physical examination should screen for valvular or

congenital heart disease, and abnormal hemodynamic responses to exercise in these patients could require early termination of testing (Fletcher et.al. 2013).

It is also important to ascertain information regarding the patient's mobility prior to the test. Good practice is therefore to trial the patient on the cycle ergometer before preparing the patient for the ECG electrode placement. Patients with severe end-stage arthritis undergoing preassessment for total hip replacement or knee replacement are capable of maximal symptom limited exercise using ergometry methods (Philbin et.al. 1995). Patients should be as relaxed as possible before the test and should be seated for 5–10 min prior to testing. The purpose and nature of the test should be clearly and fully (Sylvester et.al. 2020) explained to the patient allowing opportunities for the patient to ask questions or to clarify any concerns (Pritchard et.al. 2021).

Choice of protocol

The mode selected for the exercise test can impact the results and should be selected based on the purpose of the test and the individual being tested (Fletcher et.al. 2013). Classification is based on the manner in which the work rate is applied: (*1*) progressive incremental exercise (every minute) or continuous ramp protocol; (*2*) a multistage exercise protocol (every 3 minutes, with a "pseudo"- steady state at each level); (*3*) a constant work rate (the same work rate, usually for 5 to 30 minutes); or (*4*) a discontinuous protocol, which consists of short periods (3–4 minutes) of constant work rate exercise separated by resting periods and with loads progressively increased (rarely used clinically) (ATS/ACCP, 2003). Other testing modes such as arm ergometry, dual action ergometry, or seated stepping ergometry can be useful options for individuals with balance issues, amputation, extreme obesity, and other mobility deficiencies. Notably, when using modalities that require less muscle mass, there will be a concomitant lower peak oxygen consumption (VO2) (ACSM Guidelines, 2022). Guidelines have consistently recommended that the protocol should be individualized based on a given individual's age, exercise tolerance, or symptoms (Arena et.al. 2007, Fletcher et.al. 2013, Myers et.al. 2009, Gibbons et.al. 2002). Protocols most suitable for clinical exercise testing include a low intensity warm-up phase followed by progressive, continuous exercise in which the demand is elevated to an individual's maximal level. When performing a sign- and symptom-limited maximal exercise test, it is often recommended that the selected exercise testing protocol results in a total exercise duration between 8 and 12 min (Fletcher et.al. 2013, Myers et.al. 2009, Gibbons et.al. 2002). Limitations of specified protocols lead to modifications of the Bruce protocol and other treadmill and cycle ergometry protocols have been developed, including individual-specific ramping protocols Myers et.al 2000, ACSM Guidelines 2022). Minimal or no handrail support should be encouraged when possible, during treadmill exercise testing, because handrail support reduces the work performed at any given level and alters the relationship between VO2 and work rate.

Equipment

There is a multitude of values derived from the test from which the results are extracted. The equipment to be used below is essential for the correct conduct of the test and the validity of the results. Each individual component must be kept in good condition and

calibrated. The equipment is related to the respiratory (air, etc.), the haemodynamic (heart rate, blood pressure, saturation) and the musculoskeletal (measurements on the bike or Borg scale). The goal of cardiopulmonary exercise testing is to evaluate the organs and systems involved in the exercise response, under conditions of progressively intense physical stress. Technologic advances have made it possible for a sufficient density of data to be acquired and displayed online in an appropriately designed test lasting less than 20 minutes from start to finish (rest, unloaded, incremental exercise) (ATS/ACCP, 2003).

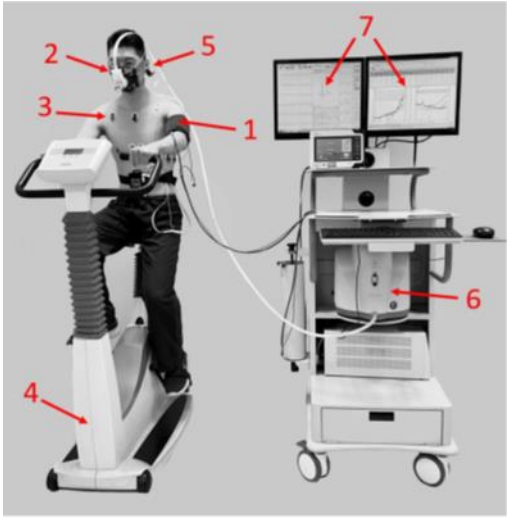

Figure 1. Adapted from Pritchard et.al. 2021. Standard CPET equipment. CPET, cardiopulmonary exercise testing. 1, blood pressure monitor; 2, mask, volume sensor and gas analyser tubing;3, 12-lead ECG; 4, ergometer (cycle, treadmill, arm crank, etc); 5, pulse oximeter (finger, earlobe and forehead placement); 6, gas analyser; 7, display of breath-by-breath data and exercise ECG. CPET, cardiopulmonary exercise testing.

Exercise equipment

In the clinical environment, cycle ergometers and treadmills are most used as these are more widely available and replicate the type of activity which most patients can easily relate to (Pritchard et.al. 2021). Having both exercise modes available is advantageous, given that some individuals have difficulty with treadmill ambulation for reasons that include imbalance and orthopedic limitations, whereas other individuals develop earlier exercise fatigue using the bicycle (Fletcher et.al. 2013). The highest values of VO2and HR are obtained with pedaling speeds of 50 to 80 rpm. Cycle ergometers are calibrated in kiloponds or watts (W); 1 W is equivalent to approximately 6 kilopond-meters per minute (kpm/min). The cycle ergometer is usually less expensive, occupies less space, and is less noisy than a treadmill. Upper body motion is usually reduced, making it easier to obtain blood pressure measurements and to record the ECG. a major limitation of cycle ergometer testing is discomfort and fatigue of the quadriceps muscles that can limit test tolerance. Leg fatigue in an inexperienced subject could cause early test termination before reaching a true VO2max. Thus, VO2max is 10% to 20% lower in cycle versus treadmill testing in those not accustomed to cycling (Myers et.al. 1991).

Exercising on a treadmill does involve upper body muscle mass due to the global nature of ambulatory movement; the effect of this is that peak VO2 can often be 5%–10% higher than on a cycle ergometer (Wasserman et.al. 2012). Cycle ergometers are a popular alternative to the treadmill in the clinical setting. These devices are physically smaller and usually less expensive (Albuaini et.al. 2007). On a cycle ergometer, the

patient can stop cycling as soon as they develop any mobility issues or are unable to continue the test, whereas those exercising on a motorised treadmill must first signal to the operator that they wish to stop before the belt is slowed to a stop (Wasserman et.al. 2012). Amputees and patients with sufficient disability or lower limb mobility issues may not be able to perform leg exercise on either a cycle or treadmill. In this instance, these individuals can perform CPET on an arm crank ergometer and generate physiological response data which is like leg ergometry (Schrieks et.al. 2011).

The action required to turn an arm crank ergometer involves and interferes with respiratory accessory muscles (ATS/ACCP, 2003) This may result in increased dyspnea and/or the early termination of exercise in those patients with respiratory disease. Recommendation: In most clinical circumstances, cycle ergometry is the preferable mode of exercise; however, depending on the reason(s) for which CPET was requested and equipment availability, a treadmill may be an acceptable alternative (ATS/ACCP, 2003).

Flow meters- Gas analyzers

Subjects can be interfaced to the metabolic cart system via a bite-block mouthpiece, which is combined with a nose clip and often stabilized by headgear or via a facemask assembly made of pliable rubber that covers the area of the nose and mouth. Although the mouthpiece/nose clip combination is the gold standard for measuring respiratory parameters during an incremental exercise test, it can be uncomfortable for some participants as it makes swallowing difficult, and promotes dry mouth, and/or throat irritations (Bell et.al. 2012). In contrast, a facemask assembly provides an alternative to mouthpiece/nose clip that allows oral and often nasal breathing, as well as swallowing (Kelly et.al. 2013). The dead space (VD) is usually larger when using a facemask compared to a mouthpiece/nose clip. In addition, parameters such as VE, tidal volume (VT), carbon dioxide output (VCO2) and respiratory rate have been reported to be changed when a facemask was used (Bell et.al. 2012, Kelly et.al. 2013, Saey et.al. 2006). Based on the evidence and patient input, both approaches are, therefore, acceptable. Use of each assembly is likely to be a personal preference and therefore, where possible, a choice should be offered to patients following discussion of the advantages and disadvantages of each (Radtke et.al. 2019).

Their quality and reproducibility play an essential role in the quality of measurement of the O2 and CO2 fractions (Cohen-Solal, Carré 2012). Two types of gas analyzers can be used: a mass spectrometer (considered the “gold” standard), which can measure all the required respiratory gases (CO2, O2 and, for some purposes, N2), and separate analyzers for O2 and CO2 (ATS, 2003). The mass spectrometer ionizes gas molecules in a high-vacuum environment/ACCP and then separates them based on mass- to-charge ratio. This enables the measurement of several gases. However, the high cost of mass spectrometers has inhibited their use in most commercial cardiopulmonary exercise systems. Discrete O2 and CO2 analyzers have been modified specifically for the demands of cardiopulmonary exercise testing (ATS/ACCP, 2003).

Haemodynamic measurements

Continuous recording of heart rhythm and evaluation of ischemic changes during exercise and recovery is crucial for safety and diagnostic reasons. The electrocardiograph should meet the specifications set by the AHA (Kligfield et.al. 2007). For optimal detection of myocardial ischemia and cardiac arrhythmias during

exercise, serial 12-lead electrocardiograms should be monitored in most clinical exercise tests (Fletcher et.al. 1990, ATS/ACCP 2003). Reporting peak HR in CPET studies is advisable (Radtke et.al. 2019) The increased prevalence of cardiovascular impairments requires monitoring of BP and ECG (ACSM Guidelines, 2000).

Pulse oximetry is used to monitor SpO2 during CPET, which gives a general oxygenation estimate providing a trend during the test (ATS 2003, Balady et.al. 2010). Sensor placement (i.e. finger, earlobe, nose, forehead) may also affect the stability and reliability of SpO2 recordings. Hand motion has been shown to reduce signal quality during finger SpO2 recordings (Trivedi et.al. 1997) suggesting use of ear or forehead sensors during cycling or treadmill exercise to be more appropriate.

Manual auscultation is still perceived as the most feasible and accurate method for monitoring BP. The exercise test should be terminated if systolic BP falls >20 mmHg compared to the highest recording during the test and in case of hypertension (systolic BP >250 mmHg; diastolic BP >120 mmHg) (ATS/ACCP 2003). The cuff should be positioned at the level of the heart and the apparatus should be calibrated (Myers et.al. 2009). BP is usually monitored every 2 min during CPET (Radtke et.al. 2019) Yet detection of exercise-induced hypertension (or, less commonly, hypotension) is an important goal in many circumstances (ATS/ACCP 2003).

Conducting the test- Termination criteria

Conducting the test

When administering clinical exercise tests, it is important to consider contraindications, the exercise test protocol and mode, test endpoint indicators, safety, medications, and staff and facility emergency preparedness (Fletcher et.al. 2013, Myers et.al. 2009). The patient should be precisely informed about how test is performed. A familiarization test is essential to avoid initial underestimation (15-20%) which would reduce the value of interpretation of subsequent examinations (Cohen-Solal, Carré 2012). As the patient should not talk during the exercise communication technique using hand signs should be defined (Cohen-Solal, Carré 2012).

The table below shows the steps in detail.

Table 2. Steps of CPET.

Clinical Status Evaluation
Clinical diagnosis and reason(s) for CPET
Health questionnaire (cardiopulmonary), physical activity profile
Medical and occupational history and physical examination
PFTs, CXR, ECG, and other appropriate laboratory tests
Determination of indications and contraindications for CPET
↓
Pretest Procedures
Abstain from smoking for at least 8h before the test
Refrain from exercise on the day of the test
Medications as instructed
Consent form

↓
Conduct of CPET
Laboratory procedures
Quality control
Equipment calibration
Protocol Selection
Incremental versus constant work rate; invasive versus noninvasive
Patient preparation
Familiarization
12-lead ECG, pulse oximetry; blood pressure
Arterial line (if warranted)
Cardiopulmonary exercise testing
↓
Interpretation of CPET Results
Data processing
Quality and consistency of results
Comparison of results with appropriate reference values
Integrative approach to interpretation of CPET results
Preparation of CPET report

Definition of abbreviations: CPET= cardiopulmonary exercise testing; CXR= chest X-ray, ECG= electrocardiogram; PFTs= pulmonary function tests.
Table. Overview of Cardiopulmonary Exercise Testing. Adapted from ATS/ACCP, 2003.

It is very important for the examiner to be aware of the criteria for terminating the test by keeping up to date with new guidelines issued by authoritative organizations to ensure patient safety as much as possible. In most cardiopulmonary exercise tests, patients should be verbally encouraged before and during the test, to give a maximal effort with the goal of achieving physiologic limitation (ATS/ACCP, 2003). The decision to terminate exercise is an important function of test supervisor.

The test termination criteria primarily depend on and vary per purpose of testing in each individual subjects. Symptom-limited testing is desirable for general evaluation, but this recommendation could be modified in several situations (Gibbons et.al. 2002).

Absolute indications	**Relative indications**
ST-segment elevation (>1.0 mm) in leads without preexisting Q waves because of prior MI (other than aVR, aVL, and V1)	Marked ST displacement (horizontal or downsloping of >2 mm, measured 60 to 80 ms after the J point [the end of the QRS complex]) in a patient with suspected ischemia
Drop in systolic blood pressure >10 mm Hg, despite an increase in workload, when accompanied by any other evidence of ischemia	Drop in systolic blood pressure >10 mm Hg (persistently below baseline) despite an increase in workload, in the absence of other evidence of ischemia

Central nervous system symptoms (e.g., ataxia, dizziness, near syncope)	Increasing chest pain
Technical difficulties in monitoring the ECG or systolic blood pressure	Fatigue, shortness of breath, wheezing, leg cramps, or claudication
Subject's request to terminate the test	Arrhythmias other than sustained VT, including multifocal ectopy, ventricular triplets, supraventricular tachycardia, and bradyarrhythmias that have the potential to become more complex or to interfere with hemodynamic stability
Moderate-to-severe angina	Exaggerated hypertensive response (systolic blood pressure >250 mm Hg or diastolic blood pressure >115 mm Hg)
Sustained ventricular tachycardia (VT) or other arrythmia that interferes with normal maintenance of cardiac output during exercise	Development of bundle-branch block that cannot immediately be distinguished from VT
Signs of poor tissue perfusion (cyanosis or pallor)	

Table 3. Indications for Termination criteria of Exercise Testing (Fletcher et al., 2013)

Furthermore, for safety reasons, the test may have to be terminated before the subject reaches a measured VO2max, volitional fatigue, or a predetermined endpoint (i.e., 50% to 70% HRR or 70% to 85% age-predicted maximal HR). Because of the individual variation in maximal HR, the upper limit of 85% of an estimated maximal HR may result in a maximal effort for some individuals (ACSM Guidelines, 2000). Symptoms can appear at any point of fatigue especially if there is a disease. The examiner should keep the patient and the ECG recording under constant observation. In situations in which the monitor stops the exercise test, the patient should be observed until the pacientis stable and physiologic variables have returned to baseline conditions. If necessary and based on the criteria of the physician, admission to the hospital may be warranted. Resuscitation equipment should always be available in the exercise laboratory (ATS/ACCP, 2003).

Sources of error

The test requires good cooperation of the patient, knowledge of the person in charge and special attention to the equipment. The causes of possible errors are hidden in them. Pritchard et.al. 2021 outlined the most common causes of error. As far as the patient is concerned, there is a case of not following the instructions given to the patient regarding the preparation and conduct of the test or not cooperating well during the test. These may result in sub-optimal effort and lower scores on important indicators of the test. Furthermore, as regards the test operator, there is a possibility that he/she may give incorrect instructions, may not choose the appropriate protocol or may not be familiar with the procedures for conducting and terminating the test. This may lead to incorrect

results about important indicators of the test and, by extension, incorrect conclusions about the condition of the subject. Similar errors may also be due to equipment problems mainly due to delayed response to gas exchange and synchronization due to poor calibration management.

Infection control

In a busy cardiopulmonary exercise-testing laboratory with a large heterogeneity of patients and disease entities examined, cross-infection can occur. Cross-infection can occur either via direct contact between patients, indirect contact with contaminated surfaces, equipment or healthcare personnel, and inhalation of aerosolized particles or droplets via airborne route, tubing, or mouthpieces/facemasks (Goodman et.al. 1991). Exercise testing should be postponed in patients with acute infections (ACSM Guidelines, 2000) Appropriate hand hygiene by healthcare workers should be applied according to established standards (Boyce et.al. 2002) and supervised occasionally to improve compliance. Sufficient time intervals between tests should be used for surface decontamination and room aeration according to local infection control guidelines (WHO, 2018). In patients known to be infectious, additional precautions may be considered. For example, to prevent inhalation of microorganisms, barrier filters may be added in case of exercise testing with mouthpieces (Kendrick et.al. 2003). Regardless of whether CPET is performed with the use of facemask or mouthpiece, after every test facemask and multi-use mouthpieces are disinfected according to manufacturers and the laboratory standards (Rutala et.al. 2019).

CPET variables

A majority of CPET variables described in traditional reports, in either tabular or graphical form, are poorly understood by the typical practitioner in terms of their clinical value for many test indications. This approach has led to a large volume of data that clinicians less versed in CPET find difficult to navigate, which may be at the core of why this valuable assessment of cardiopulmonary exercise performance is underused (Guazi et.al. 2016). An impressive number of variables are typically measured during cardiopulmonary exercise testing. However, the number of variables that are required in any situation will depend on the reason(s) for which exercise testing was requested. (ATS/ACCP, 2003) This examination provides a large amount of information and multivariate interpretation must be performed. The average CPET records thousands of measurements, including: (i) the work rate (in Watts), (ii) metabolic gas exchange measurements: O2 consumption (VO2), CO2 production (VCO2), and respiratory exchange ratio (RER) defined as VCO2 divided by VO2), (iii) ventilatory measurements: SpO2, VE, VT, respiratory rate (RR), ventilatory equivalents for O2 (VE/VO2), and CO2 (VE/ VCO2), (iv) cardiovascular variables: HR, ECG ST-segment changes, and non-invasive blood pressure(Chambers et.al. 2019).

Oxygen uptake

Oxygen uptake (VO2) is determined by cellular O2 demand up to some level that equates to maximal rate of O2 transport, which then is determined by that maximal rate

of transport (ATS/ACCP, 2003). Arena et.al. 2011 argued on the basis that VO2 is the highest demonstrable of VO2 and appears “maximal” when there is objective evidence of true physiological limit, otherwise “peak”. Also, it is the reflection of integrated function of pulmonary, cardiac, and skeletal muscle systems and depends on age, sex, exercise habits, and genetic predisposition presenting as a conventional expression of aerobic exercise capacity (Arena et.al. 2011). VO2 is measured in liters or milliliters of oxygen per minute or in milliliters per kilogram of body weight per minute and is defined by the Fick principle: VO2 equals cardiac output (CO)×C(a–v)O2, where C(a–v)O2 is the arteriovenous oxygen content difference (Wasserman et.al. 2012.) Normally, VO2 increases nearly linearly as external work (power output) increases. However, accurate determination of the external work rate in watts (or kilopond×meters [kpm] per minute) requires determining this relationship. The external work rate is accurately measured by cycle ergometry but can only be estimated by treadmill exercise.

The slope of VO2 versus external work rate reflects the efficiency of the metabolic conversion of chemical potential energy to mechanical work and the mechanical efficiency of the musculoskeletal system. Because there are a few processes that affect the metabolic efficiency of muscles, a reduction in the value of this relationship most often indicates inadequacies of O2 transport, as may occur with diseases of the heart, lungs, or circulation (ATS/ACCP, 2003). VO2 is a very helpful index and helps to the measurement of cardiovascular fitness in healthy persons. It is an objective indicator of disease severity in certain chronic disease populations and of degree of impairment and could be used as a prognostic marker in many chronic disease populations (Arena et.al. 2011).

As VO2 increases with external work, one or more determinants of VO2 approach limitations (e.g., SV, HR or tissue extraction) and VO2 versus work rate may begin to plateau. Achieving a clear plateau in VO2 has traditionally been used as the best evidence of VO2max. VO2max represents the maximal achievable level of oxidative metabolism involving large muscle groups (ATS/ACCP, 2003) However, in clinical testing situations, a clear plateau may not be achieved before symptom limitation of exercise (Myers et.al. 1990). Direct measurement of VO2 max is reliable and reproducible in normal subjects and patients (ATS/ACCP, 2003) The main determinants of normal VO2max or VO2peak are genetic factors and quantity of exercise muscle and are also depended on age, sex, and body size (ATS/ACCP, 2003). Small but normal subjects have a higher VO2 per kilogram than larger subjects. Decreases in VO2max or VO2peak are therefore general indicators of reduced exercise capacity.

Peak oxygen uptake (VO2Peak) is a parameter describing the amount of energy obtainable by aerobic metabolism per unit of time (aerobic power) at peak incremental exercise and is define as the highest volume of VO2, averaged over a 20- to 30-second period, achieved at presumed maximal effort during an incremental cardiopulmonary exercise test. (Mezzani et.al. 2017). VO2 peak declines on average by 10% per decade after the age of 30, due to decreasing maximal heart rate, stroke volume, blood flow to skeletal muscle, and skeletal muscle aerobic potential with decreasing age (Betik et.al. 2008). In addition, VO2 peak is 10 to 20% greater in men than in women of comparable

age, because of higher hemoglobin concentration and greater muscle mass and stroke volume in men (Mezzani et.al. 2017).

A reduced VO2peak may reflect problems with oxygen transport (cardiac output, O2-carrying capacity of the blood), pulmonary limitations (mechanical control of breathing or gas exchange), oxygen extraction at the tissues (tissue perfusion, tissue diffusion), neuromuscular or musculoskeletal limitations, and effort (ATS/ACCP, 2003). American Thoracic Society recommends that VO2max or VO2peak should be expressed as an absolute value and as a percentage of the predictive value. VO2max should also be referenced to body weight (in kilograms) and/or height in the formatting of the report so that the impact of body size on exercise results is readily recognized (ATS/ACCP, 2003).

CO2 output

CO2 output (VCO2) has two sources, the metabolic production of CO2 by aerobic metabolism, and non-metabolic release after "buffering" of the excess protons released during exercise (Cohen-Solal, Carré 2012). CO2 output during exercise is determined by factors like those that govern O2 uptake: cardiac output, CO2 carrying capacity of the blood, and tissue exchange are major determinants. Because CO2 is much more soluble in tissues and blood, CO2 output measured at the mouth is more strongly dependent on ventilation than is VO2. In addition, because dissolved CO2 is a weak acid, the body uses CO2 regulation to compensate for acute metabolic acidosis, which affects the pattern of VCO2 as work intensity increases above the point of anaerobic metabolism (ATS/ACCP, 2003). With anaerobic metabolism, VCO2 increases because of the chemical reaction between hydrogen ion (from lactate) and dissolved CO2. The excess CO2 may also come from reduction in the body CO2 stores because of hyperventilation (manifested as arterial hypocapnia) (ATS/ACCP, 2003). It is also important to accurately measure CO2 output, as it is the basis for the calculation of several derived variables, including (*1*) the respiratory exchange ratio, (*2*) the respiratory quotient, (*3*) P(a–a)O2, (*4*)Vd/Vt, (*5*) alveolar ventilation, and so on (ATS/ACCP, 2003).

Anaerobic Threshold

The anaerobic threshold (AT), also known as the lactate threshold, lactic acid threshold, gas exchange threshold, or ventilatory threshold, is considered an estimator of the onset of metabolic acidosis caused predominantly by the increased rate of rise of arterial lactate during exercise (ATS/ACCP, 2003). The AT is the point at which the O2 demand of the muscles exceeds the ability of the cardiopulmonary system to supply O2. Muscle cells will begin to generate ATP through anaerobic metabolism, a process which produces lactic acid. In turn, lactic acid is buffered by circulating bicarbonate, generating further CO2 (Chambers et.al. 2019). The AT is referenced to the VO2 at which this change occurs and is expressed as a percentage of the predicted value of VO2max (%VO2max predicted) (ATS/ACCP, 2003). Measurement of the AT allows the objective assessment of aerobic metabolism at submaximal exercise levels. It can

be automatically calculated by computer program but needs to be cross-checked. A low AT indicates impaired cardiovascular transport of oxygen or poor muscular oxygen utilization (Glaab et.al. 2022). Valid determination of AT is not always possible, as has been shown for very severe respiratory limitations (COPD, ILD) or significant heart failure when ventilation and/or perfusion can no longer be adequately increased in response to increasing exercise. Other reasons include an excessively steep/mild incremental ramp protocol or performance reducing factors such as arthrosis, peripheral arterial disease, or poor effort (Glaab et.al. 2022).

Respiratory Exchange Ratio

The ratio of VCO2/ VO2 is called the gas exchange ratio or respiratory exchange ratio (RER). Under steady conditions, the RER equals the respiratory quotient (RQ), whose value is determined by the fuels used for metabolic processes (ATS/ACCP, 2003). RQ is a marker of tissue metabolism reflects the percentage of lipids and carbohydrates used by the body and reflects the consumption of substrates used by the whole body (Cohen-Solal, Carré 2012). The term "RQ" is often reserved for expressing events at the tissue level, which is difficult to measure and is not determined during clinical exercise testing. The term "RER" is usually measured by gas exchange at the mouth (ATS/ACCP, 2003. The RER increases gradually with exercise intensity (Cohen-Solal, Carré 2012). RER is a good indicator of subject effort and valuable in determining intrasubject effort during serial testing (ie, pre and postintervention) (Arena et.al. 2011).

A respiratory exchange ratio higher than 1.00 implies significant anaerobic metabolism activation above the first ventilatory threshold and is further increased by hyperventilation occurring past the second ventilatory threshold. This physiological response to exercise is consistent across healthy subject and patient populations, which makes peak respiratory exchange ratio an objective descriptor of maximal effort attainment and subject motivation (i.e., of a crucial issue to guarantee reliable and clinically meaningful VO2peak values (Howley et.al. 1995). RER ≥1.10 is one of the criteria of maximum exercise but because of the individual variability of this parameter it must be associated with other criteria to stop an exercise test (Cohen-Solal, Carré 2012). Patients with severely impaired exercise tolerance can attain skeletal muscle strength exhaustion even earlier than central hemodynamic and ventilatory factors become limiting, interrupting exercise at peak respiratory exchange ratio values even lower than 1.00. Another possibility for lack of an adequate respiratory exchange ratio increase during incremental exercise is severe chronic obstructive lung disease, wherein lung hyperinflation can hinder hyperventilation past the first ventilatory threshold (Wasserman et.al. 2012). Hyperventilation, whatever its cause, is the main factor impacting the RER (Cohen-Solal, Carré 2012).

Breathing Reserve (BR)

Breathing Reserve (BR) expresses the relationship between exercise VE and maximal breathing capacity as estimated by the resting maximal voluntary ventilation (MVV) and expresses the % percentage of MVV that the patient achieved at maximal effort test

(Ναναζ, 2006). Normal athletes have reserves >20%, but variance is wide. Low breathing reserve is typical of chronic obstructive lung disease. Values <15% suggest ventilatory limitation. Normal rates range from 20-40% but further study is needed on this. BR is increased in patients with pure CHF, relatively decreased in CHF with coexisting respiratory dysfunction, and is typically decreased in chronic lung disease suggesting respiratory limitation of exercise. It is very useful in the differential diagnosis of dyspnea of cardiac or respiratory origin (Νανάς, 2006).

Minute ventilation/ carbon dioxide production (VE/ VCO2 slope)

Increased ventilation (VE) during exercise is one of the primaries means by which arterial blood regulates gases and acid–base status under conditions of the augmented metabolic demands of exercising muscles. VCO2 has two sources, the metabolic production of CO2 by aerobic metabolism, and non-metabolic release after "buffering" of the excess protons released during exercise (Cohen-Solal, Carré 2012). VE/VCO2 slope describes efficiency of pulmonary clearance of CO2 during exercise, reflects matching of pulmonary ventilation to perfusion and indirectly reflects the cardiac function secondary to the link between the cardiac and pulmonary systems (Arena et.al. 2011). A high VE/VCO2 slope may be due to hyperventilation or to a large dead space (Cohen-Solal, Carré 2012). Assessment of ventilatory efficiency provides insight into cardiopulmonary coupling and function and, when abnormal, is related capacity (Loe et.al. 2014) to lower levels of aerobic and may indicate subclinical pathophysiology that warrants further investigation (Guazi et.al. 2016). Ventilatory efficiency, commonly assessed by the VE/Vco2 slope, plays an important role in detecting elevated pulmonary pressures (Arena et.al. 2011, Arena et.al. 2010, Guazzi et.al. 2013).

Postapneic End-Tidal Carbon Dioxide Pressure (PETCO2)/

End tidal oxygen tension (PETO2)

PetCo2 expresses the partial pressure of CO2 at the end of a tidal breath exhalation and reflects both ventilation-perfusion matching in the lung and the level of arterial PCO2 (Arena et.al. 2011). The PETO2 is easily derived and commonly reported at rest, VT, and peak exercise in mm Hg units by the software packages that operate CPX carts. Normal resting values range between 36- and 44-mm Hg, increase between 3 and 8 mm Hg from rest to VT, and then decrease as an individual approaches maximal exertion. 124 (Balady et.al. 2010). Abnormalities may indicate pulmonary vascular disease and low values can also reflect acute or chronic hyperventilation, which may be confirmed by arterial blood gas analysis (Arena et.al. 2011). Numerous investigations have demonstrated a significant relationship between resting PETCO2 and cardiac output.207,208. The PetCo2 obtained during exercise has also been correlated with cardiac output in patients with heart failure209 and can reflect disease severity in this population. Resting and peak exercise PETCO2, as well as the highest increase from rest during a progressive CPX, all demonstrate independent prognostic value in patients with heart failure (Myers et.al. 2008, Arena et.al. 2007, Arena et.al. 2008). PetCO2

increases and PetO2 decreases throughout the moderate work rate range. PetO2 typically begins to increase in concert with the increase in VE/Vo2 during incremental.

With the increasing work rate, PetCO2 typically increases (although PaO2 does not) until the subsequent increase in VE/VO2 occurs, at which time PetCO2 stabilizes until the subsequent increase in VE/VCO2 occurs; then PetCO2 starts to fall concomitantly with the increase in PetO2. The period of increasing PetO2 with relatively stable PetCO2 has been termed "isocapnic buffering". A fall in PetCO2 when VE/VCO2 is high suggests hyperventilation whereas high VE/VCO2 without a fall in PetCO2 suggests increased dead space ventilation (ATS/ACCP, 2003). Caution is required in interpreting values measured from a particular patient, because they may be confounded by factors such as acute hyperventilation, increased dead space due to emphysema or other lung diseases, or rapid shallow breathing patterns, all of which will reduce the PETCO2 independently of cardiac function (Balady et.al. 2010). In patients with pulmonary hypertension, resting, VT, and peak exercise PETCO2 are significantly correlated with pulmonary pressures and can thus provide a noninvasive reflection of disease severity. CPX may also aid in the detection of exercise-induced right-to-left shunting (Balady et.al. 2010).

Blood Pressure

The normal systolic blood pressure (SBP) response to exercise is an increase with increasing workloads at a rate of ~10 mmHg per 1 MET (Fletcher et.al. 2013). On average, this response is greater among men, increases with age, and is attenuated in individuals on vasodilators, calcium channel blockers, angiotensin-converting enzyme inhibitors, and α- or β-adrenergic blockers (ACSM Guidelines, 2022). SBP responses are outlined in the following (ACSM Guidelines, 2022):

- Hypertensive response: an SBP≥210 mm Hg in men and ≥ 190 mm Hg in women during exercise is considered an exaggerated response. A peak SBP >250 mm Hg or an increase in SBP >140 mm Hg during exercise is above the pretest resting value is predictive of future resting hypertension
- Hypotensive response: a decrease of SBP below the pretest resting value or by >10 mm Hg after a preliminary increase is abnormal and often associated with myocardial ischemia, left ventricular dysfunction, and an increased risk of subsequent cardiac events. Either of these responses are indications to stop the test
- Blunted response: in individuals with a limited ability to augment cardiac output, the response of SBP during exercise will be slower compared to normal
- Postexercise response: SBP typically returns to pre-exercise levels or lower by 6 min of recovery. Studies have demonstrated that a delay in the recovery of SBP is highly related both to ischemic abnormalities and to a poor prognosis

There is normally no change or a slight decrease in diastolic blood pressure (DBP) during an exercise test. A peak DBP>90 mm HG or an increase in DBP >10 mm HG during exercise above the pretest resting value is considered an abnormal response and

may occur with exertional ischemia. A DBP >115 mm Hg is an exaggerated response and a relative indication to stop a test (Fletcher et.al. 2013).

Oxygen pulse

Oxygen pulse is the VO2/heart rate ratio reflects the amount of oxygen consumed per heartbeat (i.e., stroke volume multiplied by C(a–v) O2). Assuming normal values of arterial oxygen content and C(a–v) O2 at peak effort, peak stroke volume in milliliters can then be estimated as (oxygen pulse/15)×100, where oxygen pulse is in milliliters per beat (Wasserman 2012). Oxygen pulse is a prognostic index in certain chronic disease populations and a plateau at lower-than-expected value or decrease with increasing work rate suggests low or falling stroke volume (Arena et.al. 2011). Oxygen pulse expressed as a function of work rate has a typical hyperbolic profile with a rapid increase during the initial stages of exercise and a slow approach to an asymptotic value at the end of exercise. A flattening or downward displacement of oxygen pulse kinetics during incremental exercise likely reflects peripheral vascular perfusion or extraction or central cardiogenic performance limitations (Mezzaniet.al. 2017). The basic profile of the O2 pulse over the range in which Vo2 increases linearly with HR appears to be hyperbolic, with a rapid rise at low work rates followed by a slow approach to an asymptotic value (ATS/ACCP, 2003).

Blood oxygen levels (SpO2)

SpO2 is an estimated arterial hemoglobin saturation by noninvasive pulse oximetry, and it has a prognostic value in some lung disease populations. Decrease by >5% suggests abnormal oxygenation and usually is common in many lung diseases and right-to-left shunt, known as exercise hypoxemia. Accuracy and bias of measurements vary by device and can be affected by perfusion, motion, and ambient light (Arena et.al. 2011). The measurement of SpO2 with pulse oximetry through a fingertip probe can be affected by low perfusion or low pulse wave, hemoglobin abnormalities, low oxygen saturation, very dark skin tone, nail polish, acrylic nails (Pretto et.al. 2013), and movement during exercise. Alternate probe locations such as the earlobe of forehead can be helpful (ACSM Guidelines, 2022).

Rating of perceived exertion

The subjective rating of exercise intensity is generally considered a reliable indicator of relative fatigue. The 6-to-20 Borg scale of perceived exertion has been demonstrated to be useful in quantifying these feelings (Noble et.al. 1982). The Borg scale of perceived exertion was modified to a 1-to-10 scale for dyspnea assessment, which has been demonstrated to correlate with aerobic stress and blood lactate levels (Balady et.al. 2010). Before the exercise testing the physician have to explain the scale to the patient. The last 5-10 seconds each stage or every 2 minutes, on a ramp protocol, the physician asks the patient to determine the value of the scale and records it (ACSM Guidelines, 2022).

Heart Rate Recovery (HRR)

The normal HR response to incremental exercise is an increase with progressive workloads at a rate of ~10 beats·min-1 per 1 MET (Fletcher et.al. 2013). The rate of decline in HR following exercise (HR recovery) provides independent information related to prognosis (Fletcher et.al. 2013, Lachman et.al. 2018). A failure of the HR to decrease by at least 12 beats during the first minute or 22 beats by the end of the second minute of active postexercise recovery is strongly associated with an increased risk of mortality in individuals diagnosed with or at increased risk for ischemic heart disease (Fletcher et.al. 2013, Lachman et.al. 2018, Lauer et.al. 2001). The failure of HR to recover adequately may be related to the inability of the parasympathetic nervous system to reassert vagal control of HR, which is known to predispose individuals to ventricular dysrhythmias (Lauer et.al. 2001). Quantifying heart rate recovery provides another dimension that improves prognostic resolution to the CPET assessment in apparently healthy individuals (Arena et.al. 2010, Lauer et.al. 2005).

Supervision- Interpretation

Exercise testing should be performed under the supervision of a qualified health professional who is appropriately trained to administer exercise tests (Myers et.al. 2009). In any procedure with a risk of complications, the test administrator should be certain that the subject understands the risks and benefits of the test and written informed consent should be obtained. Good communication with the patient about testing is mandatory (Fletcher et.al. 2013). Exercise testing can be conducted safely and competently by appropriately qualified nonphysician health professionals. A medical director of an exercise testing laboratory must continue to make the final decision as to the level of physician supervision needed for exercise testing services (i.e., direct versus proximity) (Myers et.al. 2014). Exercise testing should be conducted only by well-trained personnel with sufficient knowledge of exercise physiology and ability to recognize important changes in rhythm and repolarization on the ECG (Myers et.al. 2009). Although exercise testing is considered a safe procedure (Kouidi et.al. 2001) acute MI and deaths have been reported during testing (CDC, 2001). Clinical exercise tests can be supervised by properly trained exercise physiologists, physical therapists, nurses, physician assistants, or medical technicians who are working under the direct supervision of a physician; that is, the physician must be in the immediate vicinity and available for emergencies (Helmick et.al. 1995).

The physician or senior medical (healthcare) professional conducting the test must be trained in advanced cardiopulmonary resuscitation (Fletcher et.al. 2013). Individuals who supervise exercise tests must have the cognitive and technical skills necessary to be competent to do so (Rodgers 2000). Several studies have demonstrated that the incidence of cardiovascular complications during exercise testing is no higher with experienced paramedical personnel than with direct physician supervision (Bulmer et.al. 2004, Doyle et.al. 2006). High-risk patients require that a physician be physically present (ie, in the room) during exercise testing, and responsible for supervising the test

must meet established competency standards (Rodgers et.al.2000, Thompson et.al. 2010).

Nonphysicians must be capable of screening for and identifying these high-risk patients and alerting the physician supervisor when appropriate. The physician's role as final authority for the safety and quality of testing interpretation remains paramount. Rodgers et.al. 2000, presented several cognitive skills that the supervisor needs to competently perform Exercise Tests such as knowledge of appropriate indication for exercise testing, knowledge to promptly recognize and treat complications of exercise testing and many others.

Test must be always interpretated according to level of training, sex, age and training specificities (Cohen-Solal, Carré 2012). The analysis and interpretation of CPET results requires the basic knowledge of exercise physiology along with a structured approach. Issues to be addressed in the interpretation of CPET include the following:

indications(s) for testing
assessment of the quality of exercise data collected,
comparison of measured graphic and tabular responses with appropriate normal reference values
assessment of symptoms and reason(s) for stopping exercise
correlation of exercise results with the clinical information available for the patient
preparation of an exercise report
associated clinical evaluation and information

(ATS/ACCP, 2003).

Regarding exercise capacity/performance, the maximum achieved exercise performance (VO2 peak = highest oxygen uptake upon discontinuation of exercise) is more relevant than the maximum attainable exercise capacity (VO2 max), which is the domain of sports medicine (Glaab et.al. 2022). Key variables and their interrelationships are systematically summarized in the 9-panel display of Wasserman et al. 2005. With the important preliminary issues addressed, the focus is directed at key measurements, first Vo2; then HR, VE, and SpO2; and then other variables and exercise-limiting factors (cardiovascular, ventilatory, peripheral) through a series of questions aimed at providing an integrated analysis of CPET results The first question is the usual starting point for interpretation and it is about whether the aerobic capacity (VO2max/ VO2peak) is normal (ATS/ACCP, 2003). The primary objective of the interpretation is to determine whether and to what extent there is impaired exercise capacity and what cause(s) of cardiovascular, pulmonary vascular or pulmonary origin may be primary (Glaab et.al. 2022). It is also important to note that an individual with normal peak VO2 may still have exercise limitation caused by deconditioning, obesity, anxiety, or early/mild cardiopulmonary disease. Other confounding factors such as anaemia, thyroid function, or acid–base disorders should be investigated before the examination (Glaab et.al. 2022).

Variables	Criteria of Normality
VO2max or VO2peak	> 84% predicted

Anaerobic Threshold	40% VO2max predicted; wide range of normal (40–80%)
Heart Rate (HR)	HRmax 90% age predicted
Heart Rate Reserve (HRR)	HRR < 15 beats/min
Blood Pressure	< 220/90 mm Hg
O2 pulse (VO2/HR)	> 80%
VE/ VCO2 (at AT)	< 34
Respiratory frequency (fR)	< 60 breaths/min

Table 4. Suggested normal guidelines for interpretation of cardiopulmonary exercise testing results. Maximum or peak cardiopulmonary responses except for anaerobic threshold and VE/VCO2 at AT. Adapted from American Thoracic Society, 2003.

2.2 Peak Circulatory Power (CircP)

Functional capacity is an important predictor of cardiovascular risk, as well as, of all-cause mortality in the adult population (Colber et.al. 2010). CPET is a non-invasive procedure aimed to assess patient's functional capacity being considered the gold standard for aerobic capacity or cardiorespiratory and metabolic performance assessment (Pereira et.al.2012). Peak Circulatory Power (CircP), the product of VO2peak and peak systolic blood pressure (SBP), has been shown to outperform VO2peak in the prediction of adverse events in cohorts with a variety of cardiovascular and pulmonary diseases (Tabet et.al. 2006, Tang et.al. 2018). Originally Cohen-Solal et.al. 2002 introduced CircP as a noninvasive surrogate for cardiac power, that combines gas exchange, blood flow and perfusion pressure, which may provide a more complete reflection of CRF compared with either VO2peak or SBP alone (Busque et.al. 2022). The combination of VO2 and blood pressure responses strengthens the prognostic value of the CPET, especially in the subgroup of patients with low peak VO2 and blood pressure at peak exercise (Cohen- Solal et.al. 2002). The unit of measurement of CircP is mmHg·mLO2·kg−1 min−1.

Subject demographics (sex, height, weight, waist-to-hip ratio) and lifestyle-related factors (Personal Activity Intelligence, smoking) should be considered when exercise blood pressure response and CircP are used to evaluate patients' cardiac function in CPET (Hulkkonen et.al. 2014). Cohen- Solal et.al. 2002 report that CircP should not be viewed as a perfect surrogate of cardiac power, but as a new global index that incorporates all parameters whose prognostic value has been demonstrated, such as AVO2 difference, heart rate, stroke volume, and blood pressure responses. A reduced AVO2 difference response, because of high resting value, is associated with a poor haemodynamic reserve and perhaps a worse outcome.

The circulatory power can be assessed non-invasively during exercise conducted at its maximum (Cohen-Solal et.al. 2002). Patients with a low CircP have a particularly poor prognosis (Cohen-Solal et.al. 2002). According to Mezani et.al. 2017, the highest

values of CircP being found in young athletes and in patients with hypertension with preserved systolic function, were between 3000 and 8000 mmHg ×mL/kg/min. Left ventricular systolic function could be possibly assessed by CircP during incremental exercise (Mezzani et.al. 2017). CircP is an important marker of individual's cardiovascular integrity level (Wang et al., 2017) to be addressed in rehabilitation programs (Castello-Simões et al., 2015).It is feasible to calculate CircP from any CPET non-invasively, without the need of special equipment (Cohen-Solal et al., 2002), while the invasive method depends on a moderately expensive catheter, and because of the time taken to collect the exhaled air, cannot be performed at true peak exercise (Nicholls et al., 2002). Some studies combined the invasive and the non-invasive techniques to provide even greater prognostic power, but the problems of the invasive methodology remain (Nicholls et al., 2002).

Physiology of CircP

Circulatory Power (CircP) reflects the volume of oxygen added to venous blood by lungs and transferred to the arterial circulation against a pressure gradient, by the heart (Nicholls et.al. 2002). This index represents the triple product of CO×C(a-v)O2×SBP (Mezzani et.al. 2017). In the circulatory power calculation, the gradient through which the O2 is transferred by the heart is systolic pressure as opposed to mean arterial pressure. This relates therefore to an instantaneous peak work, as opposed to the more representative mean work over a cardiac cycle. However, mean arterial pressure is difficult to measure precisely non-invasively and systolic pressure measurements are more reliable (Nicholls et.al. 2002). CircP is an important noninvasive parameter for characterizing the relationship between cardiac-generated blood flow and peripheral perfusion pressure. Both CircP and Ventilatory Power (VP) incorporate pertinent cardiac, pulmonary, and skeletal muscle physiology into a substantive composite assessment (Forman et al., 2012). Mechanisms such as autonomic control, compromised pulmonary responses and arterial stiffness may affect CircP and VP as well as physical fitness (El-Habashy et al., 2014, Monteiro et al., 2022). It is demonstrated that both CP and VP could be used as screening tools in assessing both functional significance and exercise tolerance, as the impairment of autonomic nervous modulation is related to reduced CP and VP (Bassi, et al., 2018).

Comparison with other CPET variables

Information on the impairment of exercise capacity and cardiopulmonary fitness could be obtained from the analysis of the results of the CPET parameters easy and non-invasively (Corra et al., 2009). There are many parameters that source from the CPET. Although, a few of them have been investigated as for the prognostic value regarding cardiorespiratory fitness. Peak oxygen consumption (VO2peak) continues to be considered the gold standard metric for CRF, determined through CPET (Busque et.al. 2022). However, relying solely on VO2peak has limitations: for example, studies have shown that hemodynamic indices can augment the prognostic utility of CPET test results (Reddy et.al. 2018, Forman et.al.2012, Myers et.al. 2019). Also, VO2 peak had

no prognostic value in patients on β-blocker therapy (Lund et al., 2003, Pohwani et al., 2003, Shakar et al., 2004) or remain lower in patients not on β-blocker therapy (Peterson et al., 2003, Zugck et al., 2002, O'Neill et al., 2005). As an indicator of cardiovascular capacity, peak VO2 is not effective with cardiac overload (i.e. systemic peripheral resistance) (Hulkkonen et al., 2014) and may depend in part on muscle function and O2 extraction capacity (Nicholls et al., 2002). Also, VO2 depends in the patient's motivation and response to exercise (Myers et al., 2008). It is worth noting that VO2 may specify the cardiorespiratory functional capacity in diabetic patients (Silva et al., 2019) or VO2 peak lose its prognostic value a little because ranges in diabetic patients are low (Santos et al., 2022).

It has been demonstrated that peak CircP is the only independent predictor even when peak VO2 and HRR were included in the analysis and that the prognostic power is independent from peak VO2 values and chronotropic competence when mean arterial pressure was used for its calculation (Giardini et al., 2007). Cohen-Solal et al., 2002 after a mean follow-up of 25±10 months in CHF patients demonstrated that peak CircP was the best predictor of outcome and variable predictive of prognosis among peak circulatory stroke work, peak VO2 and other CPET variables. In association with VO2 peak and VE/VCO2 slope, peak CircP had the best prognostic value in CHF patients receiving and not receiving β-blocker therapy (Tabet et al., 2006). VE/VCO2 slope can be measured in submaximal exercise too, thus maybe has advantages over VO2 peak (Tabet et al., 2006). Poor functional capacity in patients with heart failure could be determined by an elevated VE/VCO2 slope as decreased ventilatory efficiency during exercise even though VE/ VCO2 slope has been found to be effective in providing independent prognostic information (Francis et al., 2000, Kleber et al., 2000, Ponikowski et al., 2001) and may reflects the complex interaction of pulmonary, cardiac, and peripheral physiological manifestations (Fernαndez-Lao et al., 2012).

Araujo et al., 2019 observed that CircP was improved in patients with type 2 diabetes. They claimed that peak CircP and VP may be used to assess a patient's prognosis, because they examined the response of a 3-month combined exercise program and found that CircP and VP improved as opposed to VE/VCO2 slope and OUES. It should be clarified that CP assess the central and peripheral components of cardiac work, while VP combines the assessment of the hemodynamic system with ventilatory efficiency during exercise (Forman et al., 2012, Hirashaki et al., 2017). Santos et al., 2022 examined the influence of glycemic control on CP and VP in T2DM patients and found that there were no significant differences between the variables, especially CP and VP, and the main variables with glycemic control, something that was not expected. They claim that one possible reason for this result may be the low aerobic functional capacity, thus VO2peak, which has a strong correlation with these variables. In the study of Bassi et al., 2018 was found that CP and VP were important markers of cardiocirculatory limitation to exercise in DMT2 and HTN.

Prognostic role of CircP in patients

Through CPET clinicians assess the cardiovascular status with a non-invasive, easily accessible, and information-intensive way to obtain parameters (Hulkkonen et.al. 2014). In many diseases CPET could provide much information about the clinical status

and guide therapeutic decisions due to the noninvasive accessibility and prognostic importance of the available parameters (Hirashaki et.al. 2017). CP predicts more powerfully the mortality rather than VO2 peak (Lang et al., 2009.).CircP is one of the important variables obtained during CPET that can predict risk and mortality in cardiovascular disease (Forman et al., 2012) and non-cardiovascular disease (Yakal et al., 2018). Araujo et al., 2019 aimed to assess the effect of 3 months of combined resistance and aerobic exercise training on CircP and VP in patients with type 2 diabetes. They concluded that these indices may be used to assess a patient's prognosis because of the great clinical relevance of their findings. The ability to respond to aerobic exertion synergistically could be defined by CP and VP, two indices that combine parameters of CPET with systemic hemodynamics during exercise, via important physiologic measurements (Bassi et al., 2018). Tabet et al., 2006 examined the prognostic value of CircP through, CPET, in patients with Chronic Heart Failure with or without β-blocker therapy and concluded that CircP optimizes the predictive value of exercise capacity in the patients on β-blocker therapy. IPAH survivors had greater peak CircP than those who had cardiac events and patients with CircP > 1737.5 mmHg mL O2 kg-1 min -1 had better survival rate (Tang et al., 2018). Busque et al., 2022 established age- and sex- specific reference standards for peak CircP from a healthy cohort. Future studies need to investigate values also for clinical population.

2.3 Central Haemodynamic factors

2.3.1 Arterial stiffness – pulse wave velocity (PWV)

Arterial stiffness

High arterial stiffness, defined as the reduced ability of an artery to expand and contract in response to pressure changes (Cecelja et al., 2012), relates to increased risk of developing cardiovascular diseases and all-cause mortality (Dominguez et al., 2020). In the early stage of arterial stiffness, fibrous spots with small diameter are scattered on the arterial wall and, in the final stage, the arterial wall becomes homogeneously hard (Perreira et al., 2015). CVDs it is possible to appear after stiffening of the arteries, which is the first vessels modification responsible for several pathological processes, though arterial elastic properties are used for risk stratification purposes in several population (Perreira et al., 2015). Assessment of arterial stiffness provides information about the long-term effects of blood pressure and heart rate (Wilkinson et al., 2020).

Arterial stiffness is a reliable predictor of cardiovascular risk in patients with essential hypertension (Zhang et al., 2020). Vlachopoulos et al., 2019 emphasize that aortic stiffness could be used in individuals with hypertension to assess risk and as a therapeutic target to assist patient management and improve prognosis. It is also an independent predictor of risk for future cardiovascular events, which increases with aging (Myer et al., 2016, Podolec et al., 2019, Nong et al., 2016) and plays a central role in the vascular aging process (Sang et.al., 2021). Sang et al., 2021 suggest that in elderly patients, specific indicators of prognosis may be affected by other cardiovascular risk factors, while arterial wall stiffening may have a persistent and chronic effect on cardiovascular outcomes.

With increasing arterial stiffening SBP increases, while DBP decreases, resulting to increased pulse pressure. This pathophysiological result is partly attributed to early return of pressure wave reflections, synchronized early within the systolic phase of the forward propagating pressure wave (Wada et al., 1994). However, changes in BP can be considered both a cause and a consequence of arterial stiffness (Lacolley et al., 2018). Age and blood pressure are the major known cross-sectional and longitudinal correlates of aortic stiffness. Other CV risk factors have weaker associations, consistent with the hypothesis that elastic fibres undergo progressive fatigue fracture, which is driven largely by pulse pressure and heart rate (Wilkinson et. al.,2020) Altered coronary perfusion (Wada et al., 1994), myocardial hypertrophy and left ventricular dysfunction are also pathophysiological related to stiffened arteries and the increase of cardiac afterload (Tomiyama et al., 2020). ESC guidelines suggest that a very useful and important tool to evaluate the arterial system damage, vascular adaptation, and therapeutic efficacy is PWV, which considered as the gold standard method for assessing arterial stiffness, as for the management of arterial hypertension (Mancia et al., 2013).

Pulse wave velocity (PWV)

Pulse wave velocity (PWV) is defined as the velocity at which the pressure waves, generated by the systolic contraction of the heart, propagate along the arterial tree. In particular PWV is the speed at which the aortic wave travels, in m/s—is. It is usually measured in longitudinal arterial sections, mainly between the carotid and femoral vessels, illustrating the clinical relevance of this section of the vascular tree (Safar et al., 2018, Avolio et al., 2009). It can be measured using non-invasive, reproducible, relatively inexpensive techniques (Hock et al., 2012). and increases significantly and linearly with age (Reference Values for Arterial Stiffness' Collaboration, 2010). Also, it is commonly used as an effective noninvasive indicator for assessing arterial stiffness (Laurent et al., 2016), which may be an accessible tool to estimate mortality risk (Dominguez et al., 2020) Framingham Heart Study (FHS) investigators have shown that the prevalence of carotid-femoral pulse wave velocity (CFPWV) greater than 12 m/s increases from a few percent prior to age 50 years to over 60% after 70 years of age (Mitchell et al., 2014). The higher PWV corresponds to lower vessel distensibility and compliance and, therefore, to higher arterial stiffness. PWV increases with the distance from the heart, along with the elastic condition of the arterial wall, which is affected by a variety of factors in the pathological process (Wilmer et al., 2005). A normal value (<95th percentile) for CFPWV in a healthy FHS reference sample <50 years of age was 8.1 m/s (Mitchell et al., 2010). The evaluation of PWV provides complementary information to classical risk factors (age,gender) and biological analysis (cholesterol, glucose) about the elastic properties of arterial system, (Perreira et al., 2015) and together may represent a better method for more accurate diagnosis (Mancia et al., 2013, Hock et al., 2012). PWV is considered one of the most important clinical parameters for evaluate the CV risk, vascular adaptation, and therapeutic efficacy (Perreira et al., 2015).

Assessment of PWV

There are several methods used to determine PWV. Regional and local assessment of PWV are two big categories and each has its own specificities (Perreira et al., 2015). Common carotid, radial, femoral and brachial arteries are main sites where the pulse is better detectable, with carotid and femoral to be the most used for regional PWV assessment (Perreira et al., 2015). Carotid–femoral PWV is accepted as the 'gold-standard' measurement of arterial stiffness and it has been used to predict the CV events, assess the hypertensive, diabetics, and evaluate patients with chronic renal failure and coronary heart disease (Mancia et al., 2013, Laurent et al.,2006). cfPWV is largely a measurement of aortic wall stiffness because it depends on different factors such as aortic geometry and peak aortic flow (Laurent et al., 2006). A recommended way to calculate cfPWV is by the ratio of the distance (the length from the suprasternic notch to femoral artery minus the length from carotid artery to the suprasternic notch) traveled by the recorded pressure waves to the pulse transit time in m/sec. This procedure should be conducted at least twice so the average value to be used in the analysis (Papaioannou et al., 2012). It is difficult to access the signal in obese people and there is a chance for error associated with distance estimation (Perreira et al., 2015).

The current methods used to measurement of PWV can be divided in three main groups: imaging, non-imaging and optical methods (Perreira et al., 2015). Each category has advantages and disadvantages. Imaging methods (US, MRI) provide a direct measurement of the path length, though they require expensive technology. Non-imaging methods (pressure mechanotransducers) are more affordable and validated, but they only allow regional assessment. Optical methods use light wavelengths allow tissue penetration and capture the pulse waveform deep of the skin (Perreira et al., 2013). Even though are low-cost technology and based on measurement without contact, they are at an early stage of validation (Perreira et al., 2015).

The most common technique to non-invasively assess PWV is based on the acquisition of pulse waves generated by the systolic ejection at two distinct locations, separated by a distance d, by determining the time delay, or PTT, due to the pulse wave propagation along the arterial tree (Complior, SphygmoCor). The PWV parameter is then simply calculated as the linear ratio between d and the PTT (Segers et al., 2009). Pressure sensors, such as the tonometer, is considered the gold standard method for measuring PWV, but some operating skill is required to use this method which may influence the measurement (Perreira et al., 2015). With this method it is feasible to measure cfPWV and baPWV. In the ultrasound method, doppler pulses are recorded sequentially in 2 different arterial sites and compared using the R-wave of the ECG. Another non-invasive method to measure regional PWV is computerized oscillometry, which combine simultaneous acquisition and analysis of the pulsation of the artery, which is caused by the heart, as the pressure oscillation in the cuff (Perreira et al., 2015).

Local PWV measurement is clinically important in local analyses of arterial wall properties to providing diagnostic information of biomechanical properties for local artery wall (Darwich et al., 2015). MRI (non-invasive assessment of blood flow) and aortic angiography (invasive with intra-aortic measurements) are methods that determine local PWV (Perreira et al., 2015). PWV is not always feasible to be measured. Estimated PWV (ePWV) is a newly suggested index which is calculated by equations using age and blood pressure. It has been demonstrated that ePWV seems to

be predictive of future cardiovascular events and improved risk prediction compared with traditional risk scores mainly in healthy individuals and those with untreated hypertension (Greve et al., 2016, Vlachopoulos et al., 2019).

Clinical usefulness Although some studies support that age and BP are closely related to cfPWV (10-12 wilkinson), other studies have demonstrated that cfPWV is an independent predictor of CVD events (Mitchell et al., 2010, Ben-Shlomo et al., 2014, Vlachopoulos et al., 2010). In a meta-analysis using data from 17635 participants, there was no evidence that sex or smoking influenced the predictive value of cfPWV (Ben-Shlomo e al. 2014). The unique clinical value of carotid-femoral pulse wave velocity may hinge on the ability of a single assessment to provide important information concerning blood pressure progression and susceptibility to end organ damage (Wilkinson et al., 2020). Carotid-femoral pulse wave velocity should be seen as complimentary to current blood pressure, and both should be considered when calculating risk and making treatment decisions (Wilkinson et al., 2020). Application of cfPWV presents some limitations. At first, there may be differences in arterial stiffness among different races (Morris et al., 2013) and only reflects the stiffness of the large arteries and cannot fully reflect the stiffness or function of the smaller conduit arteries (Niiranen et al., 2019). Also, cfPWV can divide participants into high and low CVD risk groups, but its cut-off value is still not established (Chang et al., 2023). It is suggested that cfPWV exceeding 10 m/sec should be considered a CVD risk factor (Mancia et al., 2013, Perk et al., 2012).

Brachial ankle PWV (baPWV) has the advantages of advantages of reproducibility, simplicity, and good correlation with aortic PWV (Baier et al., 2018). High values of baPWV are affiliated with increased risk of CV events or all-cause mortality in different populations (Hoshide et al., 2016, Munakata et al., 2012, Maeda et al., 2014, Turin et al., 2010). Definition of outcomes, disease states, age and prevalence of hypertension are some of the factors that could affect the cutoff values of baPWV (Sang et al., 2021). baPWV is measured over a longer arterial path length and is a combination index reflecting central and peripheral arterial stiffness (Tanaka et al., 2018), which is more affected by peripheral arteries (Chang et al., 2023). baPWV measures the stiffness of peripheral arteries, while cfPWV is an indicator of stiffness of central elastic arteries and therefore their thresholds differ markedly because of their different measurement points (Dominguez et al., 2020). It is demonstrated that there was a better correlation between baPWV and parameters of LV and arterial structure and function rather than cfPWV (Yu et al., 2008). The large heterogeneity of the structure of arterial walls at different sites constitutes an important limitation of PWV regional measurement (Safar et al., 2007).

Using cfPWV or baPWV, can be clinically useful in hypertensive patients for the assessment of large artery stiffness. It has been demonstrated that increased cfPWV and baPWV values predict, in apparently healthy adolescents, young and middle-aged people, an increased risk of new-onset hypertension (ESH Guidelines 2023).

Clinical value of PWV

The measurement of PWV is of clinical interest in improving the predictive ability of cardiovascular risk in intermediate risk patients (Ben-Shlomo et al., 2014). PWV correlate atherosclerosis alterations and is a predictor of CV risks in hypertensive patients (Blacher et al. 1999). Also, in diabetic patients has been showed an increase in PWV. PWV may have a technical operator bias when measured in obese patients (Perreira et al., 2015). Elevated PWV and increased aortic diameter are standard features of hypertension and together form the most reliable independent predictor of cardiovascular risk in the elderly population (Blacher et al., 2015). cfPWV is recommended by AHA, ESC, ESH, for the management of arterial hypertension (Williams et al., 2018) and as the most widely studied index of arterial stiffness, fulfills most of the stringent criteria for a clinically useful biomarker (Vlachopoulos et al., 2015). cfPWV represents disease-mediated organ damage and a predictor of its development in hypertensive patients (Kaess et al., 2012). Also, elevated cfPWV is associated with an increased risk of cardiovascular death (Podolec et al., 2019). ASCVD patients it is demonstrated that are associated with increased risk of cardiovascular events, cardiovascular mortality, and all-cause mortality, identified by high baPWV (Sang et al., 2021). The predictive ability of baPWV for the risk of CV events seems to be higher in patients with CAD, than in general population (Sang et al., 2021). Aortic PWV is significantly higher in hypertensive than normotensive populations and higher in diabetic mellitus patients with concomitant hypertension, even in the presence of elevated HbA1c alone (Gnakamene et al., 2018, Smulyan et al., 2016).

2.3.2 Pressure wave reflections - augmentation index (AIx)

Pressure wave reflections

Pressure Wave reflection at the level of the central arteries consists of a major component of the left ventricular afterload (Papaioannou et al., 2019). Wave reflection occurring during the cardiac cycle, especially at the level of ascending aorta, is an important determinant of left ventricular load and coronary blood flow (Papaioannou et al., 2019). Increase in ventricular load occurs when the reflected waves arrive at the ascending aorta at early systole augment systolic blood pressure. Coronary perfusion occurs when reflected waves arrive during late systole or even diastole and though increase mean diastolic blood pressure (Laurent et al., 2016). Then onwards, arises a global reflected wave that arrives at the proximal aorta either during early systole, leading to a secondary systolic pressure peak and increased central pulse pressure, or delayed during late systole after the systolic pressure peak (Vlachopoulos et al., 2000, Nichols et al., 2005). The distance to the reflecting site, the speed of wave transmission (determined by arterial stiffness) and the intensity of the reflected waves determine the wave reflections (Vlachopoulos et al., 2000, Mitchell et al., 2005).

Augmentation index

Augmentation index (AIx), defined as the ratio of the augmentation of SBP to pulse pressure (PP), is the most widely applied surrogate of wave reflection and various algorithms of pulse wave analysis been used to determine it (Papaioannou et al., 2019). AIx should not be regarded as a surrogate of local or regional arterial stiffness (Vyas et al., 2007). AIx is an indirect measure of arterial stiffness, but mainly a direct measure of pressure wave reflection (Safar et al., 2008) and one of the key factors to determine central BP (Shimizu et al., 2008). AIx does not directly quantify the magnitude of the wave reflection but rather the interaction of the forward and backward traveling waves, since it expresses the late systolic pressure augmentation as a percentage of pulse pressure (Protogerou et al., 2007). AIx predicts clinical events independently of peripheral pressures and its central predictive value is independent of blood pressure and heart rate (Vlachopoulos et al., 2010).

Major determinants that affect AIx are the arrival time of the pulse wave reflection, the properties of peripheral muscular arteries and arterioles that change the amplitude of the reflected wave and the left ventricular contractility (Shimizu et al., 2008). AIx increases steeply with age in younger subjects, increases more gradually in subjects aged 50 to 60 years, and thereafter reaches a plateau (Fantin et al. 2007, Wojciechowska et al. 2006, McEniery et al. 2005, Mitchell et al. 2004). Increased AIx was associated with adverse cardiovascular events and mortality (Protogerou et al., 2007). . AIx has been associated with cardiovascular diseases and higher AIx with target organ damage and aortic atherosclerosis (Shimizu et al., 2008. Although men have greater cardiovascular risk, AIx has been observed higher in women than in men. Also, height, age and gender should be considered when determining AIx (Shimizu et al., 2008).

Measurement of AIx

AIx is ideally calculated based on direct invasive measurement but cannot performed routinely (Shimizu et al., 2008). There are non-invasive techniques to measure central blood pressure and AIx, such as applanation tonometry or automated oscillometry, either directly at the carotid artery (without the use of transfer functions or mathematical model) or indirectly at the aortic level by use of mathematical transformation of peripheral arterial pulses (Papaioannou et al., 2009). Carotid AIx is consistently lower than aortic AIx (Chen et al., 1996), but it is insufficient in patients with atherosclerotic plaques or calcified arteries (Shimizu et al., 2008). Radial AIx measurement is obtained directly from radial artery has strong correlation with aortic AIx and carotid AIx (Melenovsky et al. 2007, Sugawara et al., 2007, Segers et al. 2005, Filipovsky et al. 2005, Kohara et al. 2005). Usually, AIx is calculated using the formula AIx = 100 X (Augmentation pressure)/ (Pulse Pressure) (O'Rourke et al., 2001, Barraclough et al., 2017). The technique of applanation tonometry is widely used to evaluate central pressure and mostly wave reflections through the non-invasive use of the parameter AIx (Safar et al., 2008). There are different devices such as Mobil-O-Graph, Complior (directly central/ carotid pressure waveforms without mathematical models and transfer function) and Arteriograph by which been demonstrated that have significant differences in central AIx estimation (Papaioannou et al., 2019). Mobil-O-Graph device showed the highest agreement (lowest bias) with the Complior system as regards to the

AIx measurement (Papaioannou et al., 2019). There is no established gold standard method among the non-invasive available technologies for central AIx estimation (Papaioannou et al., 2019).

Carotid Intima Media Thickness (cIMT)

Atherosclerosis is a chronic inflammatory state in which there is localized accumulation of lipids and inflammatory cells that make up atherosclerotic plaques. It is the major underlying pathological process of CVD that begins in early life and after an asymptomatic period it leads to clinical conditions such as stroke and other CVD diseases (McGill et al., 2000). cIMT is a well-used method of assessing atherosclerosis at the subclinical stage (Zaid et al., 2022). It is defined as the thickness of the intimal and medial layer of the carotid artery wall and can be measured noninvasively using ultrasound imaging (Libby et al., 2011). The establishment of an optimized ultrasonographic protocol for the measurement and assessment of carotid IMT has the potential to enhance the predictive role of carotid IMT in cardiovascular disease risk estimation. Also, it can serve as a valuable tool in identifying individuals who may avoid developing future cardiovascular disease (Ling et al., 2023).

Measurement of cIMT with B-mode ultrasound is a noninvasive, sensitive, and highly reproducible technique for identifying and quantifying arterial injury and cardiovascular disease risk (Mulvagh et al., 2008). The ASE Consensus Statement recommended that carotid ultrasound with cIMT measurement and evaluation for plaque presence be considered in intermediate-risk patients, in patients with a family history of premature cardiovascular disease in a first-degree relative, in individuals younger than 60 years old with severe abnormalities of a single risk factor, and in women younger than 60 years old with two or more risk factors (Mulvagh et al., 2008). For younger adults (18 to 42 years old), strong relationships between increasing risk factor burden and cIMT, as well as between cIMT and emerging risk factors, have been demonstrated. Mean values of cIMT in adults' range around 650 to 900 μm and increase—on average—at a rate of 0 to 40 μm/y. (Lorenz et al., 2012, Willeit et al., 2016). IMT measurements could constitute an important tool to identify and target intermediate risk subjects in preventive medicine (Touboul et al., 2006, PARC study). Exercise was associated with reduced cIMT in adults. Wang et al., 2022, after a systematic review and meta-analysis with 1370 participants, concluded that aerobic exercise is associated with a greater decline in cIMT than other forms of exercise.

cIMT has an important clinical value as a surrogate measure of the burden of carotid atherosclerosis and a predictor of CVD for primary prevention (Libby et al., 2011). In addition, cIMT detects early arterial disease in asymptomatic individuals and is significantly associated to a higher risk of incident myocardial infarction and stroke. A careful analysis of cIMT research reveals considerable inconsistencies, such as whether plaques were included in the cIMT measurement, including the carotid segments evaluated common carotid artery (CCA-IMT), internal carotid artery (ICA-IMT), carotid bifurcation (bif-IMT), or the combined segments (combined- IMT) (ARIC study). CCA-IMT is linked to systemic atherosclerosis and vascular remodeling in response to hemodynamic changes (ARIC study). CCA-IMT, rather than ICA-IMT and

bif-IMT, is more often used in clinical practice and clinical studies because measurements in this segment are more stable and reproducible (Simon et al., 2002).

IMT components include not only modifiable and non-modifiable factors (mainly age and gender-related risk factors) like the Framingham score does, but also genetic, biological, and other unknown factors which may play a specific role in different individuals (Touboul et al., 2006). Each component of the Framingham score (age, sex, HDL cholesterol, systolic blood pressure) was significantly associated with CCA-IMT after adjustments for age and gender (Touboul et al., 2006). CCAIMT was shown to be a simple, non-invasive test with a low cost and a high level of accuracy, which provided information that was not redundant with the Framingham score (Touboul et al., 2006). In the Carotid Atherosclerosis Progression Study (CAPS), cIMT predicted CVD events even among 2436 individuals <50 years old (mean, 38.7 years; standard deviation, 7.0 years). In that study, the relative risk associated with increased CIMT appeared to be higher among younger than older adults (Lorenz et al., 2010).

2.4 CircP: in hypertensives; the role of PWVV, AIx & IMT

High blood pressure is one of the most important risk factors for ischemic heart disease, stroke, other cardiovascular diseases (CVDs), chronic kidney disease and dementia. Elevated blood pressure is a leading preventable cause of CV mortality and disease burden globally and in most regions of the world (Zhou et al., 2021). The main factor about CircP (CRF), PWV (arterial stiffness), AIx (pressure wave reflection) and IMT (carotid remodeling) in hypertension is blood pressure. Elevated blood pressure is a major modifiable cardiovascular disease (CVD) risk factor worldwide (Mancia et al., 2013). CircP has been demonstrated that had the best prognostic value and was stronger independent predictor of cardiac events among other CPET parameters (Tang et al., 2018). So, CircP may be a noninvasive starting point of help to modify elevated blood pressure. Despite all the information that CircP can provide about CRF, it is not routinely applied neither in clinical setting, nor on the general population. PWV and AIx are central noninvasive haemodynamic factors that are routinely applied in clinical setting for the assessment of arterial stiffness. Hypertension and arterial stiffness are closely related to each other. When BP is high, arterial stiffness progresses, and conversely when arterial stiffness progresses, BP also increases. Arterial stiffness information can be used in hypertensive patients to predict the cardiovascular risk (Kim 2023). Evidence from the Framingham and European studies has shown that increase of arterial stiffness is highly prevalent in the hypertensive population [253,275,276]. Improvement in PWV values, are associated with improved prognosis in patients with resistant hypertension or on dialysis (Cardoso et al., 2022). In pre-hypertensive and low-risk hypertensive patients, central hemodynamic measures were found to correlate with IMT when oscillometer method was used. (Barroso et al., 2021). It is important in clinical practice to have non-invasive ways of assessing and identifying patients and their condition accordingly. The correlation of these four indicators should be considered when calculating risk, making treatment decisions, and giving guidelines for exercise to hypertensive patients.

3. SPECIFIC SECTION

3.1 Hypothesis- Aim

Circulatory Power (CircP) provide a complete reflection of CRF and predicts adverse events in cohorts of cardiovascular and pulmonary diseases (Busque et al., 2022). In the current literature, CircP and its prognostic value has been studied in healthy and limited clinical population. As far as people with hypertension, there are no data, that investigate the comparison of CircP values between healthy and hypertensive individuals.

Thus, the primary objective of the present study is to investigate whether the CircP values are higher in normotensive than in hypertensive patients. Moreover, there are no studies so far that correlate PWV, AIx and cIMT simultaneously, with indices coming out of a cardiopulmonary exercise test, and particularly CircP. Thus, the secondary purpose of the present study is to show whether there is a correlation bet ween CircP and aortic stiffness, pressure wave reflections and carotid artery remodeling, respectively. The ultimate aim is CircP to be considered as a remarkable tool for the assessment of CRF in hypertensive patients and to enhance the assessment of carotid remodeling and arterial stiffness after a cardiopulmonary exercise test.

There are two hypotheses in the current study. Firstly, that normotensive have higher values of CircP than hypertensive patients and secondly, that CircP will be significantly associated with central haemodynamic factors and carotid remodeling.

3.2 Material and Methods

3.2.1 Study design

All measurements were performed in morning hours under standardized laboratory conditions, for each measurement separately and according to specific instructions. On the first visit all participants underwent measurements of central hemodynamic indices, the conditions of which will be analyzed in a subsequent subsection. The exclusion criteria for the whole study were age less than 18 years, absence of sinus rhythm during the laboratory testing, known non-hypertensive cause of LVH (e.g. hypertrophic cardiomyopathy, aortic stenosis), the presence of secondary hypertension, any change in medication for cardiovascular disease in the last month, and failure to provide an up-to-date informed consent or unwillingness/inability to comply with the study protocol. All participants were asked to abstain from food and any vasoactive substance or medication on the morning of morning of the examination (Papaioannou et al., 2017). On the second visit all participants underwent a cardiopulmonary exercise test, of which the procedure will be analyzed in a subsequent subsection. They were asked to refrain from exercise on the day of the test, smoking at least 7 hours before, avoid drinking coffee or alcohol prior the test and eat less than 2 hours before. Also, they should be wearing comfortable clothes/shoes, and take all routine medication.

3.2.2 Participants

The present study included 34 participants, 11 women (7 hypertensive) and 23 men (20 hypertensive) (Table 1). All participants gave written informed consent to participate in the study and were informed of the potential benefits of the measurements in terms of prognosis and diagnosis. The normotensive group consisted of 7 participants (4 females) and 4 of them were dyslipidemic. In the hypertensive group were 27 participants (7 females), of which 26 were dyslipidemic, 6 had type 1 diabetes and 1 had type 2 diabetes. All individuals were examined in the laboratory for CV disease risk estimation.

Table 1. Demographic Characteristics

	Normotensive (N=7)	Hypertensive (N=27)	p-value
Age (years)	46,57 ± 14,270	55,96 ± 11,746	0,146
Gender; females (%) (n)	(11,8%) (n=4)	(20,6%) (n=7)	
Height (cm)	171,57 ± 8,04	173,19 ± 9,82	0,661
Weight (kg)	70,25 ± 17,64	88,08 ± 15,55	0,039
BMI (kg/m2)	23,74 ± 4,59	29,19 ± 4,27	0,02
Type 1 diabetic (%) (n)	n=0	(18%) n=6	0,009
Type 2 diabetic (%) (n)	n=0	(3%) (n=1)	
Dyslipidemic (%) (n)	(11,7%) n=4	(76,3%) n=26	0,102

Continuous variables are expressed as Mean ±SD.

3.2.3 Measurements

Measurement of Carotid-Femoral Pulse Wave Velocity (cfPWV)

cfPWV was measured in the morning after at least 10min of rest in supine position under controlled room temperature, using the SphygmoCor apparatus (AtCor Medical, Sydney, Australia), by the same operator. Pressure waveforms were recorded, first at the carotid artery and a few seconds later at the femoral artery, by using a high-fidelity handheld tonometer (SPT-301, Millar Instruments Inc. Houston, TX, USA)

(Papaioannou et al., 2017). cfPW sequences were synchronized by using the simultaneously recorded ECG. Pulse transit time from the carotid to the femoral artery was estimated by the tangential method, implemented by the SphygmoCor system. The cf-PWV was calculated by the ratio of the distance traveled by the recorded pressure waves to the pulse transit time (in m/sec). The distance was determined as the length from the suprasternic notch to femoral artery minus the length from carotid artery to the suprasternic notch. At least two repeated measurements of cf-PWV were performed, and their average value was used in the analysis (Papaioannou et al., 2012).

Measurement of Augmentation Index (AIx)AIx was measured in the morning after at least 10min of rest in supine position under controlled room tempretarute using SphygmoCor apparatus (AtCor Medical, Sydney, Australia), as cfPWV. AIx was assessed as an index of pressure wave reflections. Central pulse waveformes were analyzed and AIx was calculated by using the formula AIx = 100 X (Augmentation pressure)/ (Pulse Pressure) (Papaioannou et al., 2019).

Measurement of Carotid Intima Media Thickness (cIMT)

cIMT was measured in the morning after at least 10min of rest in supine position under controlled room temperature with an B mode high-frequency ultrasonography (Vivid 7 Pro; GE Healthcare, Fairfield, CT) (Argyris et al., 2022). In addition, cIMT was measured in adjacent to any plaque (if present) at the far wall of the common carotid artery in end-diastole of the cardiac cycle using semiautomatic software. The internal diameter of the common carotid artery was also measured. Two sequential images were obtained and measured. The average measurements were used to calculate the carotid cross-sectional wall area (CSA) of the common carotid artery (Argyris et al., 2022).

Measurement of Circulatory Power (CircP)

All participants underwent symptom limited incremental CPET on cycle ergometer (Ergoline-Ergoselect 200, Serinth) in morning hours, under standardized laboratory conditions (controlled room temperature). All participants were informed about the test procedure. After each participant had partially removed his/her clothing to connect to the electrocardiogram, he/she got on the cycle ergometer to connect to the rest of equipment. The equipment included a pulse oximeter, a blood pressure monitor connected to the cycle ergometer, ECG leads, and a facemask connected to the gas analyzer. When the connection was completed, the participant pedaled two or three times in order to familiarizing with the equipment and the cycle ergometer. The instructions given were to reach up to 60 rpm, to hold the bicycle handlebars steady and not to speak prior, during and at the recovery time because the analysis of the results would be affected. Special attention was given to understanding when to stop the procedure, before the termination of the test, with wave of the hand in case of chest pain, dizziness, or any other side effect. Collection of gas exchange resulted from the use of calibrated computer-based system (COSMED Quark CPET, OMNIA software, Serinth). Two first minutes were for rest period and next two for warmup while the workload was gradually increasing. The workload (W) was continuously increased in

a linear “ramp” pattern of 10 or 15 W min−1, depending on the physical fitness. Ideally, the individualized, breath-by-breath, incremental exercise testing duration was between 8 and 12 min (Bassi et al., 2015), Two minutes after the exercise duration were for recovery with the patients sitting on the bicycle, After, the pulse and blood pressure were returned in normal, they were disconnected from the equipment. All measurements were recorded according to published standards (Balady et al., 2010).

3.2.4 Statistical analysis

Statistical analysis was performed using SPSS 25.0 (IBM, Chicago, Illinois, USA). Significance was defined as $P<0.05$. Continuous values were expressed as mean ±SD and noncontinuous as absolute numbers and percentage. Pearson correlation coefficient was applied to test the linear association of CircP with cfPWV, AIx and IMT. The statistical analysis of the data was performed with 2 independent sample t-tests and multiple linear regression analysis.

4. Results

4.1 CircP values between normotensive and hypertensive

The first hypothesis has been verified. As previously stated CircP index is derived from the product of VO2 peak and SBP peak. Both normotensive and hypertensive participants had approximately same values as regards peak SBP during CPET. However, VO2 peak values were slightly greater in normotensive than hypertensive participants. A reduced VO2peak is the starting point in the evaluation of reduced exercise tolerance (ATS/ACCP, 2003). The combination of all these metrics had as result CircP values to be higher in normotensive than in hypertensive participants (Table 2).

Table 2. Baseline and Peak CPET results (Mean±SD)

	Normotensive	Hypertensive	p-value
Resting SBP (mmHg)	107,14 ± 12,60	122,92 ± 19,28	0,021
Peak SBP (mmHg)	177,29 ± 15,27	176,67 ± 15,90	0,926
Resting DBP (mmHg)	68,29 ± 4,68	79,31 ± 12,97	0,001
Peak DBP (mmHg)	75,00	93,83 ±	0,032

	± 13,78	24,21	
VO2peak (ml/min/kg)	24,40 ± 10,30	18,12 ± 4,45	0,151
Peak CircP (mmHg . mL 02 . Kg -1. min -1)	4333,98 ± 1920,78	3193,64 ± 797,29	0,171

4.2 Comparing Circulatory Power (CircP) index and central haemodynamic factors

CircP index had a statistically significant correlation with almost all the factors that was associated (Table 3). Specifically, CircP was found to depend considerably on Age p-value 0,004 ($p<0,01$) and BMI p- value 0,028 ($p<0,05$). Aortic stiffness, expressed by PWVc-f_Lab (0,057), PWVc-r_Lab (0,051) and PWV rest (0,172), was found that had no statistical significance with CircP. In contrast, pressure wave reflections were found to have significant correlation with CircP, as results from AI%_Lab ($p<0,001$) and AI_75bpm_Lab (0,005; $p<0,01$). Furthermore, carotid artery remodeling was found to be significantly associated with CircP. Noteworthy, is that LCC_IMT (0,015; $p<0,05$) had significant difference from RCC_IMT (0,004; $p<0,01$).

Table 3. Correlation of CircP with haemodynamic factors

	CircP	p-value
Age	-0,486	0,004
BMI	-0,377	0,028
PWVc-f_Lab	-0,364	0,057
PWVc-r_Lab	0,192	0,51
PWV rest	-0,295	0,172
AI%_Lab	-0,6	<0,001
AI_75bpm_Lab	-0,516	0,005
LCC_IMTav2_1	-0,425	0,015
RCC_IMTav2_1	-0,496	0,004

5. Discussion

The purpose of the present study was to investigate, for the first time, CircP index in hypertensive and normotensive population, as well as whether there is any association between CircP and central haemodynamic factors and carotid remodeling. The main findings were that: 1) CircP had greater values in normotensive participants than in hypertensive patients, 2) CircP was found to depend considerably on age and body mass

index and 3) CircP was correlated with arterial stiffness (PWV) and had a strong association with pressure wave reflections (AIx) and, left and right carotid remodeling (cIMT).

CRF can be measured directly expressed as peak VO2, derived from CPET (Ross et al., 2016). The results showed that hypertensive patients had lower CircP, suggesting that the hypertensive group may had lower CRF. Castello-Simoes et al., 2015 aimed to evaluate CircP in patients with coronary artery disease (CAD). As in this study, clinical population had lower values as regards CircP. Also, they found that CircP positively correlated with aerobic functional classification evaluated by peak VO2. In the present study, it was rather unexpected that, even though the resting SBP was different in both groups (table 2), the peak SBP was pretty much the same. This could be possibly explained cause of the action of anti-hypertensive drugs during CPET. It has been reported that various antihypertensive treatments, such as angiotensin receptor antagonist and aldosterone antagonist, are known to modulate hypertensive response to exercise in patients with hypertension (Youn et al., 2015). Tabet et al., 2006 demonstrated that peak CircP optimized the predictive value of exercise capacity in patients with CHF who were receiving β-blocker therapy. The findings after a CPET should be taken into consideration when assessing healthy or patient participant to help prevent future cardiovascular events. Interpretation of CPET could be useful for the detection of masked hypertension and the evaluation of the effectiveness of antihypertensive treatment in patients with hypertension (Youn et al., 2015). Standards for CircP are needed to enhance the interpretation in clinical or non-clinical population as for exercise responses and improve patient risk assessment and treatment plans (Busque et al., 2022).

Busque et al., 2022 aimed to establish age and sex specific refence standards from a healthy cohort, across most of the adult life span, derived from Fitness Registry and the Importance of Exercise: A National Database (FRIEND). They found that sex, exercise mode, age and BMI were the most significant contributors. In the current study CircP was found to depend considerably on age ($p<0,01$) and BMI ($p<0,05$). Age plays an important role because aging has been shown to affect VO2peak (Simoes et al., 2013) and to result in a decrease in CircP (Busque et al., 2022). Furthermore, the participants were normal to overweight in BMI classification. Obesity has the effect of increasing VO2 peak and complicates its interpretation. Hulkkonen et al., 2014 presented values of CircP derived from females and male participants of Cardiovascular Risk in Young Finns Study. They concluded that demographic characteristics and lifestyle should be considered when evaluate patients' cardiac function in CPET. It is important to mention that they measured CircP with two types: as the product of VO2 peak and peak SBP and, as the product of VO2peak and MAP. They mention that irrespective of whether BP based on SBP or MAP was used, both methods of calculation applicable when the studied indices are formed. Nevertheless, MAP method is under review cause some studies mention that this measurement is not accurate but other studies mention that SBP provides information on a short amount of time of cardiac cycle (Giardini et al., 2007). Standards for CircP were also presented by Ashikaga et al., 2023 in a healthy Japanese population. They include them as values for the evaluation of different factors correlated with severity in diseases primarily heart failure. VO2 peak and SBP peak are

independent reflections of CRF, so establishing reference standards for CircP may provide additional benefits when interpreting CPET response (Busque et al., 2022).

It is well known that higher CRF is associated with lower cardiovascular morbidity. In the current study, was found that CircP has a strong association with central haemodynamic factors and carotid remodeling. There are no other studies that have investigated this correlation. Despite this, there are studies that correlate hemodynamic factors and carotid remodeling with other CPET factors. CircP is the product of VO2peak and peak SBP so, more emphasis will be given to these parameters. Witt et al., 2022 assessed CRF, defined as VO2peak, using CPET. They found that there is association between CRF and central as well as peripheral PWV and AIx values in the adult general population. Huang et al., 2016 in their review article mention that a greater improvement in VO2 was associated with larger reductions in PWV. Correspondingly, Nayor et al., 2023 found that lower CRF (peak VO2) was associated with higher CFPWV, higher characteristic impedance and higher AIx. Also, there was a consistency of the association between CFPWV and peak VO2 across the age, sex and cardiovascular risk profile, but with attenuation in individuals with obesity.

Improvement of risk prediction is particularly important in patients at low or intermediate risk (Vlachopoulos et al., 2010). Hypertension-mediated organ damage (HMOD) assessment by cfPWV and cIMT plays major role in risk stratification of patients with hypertension, (ESH, ESC, 2007). Prehypertensive individuals have a greater risk of developing hypertension and cardiovascular disease than normotensive individuals (Kim et al., 2017). Sholl et al., 2015 in a large preventive study (7300 participants) demonstrated that improved CRF is a major determinant of cIMT and slightly abolish the adverse consequences of cardiovascular disease risk factors on common CIMT. Jae et al., 2007 reported that higher levels of CRF are inversely associated with prevalence of carotid atherosclerosis (cIMT) in middle-aged hypertensive men. Furthermore, Kim et al., 2017 in their study of 442 middle-aged women, have reported that good CRF (peak VO2) is associated with a slower progression of early atherosclerosis (cIMT).

CRF is inversely related to all-cause mortality in men and women. Moreover, depends on multiple genetic characteristics, though it is highly trainable through exercise. Regular aerobic training as well as resistance training are factors that have remarkable benefits for cardiovascular health and arterial health improvement, respectively (Zaman et al., 2024). CPET provides further information on functional status and prognosis in addition to variables that are usually recommended for monitoring, such as cardiac biomarker blood levels and echocardiographic variables (Nicol et al., 2020). The association of CircP with arterial stiffness, pressure wave analysis and carotid remodeling provides a potential pathophysiological model regarding the mechanism of CVD disease. Further research is needed to elucidate this model.

6. Limitations- Proposal for future research

There are certain characteristics and particularities of the present study that should be considered when interpreting and using its findings. The results of the study were derived from a specific age range of mainly middle-aged participants. From the third decade of life, women show a steeper blood pressure gradient, yet hypertension is more

common in men. Connelly et al., 2022 claimed that the prevalence of hypertension accelerates comparatively with age. The sexual dimorphism in blood pressure begins at puberty and persists through adult age (Yanes et al., 2011). So, subsequent studies should investigate other age groups. Furthermore, the participants where both women and men. Gender-bias may occur cause of the different number of men and women in each group. Hypertension is more prevalent in men than in women (Shaw et al., 2006). There are limited data in exercise science and sports medicine for women, and especially in women with high blood pressure and the effect of exercise training in arterial stiffness (Zaman et al., 2023). Studies focusing on women are needed in every field of scientific research. Four of the normotensive participants had dyslipidemia. Further studies need to consider the specific characteristics of the participants to consolidate these findings. Moreover, research studies suggest that SBP is more reliable for measuring CircP. Further surveys should investigate if measurement of CircP, with aortic pressure rather than cuff pressure, is feasible and reliable. This would make CircP more representative for population with advanced arterial stiffness.

7. Conclusion

CircP is higher in normotensive than in hypertensive individuals, and it is significantly associated with pressure wave reflection and carotid remodeling. Large, controlled trials are needed to verify the prognostic value of CircP in hypertensive patients and to establish the correlation of CircP with arterials stiffness, pressure wave reflections and carotid remodeling.

8. References

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