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ΔΙΠΛΩΜΑΤΙΚΗ ΕΡΓΑΣΙΑ

«Καρδιακή αποκατάσταση σε καχεκτικούς ασθενείς με χρόνια καρδιακή ανεπάρκεια.»

«Cardiac rehabilitation in cachectic-frail patients with chronic heart failure.»

ΕΛΕΝΗ ΠΑΡΑΣΚΕΥΗ ΒΛΑΣΤΑΡΗ

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ΚΑΘΗΓΗΤΗΣ ΣΠΥΡΟΣ ΖΑΚΥΝΘΙΝΟΣ

Περιεχόμενα/ Index

List of abbreviations

AT: anaerobic threshold

BMI: Body Mass Index

Bmp: Beats per minute

BNP: B-type Natriuretic Peptide

CHF: Chronic Heart Failure

CR: cardiac rehabilitation

CT: Aerobic continuous training

CT: Computed Tomography Scan

DEXA: Dual Energy X-ray Absorptiometry

ECG: Electrocardiogram

EF: Ejection Fraction

EWGSOP: European Working Group On Sarcopenia On Older People

FFMI: Fat Free Mass Index

FI-CGA: FI-comprehensive Geriatric assessment

HF: Heat Failure

HIIT: High Intensity Interval Training

HR: Heart rate

HRQoL: Health related quality of life

Hz: Herds

IGF-I: Insulin Like Growth Factor -1

IT: Aerobic interval training

KCCQ: Kansas City Cardiomyopathy Questionnaire

LFES: Low Frequency Electrical Stimulation

LVEDD: Left Ventricular End Diastolic Diameter

LVEF: Left Ventricular Ejection Fraction

mA: Milli-ampere

MET: Metabolic Equivalent

MLwHFQ: Minnesota Living with Heart Failure Questionnaire

MVC: Maximum Voluntary Contraction

N: Number of participants

NMES: Neuromuscular stimulation

NYHA: New York Heart Association

Peak HR: Heart rate peak

PImax: Maximal Inspiratory mouth pressure

QoL: Quality of life

RM: Repetition maximum

RPP: Rate Pressure Product

RST: Resistance/Strength Training

RT: Resistance Training

SMM: Skeletal Muscle Mass assessment

SMMI: Skeletal Muscle Mass Index

SOF: Study of Osteoporosis Fracture index”

SPPB: Short Physical Performance Battery

ST: Strength Training

TBK or PBK: Total or partial Body potassium per fat-free soft tissue measurement

TNF-a: Tumor Necrosis Factor –alpha

VE/VCO2 slope: The minute Ventilation Carbon Dioxide production relationship

VO2 max: Maximum Oxygen uptake

VO2 peak: Peak Oxygen uptake

WRp: Work Readiness profile

1RM: 1 repetition maximum

6MWT: Six Minute Walking Test

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Abstract

Chronic heart failure (CHF) is a complex clinical syndrome which leads to a significant morbidity, institutionalisation and mortality, as well as to an enormous socio-economic burden. The causes of CHF vary, but the consequences seem to be detrimental for the patient's health, physical ability and quality of life (QoL). Reduced peripheral blood flow, increased oxidative stress and inflammatory factors, skeletal muscle atrophy and endothelial dysfunction are some of the pathophysiologic mechanisms leading to poor prognosis. CHF prevalence increases strongly with age as it mainly affects the elderly population with numbers reaching approximately 2% of the population. The numbers of affected people are expected to rise with the increased overall life expectancy. It is therefore expected that many of the CHF patients may be frail at the onset of the disease or become frail during its course. Frailty is a geriatric syndrome characterised by a vulnerability status associated with declining function of multiple physiological systems and loss of physiological reserves. Moreover, alterations to the body composition (i.e. skeletal muscle, fat and bone density), are frequent in CHF. Cachexia is recognized as a complex multi-factorial syndrome in chronic diseases that leads to weight loss and is a common consequence of CHF. Cachexia is defined as a non-edematous weight loss of more than 7,5% within over 6 months. Sarcopenia is also present in these patients and it means loss of muscle mass without necessarily weight loss because the functional muscle can be replaced by adipocytes. Different measuring instruments are used to define and assess sarcopenia, frailty and cardiac cachexia; nevertheless, there is no specific officially agreed method to detect them. The way to treat sarcopenia and cardiac cachexia and improve frailty status in patients with CHF is still a great challenge. Apart from drug therapy and nutritional supplementation, exercise-based cardiac rehabilitation (CR) could have been a way to improve aspects related to patient's subjective and objective parameters of health and life quality such as physical ability, capillary density, vascular function, self-efficacy, fatigue, and stress. The purpose of this review was to investigate the role of exercise-based CR in CHF patients, along with frailty, cachexia or sarcopenia, based on the related bibliography. It was hypothesised that, even if CR, and more specifically exercise training, does not reverse the process of cachexia, frailty, sarcopenia and CHF; it could at least constitute a drastic change in patient's lives. Relevant data and information, from approximately 90 published papers, were extracted and used as reference. Various types of exercise-based CR were studied as regards their effect on CHF patients such as: aerobics exercise, calisthenics, strength training, respiratory muscles training, neuromusclular stimulation (NMES), yoga, hydrotherapy, tai chi. These different exercise protocols offer a plethora of benefits and are shown to increase QoL. There is no clear answer regarding morbidity and mortality even if the results seem optimistic. Exercise-based CR when methodically applied may be a powerful way to drastically and optimistically change people's lives. However, CR programs for CHF patients so far are not orientated in sarcopenia, cardiac cachexia and frailty. More answers are needed regarding the type of exercise, the methods, and other parameters of exercise which play a leading role in the result exercise-based CR may have.

Key words: Heart failure, frailty, cachexia, sarcopenia, cardiac rehabilitation, exercise training

Περίληψη

Η χρόνια καρδιακή ανεπάρκεια (ΧΚΑ) είναι ένα πολύπλοκο κλινικό σύνδρομο το οποίο αυξάνει τη νοσηρότητα, και θνησιμότητα, και έχει τεράστιο κοινωνικό και οικονομικό κόστος. Οι αιτίες που προκαλούν ΧΚΑ ποικίλλουν, αλλά οι συνέπειες φαίνεται να είναι επιζήμιες για την υγεία, τη φυσική ικανότητα και την ποιότητα ζωής των ασθενών. Μειωμένη περιφερική ροή , αυξημένο οξειδωτικό στρες, φλεγμονώδεις παράγοντες, ατροφία των σκελετικών μυών και ενδοθηλιακή δυσλειτουργία είναι μερικοί από τους παθοφυσιολογικούς μηχανισμούς που οδηγούν σε κακή πρόγνωση. Ο επιπολασμός της ΧΚΑ αυξάνεται κατά πολύ με την ηλικία καθώς επηρεάζει κυρίως τον ηλικιωμένο πληθυσμό με αριθμούς που φθάνουν στο 2% περίπου του πληθυσμού. Ο αριθμός των ασθενών αναμένεται να αυξηθεί μελλοντικά καθώς αυξάνεται και το συνολικό προσδόκιμο ζωής. Ως εκ τούτου, αναμένεται ότι πολλοί από τους ασθενείς με ΧΚΑ να είναι αδύναμοι-άτονοι (“frail”) κατά την έναρξη της νόσου ή να καταστούν κατά τη διάρκεια της πορείας της. Η αδυναμία-ατονία (“frailty”) είναι ένα γηριατρικό σύνδρομο που χαρακτηρίζεται από μια κατάσταση ευπάθειας που σχετίζεται με την έκπτωση της λειτουργίας πολλών φυσιολογικών συστημάτων και την απώλεια φυσιολογικών αποθεμάτων. Επιπλέον, οι μεταβολές στη σύνθεση του σώματος (για παράδειγμα στον σκελετικό μυ, την οστική πυκνότητα και την πυκνότητα του λιπώδους ιστού) είναι συχνές σε ασθενείς με ΧΚΑ. Η καχεξία αναγνωρίζεται ως ένα σύνθετο σύνδρομο πολλαπλών παραγόντων σε χρόνιες παθήσεις που οδηγεί σε απώλεια βάρους και αποτελεί κοινή συνέπεια της ΧΚΑ. Η καχεξία ορίζεται ως απώλεια βάρους άνω του 7,5% εντός 6 μηνών σε ασθενή ο οποίος δεν παρουσιάζει οίδημα. Η σαρκοπενία είναι επίσης παρούσα σε αυτούς τους ασθενείς και υποδηλοί απώλεια μυϊκής μάζας χωρίς απαραίτητα απώλεια βάρους, επειδή το ποσοστό απώλειας μυϊκού ιστού μπορεί να αντικατασταθεί από λιπώδη ιστό. Διαφορετικοί τρόποι μέτρησης χρησιμοποιούνται για τον καθορισμό και την αξιολόγηση της σαρκοπενίας, της αδυναμίας-ατονίας και της καρδιακής καχεξίας. Ωστόσο, δεν υπάρχει ειδική επίσημη μέθοδος για την ανίχνευσή τους. Ο τρόπος αντιμετώπισης της σαρκοπενίας και της καρδιακής καχεξίας και η βελτίωση της κατάστασης αδυναμίας σε ασθενείς με ΧΚΑ εξακολουθεί να αποτελεί μεγάλη επιστημονική πρόκληση. Εκτός από τη φαρμακευτική θεραπεία και τα συμπληρώματα διατροφής, η καρδιακή αποκατάσταση (ΚΑ) με βάση την άσκηση θα μπορούσε να αποτελέσει ένα τρόπο βελτίωσης των υποκειμενικών και αντικειμενικών παραμέτρων της υγείας και της ποιότητας ζωής του ασθενούς, όπως η φυσική ικανότητα, η κόπωση, και το άγχος. Σκοπός της προκειμένης ανασκόπησης είναι να διερευνηθεί ο ρόλος της ΚΑ με βάση την άσκηση σε ασθενείς με ΧΚΑ, που ταυτόχρονα πάσχουν από αδυναμία-ατονία, καχεξία ή σαρκοπενία, βασιζόμενη στην σχετική βιβλιογραφία.

Δεδομένα και πληροφορίες, από περίπου 90 δημοσιευμένα άρθρα, χρησιμοποιήθηκαν ως βιβλιογραφική αναφορά. Μελετήθηκαν διάφοροι τύποι άσκησης για ΚΑ ως προς την επίδρασή τους σε ασθενείς με ΧΚΑ όπως: άσκηση με αεροβική γυμναστική, καλλισθενική άσκηση, προπόνηση δύναμης, προπόνηση αναπνευστικών μυών, νευρομυϊκή διέγερση, γιόγκα, υδροθεραπεία, “tai chi”. Αυτά τα διαφορετικά πρωτόκολλα άσκησης παρέχουν πληθώρα από οφέλη και δείχνουν ότι αυξάνουν την ποιότητα ζωής. Δεν υπάρχει σαφής απάντηση όσον αφορά τη νοσηρότητα και τη θνησιμότητα, ακόμη και αν τα αποτελέσματα φαίνονται ελπιδοφόρα. Η άσκηση με βάση την ΚΑ όταν εφαρμόζεται μεθοδικά μπορεί να είναι ένας ισχυρός τρόπος για να αλλάξουν δραστικά

και αισιόδοξα οι ζωές των ανθρώπων. Ωστόσο, τα προγράμματα ΚΑ για ασθενείς με ΧΚΑ μέχρι στιγμής δεν είναι προσανατολισμένα αποκλειστικά στην σαρκοπενία, την καρδιακή καχεξία και την αδυναμία-ατονία. Απαιτούνται περισσότερες απαντήσεις σχετικά με τον τύπο της άσκησης, τις μεθόδους και άλλες παραμέτρους που παίζουν κρίσιμο ρόλο στο αποτέλεσμα που μπορεί να έχει η ΚΑ με βάση την άσκηση έτσι ώστε να υπάρξουν ασφαλή συμπεράσματα.

Λέξεις-κλειδιά: Καρδιακή ανεπάρκεια, αδυναμία, καχεξία, σαρκοπενία, καρδιακή αποκατάσταση, άσκηση

Introduction

Besides the evolution of science and technology no one yet has achieved to reverse time and its consequences. The aging of the population is a worldwide phenomenon. It is predicted that by the year 2050 the number of the elderly (aged over 60) is going to reach 22% of the world's population. (http://www.silvereco.org/en/statistics/, 2019). Aging is usually accompanied by a number of diseases and co-morbidities which affect various aspects of people's lives. Sarcopenia, frailty and cachexia are common consequences of chronic debilitating diseases and are closely related. Sarcopenia is derived from Greek and it is generally defined as "lack of flesh". It was defined as an age related reduction of skeletal muscle mass and function, by Rosenberg in 1988 (Kim and Choi, 2013). Ever since, many other definitions have been formed, yet practically the term is not clearly defined. Sarcopenia does not necessarily mean loss of weight; another alternative to sarcopenia is "obesity sarcopenia" where there is lack of skeletal muscle over a simultaneous increase of fat percentage. (Kim and Choi, 2013; Morley et al., 2014) Sarcopenia, is accompanied by a number of other symptoms such as reduced mobility, lack of physical activity, strength and stamina. These are characteristics that are also evident in frailty. It is predicted that along with the aging of population, incidents of sarcopenia, as well as frailty, are going to rise. Simply put, sarcopenia can cause frailty. (Morley et al., 2014)

Therefore, sarcopenia and frailty are interlinked. Frailty is another condition that often occurs with aging, however it is not clear whether sarcopenia causes frailty or frailty is a hallmark of sarcopenia; resembling the problem with “the egg and the chicken”. (Cesari, Landi, Vellas, Bernabei & Marzetti, 2014) The term frailty generally refers to weakness. From the geriatric point of view it is a syndrome of homeostatic reserves depletion, which may lead to health status conditions and implications, such as lack of body balance, deteriorating or fluctuating disability, increased hospitalisations and mortality. (Cesary, et al., 2014; Clegg Young, Iliffe, Rikkert & Rockwood, 2013). There has been a plethora of definitions, likely to be sarcopenia; nevertheless it seems that there is a need to define frailty with a more operational and clinically relevant approach. (Cesary et al., 2014; Rockwood, 2005). Nevertheless, physical frailty’s phenotype has been clearly associated with fatigue, weakness, and exhaustion, as well as simultaneous reductions of body weight and, physical abilities such as strength, balance or gait (Rockwood, 2005; Fried et al., 2001).

Aging is often accompanied with not only sarcopenia and frailty, but cachexia as well; these terms are often related to each other. When sarcopenia causes weight loss it is indicative that cachexia may be developed. (Morley, von Haehling, Anker & Vellas, 2014) Cachexia, the origin of the word is Greek, with the prefix (“Cach” in Latin -“Κακ” in Greek) meaning bad (and the future tense of the verb “have” in Greek-“έχω”) of referring to being in a bad state, often related to malnutrition (etymoline. com; Lainscak, Filippatos, Gheorghiade, Fonarow & Anker, 2008). It is a complex multi-factorial metabolic syndrome related to malnutrition, weight loss, and muscle mass depletion while in some cases maintaining fat mass, protein apoptosis, inflammation and weakness (Evans et al., 2008). Often named as the “last illness”, as it is indicative that energy, strength, stamina, and self-efficacy are deteriorating along with any other combined health disease that coexists (Lok, 2015). It was initially described by Hippocrates, (Katz and Katz, 1962; King, Smith, Chapman, Stockdale & Lye, 1996), there is a gap between theory and practice as there is no accepted operational definition describing this condition; while, similar defining issues occur among these three terms: sarcopenia, frailty and cachexia.

The above three parameters commonly appear in chronic heart failure (CHF). Chronic heart failure, is a disease characterised by a specific clinical condition: inability of the heart to provide body tissues with adequate blood, causing fatigue, weakness, dyspnea, fluid retention or edema (in the legs, feet, abdomen), due to heart malfunction (Hopper and Easton, 2017), (https://www.mayoclinic.org/diseases-conditions/heart-failure/symptoms-causes/syc-20373142). Chronic heart failure is often accompanied by sarcopenia, frailty and/or cachexia. It is a growing international problem for public health and due, in no small part, to the rising number of the elderly in the general population, and because of this, it is predicted that the number of heart failure (HF) patients is going to increase. (Hunt et al., 2005; Thomas and Rich, 2007) The socioeconomic burden of the patients to themselves, and their family, as well as the healthcare costs, reflect the need to manage this problem. However, the American Heart Association reports that there has been an improvement not only in the management of heart diseases, but also in the survival of the patients, as a result of the evolution of science (Mozzaffarian et al., 2015). While, the European Society of Cardiology emphasises that HF may be prevented or delayed with specific interventions (Ponikowski et al., 2016), these improvements result in an increase of the population living and aging with this condition, thus increasing the end-stage consequences of the disease. Cardiac rehabilitation, from the spectrum of the physical exercise, may be the key to tackle some of the negative consequences. The purpose of this review is to investigate the role of cardiac rehabilitation (CR) in CHF patients with frailty, cachexia or sarcopenia, based on the related bibliography. It is hypothesised that, even if CR, and more specifically exercise-based CR, does not reverse the process of this syndrome; it could at least constitute a drastic hopeful change in patients' lives.

Methods

The "Pub-med" and the "Scopus" databases were used for this research. Relevant data and information, from approximately 100 published papers, were extracted and used as reference. A number of older state-of-the-art and recent articles including clinical trials, reviews, meta-analyses related to sarcopenia, cachexia, frailty and CHF as independent and/or combined terms, were searched as well as studies with exercise interventions. Studies conducted on animals were excluded. The research was restricted on outcomes from patients with reduced ejection fraction, as those with preserved ejection fraction are not investigated enough by the scientific community, and may have different adaptations and reactions to physical exercise.

An insight to sarcopenia and its relation to heart failure

It would be essential to analyse the variables of this review before focusing on the results. Sarcopenia is not a condition that appears suddenly. Muscle mass is reduced over the years with specific mechanisms. This is why it is often described as an age-related change (Morley et al., 2014). Nevertheless, even if this thesis focuses on the elderly, it must be noted that sarcopenia, in some cases, may occur in young people, too. Some of its mechanisms are associated with aging, others with nutrition, the endocrine system, neuro-degenerative diseases, or cachexia (Cruiz-Jentoft et al., 2010). Therefore, chronic inflammation, increased mitochondrial oxidation and cell apoptosis, reduced levels of anabolic hormones, lack of physical activity and nutrients, vitamins, minerals important for muscle metabolism (such as protein and vitamin D), are evident (Morley et al., 2014; Nascimento et al., 2018).

There are different stages and categories of sarcopenia that impact the patients to a differing degree (Cruiz-Jentoft et al., 2010). “Primary sarcopenia” is caused by merely one factor, aging; “secondary sarcopenia” is due to more than one of the above mentioned mechanisms (Cruiz-Jentoft et al., 2010). In some other cases, sarcopenia is more complex and multi-factorial which makes it more difficult to categorise. (Cruiz-Jentoft et al., 2010) Dividing sarcopenia into stages is a useful way to assess its progress, find relevant treatments, CR programs and describe it in a clinical or literature context. (Cruiz-Jentoft et al., 2010) According to the “European working group on sarcopenia on older people” (EWGSOP) there are three stages: “pre-sarcopenia” characterized by lack muscle tissue with no influence on strength or physical performance, “sarcopenia” where reduced strength or physical performance are evident along with low muscle mass, and “severe sarcopenia” the stage which includes all these three parameters (Cruiz-Jentoft et al., 2010).

Sarcopenia evaluating methods

Different measurement methods of muscle mass, strength, and function are used to detect sarcopenia. Body imaging methods, such as the “dual energy X-ray absorptiometry” (DEXA scan), the “computed tomography” (CT scan), the “magnetic resonance imaging” (MRI scan), and the bioimpedance analysis (BIA) which estimates the volume of fat and muscle tissue (Cruiz-Jentoft et al., 2010; Kim and Choi, 2013; Tsuchita et al., 2017; Collamati et al., 2016). Other methods, for estimation of skeletal muscle mass, are the “total or partial body potassium per fat-free soft tissue” (TBK or PBK) measurement and the simpler alternative of partial body potassium of the arm, the fat free mass index (FFMI), as well as some less reliable anthropometric methods such as the arm and calf circumferences (Cruiz-Jentoft et al., 2010; Tsuchita et al., 2017). Except of the body mass composition, strength and physical ability are parameters related to sarcopenia too. Muscle strength is measured with handgrip strength, knee extension/flexion and the strength of respiratory muscles with peak expiratory flow (PEF) (Cruiz-Jentoft et al., 2010). Physical performance is estimated with a variety of tests, such as: the “six minute walking test” (6MWT), the “short physical performance battery” (SPPB), the “usual gait speed test”, the “timed get-up-and-go test”, and the “stair climb power test” (Cruiz-Jentoft et al., 2010).

It must be mentioned that, in the cases where body weight is maintained, this does not necessarily constitute a negative indication (Coats, 2012). There has already been reference to obesity sarcopenia in the introduction of this review. This is a type of sarcopenia where the body weight is not reduced, but muscle mass is replaced by fat (Kim and Choi, 2013; Morley et al., 2014). The "obesity paradox" with CHF lays on the fact that often patients with body mass index (BMI) ≥ 27.8 kg/m2 seem to have better prognosis compared to those who were underweight (Horwitch et al., 2018; Davos et al., 2003). Therefore, losing weight is not a panacea for all cardiac illnesses. This circumstance underlies a need to see the disease from different points of view and apply combined treatments with hormonal therapy, nutrition and exercise as a form of CR. (Nascimento et al., 2018; Collamati et al., 2016).

Sarcopenia and its relation to CHF

It is estimated that, 2% of the elderly population in developed countries suffers from HF (Saitoh et al., 2016; Springer, Sprinker & Anker, 2017), (Collamati et al., 2016). Sarcopenia is highly prevalent amongst the CHF patients, given that 20% of the patients are diagnosed with muscle wasting (Saitoh et al., 2016; Springer et al., 2017; Tsuchita et al., 2017). Reduced anabolic activity, impaired protein synthesis, and inflammation are observed in CHF making obvious the fact that a possible sarcopenia, cachexia or frailty could co-exist with CHF (Saitoh et al., 2016; Springer et al., 2017). Medication, such as statins and b' blockers, may influence the neuromuscular system and physical ability (Springer et al., 2017).

Treatment and prevention of sarcopenia

Although, CHF treatment has been evolved, and patients' life expectancy is extended, compared to previous years, treatments to tackle sarcopenia with CHF are still few (Collamati et al., 2016; Springer et al., 2017). It is stated that, one of the challenges regarding sarcopenia is to figure out the importance of physical activity and the type of exercise which is ideal for such people (Cruz-Jentof et al., 2010). Sarcopenia is a progressive condition; therefore it may be prevented or treated with specific physical exercise interventions and combined CR programs conducted with specialised personnel (Rolland et al., 2008; Robinson, Denison, Cooper & Aihie Sayer, 2015). Physical exercise is referred to as "one of the most effective interventions" for sarcopenia according to scientists (Collamati et al., 2016, p.p.5/10). Researchers underline the significance of an active way of living, as well as the role of physical exercise as a part of CR for sarcopenic patients with or even without CHF (Rolland et al., 2008; Collamati et al. 2016). Resistance training is referred to as "the best approach to prevent and treat sarcopenia" (Rolland et al., 2008, p.p.8/49), both strength training and active lifestyle increase muscle mass, strength and function; nevertheless there is lack of clinical trials with CHF patients suffering from sarcopenia. (Rolland et al., 2008).

Understanding frailty

Sarcopenia is a major role of frailty (Robinson, Denison, Cooper & Aihie Sayer, 2015). Both share some mechanisms and are highly connected, besides the fact that they constitute different pathological conditions (Nascimento et al., 2018; Cederholm, 2015). Although the pathophysiology of frailty is not simple, a number of mechanisms, which again have to do with frailty, cause homeostatic reserves to decline, (Clegg, Young, Iliffe, Rikkert, & Rockwood, 2013); its phenotype has been specifically described (Fried et al., 2001; Morley et al., 2014). Frailty occurs in the immune system, the brain, the endocrine system, and the skeletal muscles. Free radicals, oxidative stress, mitochondrial dysfunction, apoptosis, increased inflammatory factors, fatigue, insulin resistance, lack of nutrients, reduced levels of anabolic hormones are present in frailty too (Nascimento et al., 2018; Vigorito et al., 2016). It appears that the free radicals are more systemic in frailty than in sarcopenia (Nascimento et al., 2018).

Frailty measurements

Fried's phenotype method divides patients into pre-frail, frail and non-frail according to five different criteria: weight loss, exhaustion, physical activity, walking time and grip strength. (Fried et al., 2001; Pritchard et al., 2017). Frailty is measured with a number of instruments. Some of them are: The "Groninger and the "Tilburg" frailty indicators, the "SHARE frailty instrument", the "deficit index", the "study of osteoporosis fracture index" (SOF), the "Gerontopole frailty screening", the "clinical frailty" and the "FRAIL" and the "Edmonton frailty" scales, the "FI-comprehensive Geriatric assessment" (FI-CGA)

(Vigorito et al., 2016; Mc Nallan et al., 2013). Body composition measurements (BMI) and questionnaires are also used for a rough estimation of cachexia (Mc Nallan et al., 2013). The assessment of frailty is a useful tool that should be applied in CR with specific scales so as to personalise treatment in each patients' needs (Vigorito et al., 2016).

CHF and frailty

The prevalence of frailty in CHF ranges between 15-74% (Vigorito et al., 2016). The presence of frailty in CHF is an indication of poor prognosis, hospitalisations and a negative impact on patient's lives (Vigorito et al., 2016). Not only bad quality of life (QoL), but also disability is a common issue for frail HF patients (Vigorito et al., 2016).

Frailty prevention and management

More specifically, besides the heavy burden in patients' health and QoL, frailty is a treatable, up to an extent; condition (Morley et al., 2014). The frailty "consensus statement" recommends exercise and nutrition amongst the treatment strategies (Morley et al., 2014). It is already known that exercise base CR has a beneficial impact on patients (Morley et al., 2014; Vigorito et al., 2016). Treatment of patients should cover both sarcopenia and frailty with combined methods (Cederholm, 2015). If there were more organised ways to recognise and treat frailty and sarcopenia with the implementation of "simple management strategies", there would have been a great improvement in patients efficacy, function and QoL (Morley et al., 2014), (Vigorito et al., 2016). The type of exercise which is more effective for the elderly frail HF patients is not specified yet (Okoshi et al., 2016); nevertheless it is proven that strength training could prevent frailty in patients who have frailty regardless of the accompanied chronic disease (Nascimento et al., 2018).

Looking into cachexia

Cachexia and sarcopenia in chronic heart failure

Sarcopenia may lead to cachexia (Morley et al., 2014). In advanced stages of CHF, it is not possible to clearly define whether muscle fiber reduction is due to sarcopenia or cachexia, the consequences overlap (Collamati et al., 2016). Cachexia is highly prevalent in chronic diseases, in late stages in particular; even if it cannot be estimated with precision, 16% to 42% of patients with HF suffer from cachexia (Tan. and Fearon, 2008; Cheriyedath, 2018; Lok, 2015; Okoshi et al., 2016; Anker et al., 2003). Cachexia is described as “a progressive depletion of body habitus associated with certain chronic diseases” (Tan and Fearon, 2008, p.p.1/7).

Cardiac cachexia

This research focuses on cardiac cachexia. “Cardiac cachexia” is more specifically defined as “*non-intentional and non-edematous weight loss > 7.5% of the pre-morbid normal weight occurring over a time period of > 6 months”* (Anker and Coats, 1999; Okoshi et al., 2016). This type of cachexia is a common phenomenon in CHF (Anker and Coats, 1999). Although, its description and first definition dates back to centuries, as it was initially coined by Hippocrates as a situation where “the flesh is consumed[…]the feet and legs swell, the shoulders clavicles and thighs melt away”, but its pathogenesis has not been investigated enough (King et al., 1996; Katz and Katz, 1962; Pittman and Cohen, 1964). The risk of cardiac cachexia development usually signifies a poor prognosis for CHF patients (Springer et al., 2017). The pathophysiology of cardiac cachexia which in the past seemed unapproachable has now been better understood through research constituting a great step toward finding a specified treatment (Anker et al., 1997; Griva, 2016). Nevertheless, the pathophysiology of cardiac cachexia is complex and still remains unclear as research on this field is still nascent (Shewan, 2017; Horwitch et al., 2018). Immune and neuroendocrine abnormalities are present. As a result, cachectic patients have diminished muscle fiber quality, quantity and function and are prone to weakness and exhaustion (Anker and Coats, 1999; Evans et al., 2010). It could be stated that changes in body composition, weight loss, muscle wasting, with or without fat mass reduction, is one of the major issues. Moreover, anabolic hormones are decreased in cachexia, as there is increased catabolism over anabolism, cytokines such as tumour necrosis factor-alpha (TNF-α) typically appear, as well as insulin resistance. (Griva, 2015; Evans, 2010). Additionally, malnutrition is highly correlated to cachexia and should not be underestimated (Coats, 2012).

Cardiac cachexia assessment

Cardiac cachexia plays a drastic role in CHF prognosis (Okoshi et al., 2016). There is no commonly agreed approach in diagnosing this syndrome (Ali and Garcia, 2014). Cachexia, can be assessed by indirect ways such as the body composition. There are no specific cachexia scales to precisely measure the condition (Coats, 2012). Nevertheless, there are some instruments to assess cachexia and its impact. Muscle fiber percentage can be evaluated by body imaging methods which are used in any case muscle, fat and bone mass need to be measured. For example, the "dual energy X-ray absorptiometry" (DEXA), "computed tomography" (CT) scan and magnetic resonance imaging, assessment of skeletal muscle mass (SMM), (Antoun et al., 2018). One simple strength measurement is the handgrip strength test (Okoshi et al., 2016; Ebner, Elsner, Springer & von Haehling, 2014). The "gait speed" is applicable to assess functional capacity in geriatric patients (Peel et al., 2013). The condition of the muscles, along with the neuro-musclular and muscular-skeletal system, are the most significant parameters of exercise capacity in patients with CHF (Ebner, Elsner, Springer & von Haehling, 2014). Exercise tolerance may be impaired not only due to reduced muscle percentage, strength and muscular quality, but also due to co-existing cardio-respiratory issues that burden the CHF patients. Physical capacity is measured by the broadly used methods which are applied in any case cardiac and respiratory parameters need to be evaluated: the 6MWT, cardiopulmonary exercise test, and other tests (Ebner, Elsner, Springer & von Haehling, 2014; Ebner & von Haehling, 2018). The implementation of useful precise and reliable diagnostic tools to assess sarcopenia, cachexia and frailty may contribute to the evaluation of patients' probability to face these syndromes as co-morbidity to already existing chronic diseases (Ebner, Elsner, Springer & von Haehling, 2014).

Cachexia prevention and treatment

For many decades, cachexia has been a subject of scientific interest and research; the detrimental consequences of cachexia and its relation with CHF are already proven. There are some "promising results" that specific medication may offer, such as the "ghrelin receptor agonists" (anamorelin), the "selective androgen receptor modulators" (enobosarm) and "beta-blockers" (espindolol) (Griva, 2005). However, there is yet no approved targeted treatment for CHF patients to tackle this multi-dimensional syndrome (Lainsack, 2008; Ali and Garcia, 2014), other than exercise training (Ali and Garcia, 2014; Ebner, Elsner, Springer & von Haehling, 2014; Lainsack, 2008). Besides the lack of randomized controlled clinical trials with a considerable sample (over 1000 patients), there is a steadily increasing trend of publications regarding the issue, signaling a hopeful future (Shewan, 2017). Different studies and experiments regarding the pathophysiology, diagnosis, treatment of cardiac cachexia, such as the study of molecular pathways associated with muscle degradation, are being conducted and it is expected that a drastic way of tackling cardiac cachexia will be found one day (Ebner, Elsner, Springer & von Haehling, 2014; Shewan, 2017).

Except for the option of drug therapy, exercise-based CR with a combination of nutrition and exercise programs with strength and aerobic training appear to be beneficial as they promote anabolism and positive muscle changes. (Ali and Garcia, 2014; Ebner & von Haehling, 2018). In the results section, exercise-based CR programs are discussed, which generally refer to CHF patients but not those who suffer from frailty, sarcopenia or cachexia.

Chronic heart failure

There has been a brief reference in the introduction of this review, some additional details are worthwhile mentioning. Chronic heart failure is defined as a syndrome which is characterised by inadequate cardiac output compared to the metabolic needs of the body influencing venous return (Hopper and Easton, 2017). Chronic heart failure is a consequence of a number of patho-physiological parameters which lead to impaired or lost myocardial cells of the heart. This heart injury produces a series of neuro-hormonal and physical changes which, initially, maybe beneficial, to tackle the issue, but in the long-term are detrimental for the whole body of every patient. That is to say, the sympathetic nervous system causes the heart rate to raise, as well as heart contractility to be increased, the rennin-angiotensin-aldostherone pathway activated, water retained, sodium reabsorbed and natriuretic peptides released, vasoconstriction to be present (Hopper and Easton, 2017). The clinical diagnosis of CHF is achieved with echocardiogram to determine the “underlying mechanism”/primary cause of CHF and to assess the ejection fraction (Hopper and Easton, 2017). The left ventricular ejection fraction in CHF can be either maintained or reduced; if it is a minimum of 50% it is classified as “preserved ejection fraction” and if it is lower than 40% it is categorised as “reduced ejection fraction” and the CHF is named accordingly.

There are different stages of CHF, which are classified as New York Heart Association, (NYHA), I-IV. In “appendix-table” II there is a table describing each stage. As stages proceed, gradually symptoms get more intense and exercise-based CR may produce different results. In CHF, there are cardiac, respiratory limitations and peripheral limitations. Moreover, skeletal muscles type alterations in mitochondrial context and switches from type I to type II muscle fibers are evident. (Suilivan, Green, Cobb, 1990) Sarcopenia, frailty and cardiac cachexia occur in the elderly CHF patients as a typical condition. Exercise-based CR may reverse or prevent the worsening of the negative consequences of CHF. In the results section the benefits of exercise-based CR are discussed.

Results

Benefits of exercise-based CR in CHF

Exercise was strictly not allowed to CHF patients in the past, nowadays not only is it recommended as a part of the treatment but also considered as a safe and necessary part of CR (Keteyian, 2011). The European Society of Cardiology recommends that exercise training could possibly benefit CHF patients with cachexia, sarcopenia and frailty; yet the exact role of exercise-based rehabilitation requires further investigation (Ponikowsi et al., 2016). Exercise-based CR has such positive effects that the American College of Cardiology as well as the American Heart Association has recognised exercise training in CHF patients "as a beneficial intervention" (Fletcher et al., 2012, pp. 2/8; Hunt et al., 2005), these benefits will be separately addressed in the different types of exercise sections.

CHF and exercise training

Patients with CHF are characterized by reduced exercise tolerance and dyspnea which can be considered as key features of this chronic disease. Furthermore, peakVO_2, anaerobic threshold, the mitochondrial volume and density, as well as oxidative enzymes are reduced and changes in the distribution of muscle fibers are present. (Adsett and Mullin, 2010). The elderly patients with CHF often suffer from reduced physical ability, muscle and heart deconditioning, heart remodeling, and possibly from frailty and/or sarcopenia and/or cachexia, all related to muscle depletion, increased inflammatory factors and other implications which were analysed above. As implied from the existing literature, frail, cachectic and/or sarcopenic patients with CHF could benefit from exercise-based CR. It is also stated that age-related sarcopenia may be a reason to reduced physical activity (Evans, 2010). Parameters such as intensity, duration, frequency and the type of exercise play a crucial role in the impact exercise-based CR may have to the patient. A closer view of these parameters may assist in concluding how CR should be oriented, giving possible answers to the topic and directions for future research. The decline in physical function and muscle wasting can precipitate the process of CHF (Amiya and Taya, 2018). Nevertheless, exercise-based CR in CHF plausibly has the ability to improve physical fitness, the muscular system, the vascular system, endothelium function, the autonomic balance, QoL, and morbidity; but on mortality the results are not clear (Amiya and Taya, 2018; Scottish intercollegiate guidelines network, Cardiac Rehabilitation; Meyer et al., 2013; van Tol et al., 2006). It is shown that exercise-based CR in CHF patients increases skeletal muscle metabolism, capillary density, nitric oxide balance, angiogenesis, and reduces oxidative stress, sympathetic action, arrhythmias and has no negative impact on left ventricular remodeling (Gasiorowski and Dutkiewicz, 2013); these facts could benefit the category of patients who suffer from CHF and frailty or sarcopenia or cachexia, yet there is not enough evidence to prove this.

It would be essential to clarify that patients before following a CR program need to be stable. Moreover, all basic exercise principles should be applied. The warm up, cool down, and gradual increase of the workload, are essential regardless of the type of exercise. The fact that exercise is applied to patients' population must not be underestimated; the absolute and relative contra-indications are listed in the "table" III.

The “Valsalva maneuver” should be avoided as it dramatically increases blood pressure and the after-load adding great stress in the heart. All patients participating in exercise-based CR programs should be taught how to properly breathe avoiding apnea, especially during resistance training (Piepoli et al., 2011). Monitoring the rate-pressure product (RPP)/ double product is important during exercise, because the increase in systolic pressure and heart rate can induce unfavourable symptoms to CHF.

Aerobic exercise

Endurance training is traditionally a part of exercise-based CR and is proven to be a simple, safe, effective, and nearly costless intervention that offers tremendous benefits to HF patients (Haykowsky et al., 2007; Ades et al., 2013). Most researchers agree that it significantly increases peakVO_2, which is a value that indicates exercise capacity and is an independent predictor of events (Haykowsky et al., 2007; Haykowsky et al., 2016; Belardinelli et al., 2012).

Bernadrinelli et al. (2012) published a randomized control trial with 123 patients which lasted ten years and showed significantly improved VE/VCO_2 slope, QoL and reduced mortality and morbidity (Bernadrinelli et al., 2012). It is worthwhile mentioning that, Haykowsky et al. in their review, clearly state the influence of aerobic training with or without the combined strength training improved not only peakVO_2 and QoL, but also muscle strength and HF-related hospitalisations (Haykowsky et al., 2013). Indirectly, it could be assumed that, even if there is no reference to sarcopenic, cachectic or frail CHF patients, these benefits, and muscle mass increase in particular, will positively influence the category of patients this thesis focuses on.

Additionally, patients who conducted aerobic exercise had improved autonomic balance and endothelial function, parameters that are inhibited in CHF patients (Adsett and Mullins, 2010). More specifically, through the endothelial improvement there is a better autonomic balance and therefore vasoconstriction is replaced by vasodilation; thus, total peripheral vascular resistance (TPR) is reduced and peripheral perfusion is enhanced with aerobic exercise interventions (Adsett and Mullins, 2010). Improvement in central hemodynamics such as the cardiac output is also presented by some researches (Adsett and Mullins, 2010). In the meta-analysis of Haykowsky et al., it is underlined that aerobic exercise can reverse left ventricular remodeling (Haykowsky et al., 2007).

Moreover, endurance training is not only beneficial for the homeostasis of the body, but for the muscular system too. Aerobic training promotes anabolism and reduces inflammatory factors according to some scientists. (Giellen et al., 2003; Adsett and Mullins, 2010; Hollrieget et al., 2013). This fact is highly related to patients who may suffer from frailty, cachexia, or sarcopenia as well, given that catabolism and increased inflammatory factors are evident. What is more, CHF patients conducting aerobic exercise can benefit from changes the left ventricular remodeling (Haykowsky et al., 2007). Another advantage of this type of exercise is that it could possibly produce beneficial changes to the muscular system of the patients. In a small research, significant reverses of muscle fiber distribution and re-shift from to type II to the fatigue resistant type I muscle fibers, a significant increase in the mitochondrial surface, but not in the number of mitochondria, are highlighted; suggesting that endurance training may produce positive adaptations in the muscle structure (Hambrect et al., 1997). In some other clinical trials with a small number of participants, anabolic hormones such as the growth hormone (GH) are increased but with no statistical importance (Hambercht et al., 2005). The insulin like growth factor -1 (IGF-I) which is declined in cachectic patients is also improved with no statistical importance (Hambrecht et al., 2005). Additionally, the Rnf28 protein of skeletal muscles was significantly reduced leading to a muscle fiber cross sectional area increase (Hollriegel et al., 2013). Another trial conducted by Lenk et al., again with a small number of patients and endurance training intervention, highlighted a significant drop in the values of myostatin, which regulates and determines muscle mass growth and is raised in patients with CHF (Lenk et al., 2012). These adaptations can have a drastic impact on patients' health and functional status, as well as on their QoL, morbidity and mortality, these three parameters will be examined in separated paragraphs. Moreover, improvements in the B-type natriuretic peptide (BNP) levels are evident; BNP offers information about the clinical stability in HF and could be used to indicate the patients' condition and readiness to start exercise-based CR (Amiya and Taya, 2018).

On the other side of the coin, O'Connor et al., in a considerably large trial with 2331 participants did not demonstrate the advantageous impact of moderate to vigorous intensity continuous aerobic exercise on mortality, but this may be due to the limitations of the trial as well as the reduced adherence of the patients who participated, which can influence and predict the outcome in CHF (O'Connor et al., 2009; Ismail et al., 2013; Piepoli et al., 2011). However, Ismail et al. (2013) proved that high intensity aerobic exercise has no relation to mortality and reduced adherence (Ismail et al., 2013).

Prescription of aerobic exercise

Most aerobic training protocols for CHF patients mainly include cycling, and walking; the duration ranges between 15' to an hour, for 3-6 days a week, the intensity is usually 50-80% of HR reserve (Adsett and Mullins, 2010). High intensity interval aerobic training is another option that will be mentioned below. The warm up and cool down are very important and is usually around the 30% of peakVO_2. Other forms of aerobic training such as dancing, mountain skiing, and rowing are not sufficiently investigated. There is no single, specific aerobic intervention targeting the type of patients this research focuses.

Interval training

High intensity interval training is a safe alternative to the ordinary continuous aerobic training (Wewege et al., 2017). Interval aerobic training incorporates some repeated and alternating bouts of high intensity with intervals of no exercise or of low intensity; what makes it different from the continuous aerobic training is the design of the program and the volume of exercise intervention. Exercise protocols vary as regards the structure, duration, intensity, and intervals which can be active in lower intensity, or total rest, the repetition and the time of the intervals. That is to say, there are programs of 70-75% and 90-95%, followed by 50-70% of peak heart rate (HR) four minutes each, repeated four times (Wisloff et al., 2007); and other with one minute exercise of 70% peakVO_2 and one minute rest (Smart and Steel, 2012), usually 3-5 times per week. The recovery time in between the exercise should be adequate and the ratio between work and recovery can vary from 1:1, for example 30s exercise 30s rest, to 1:3 or even longer time of active or passive recovery (Smart and Steel, 2012) It is also proposed that, protocols can range between low (50% of the power output based on the “ramp” or the “incremental bicycle” test) and high-intensity (90-95% of exercise peak capacity) interval training depending on each patients needs (Piepoli et al., 2011).

The benefits of interval training seem to be superior to those of continuous training. A remarkable advantage is that patients who are unable to complete a continuous aerobic exercise program have many chances to successfully follow an interval aerobic training program. The cachectic, sarcopenic, frail CHF patients could possibly be benefited more as they may face difficulty in completing a continuous aerobic program, yet there is no evidence to support this idea. The fluctuation of the intensity from high to low amongst the bouts potentially gives patients’ the chance to recover from their effort and reach higher levels of intensity after the recovery; therefore better adaptations are induced. The first clinical trial regarding CHF patients and high intensity interval training was conducted by Meyer et al. (1996) showing significant improvements in peakVO_2 and the results of the 6 minute walking test, ever since many other scientific articles have been published (Meyer et al., 1996). Aerobic interval training seems to improve functional capacity more effectively compared to continuous training (Amiya and Taya, 2018). A trial with a relatively small number of participants (10) underlined that interval training improves not only aerobic capacity and exercise tolerance, but also muscle fiber distribution in the body and fiber type allocation, suggesting that interval training could have anabolic effects (Tzanis et al., 2014). The outcome of this trial showed promising results as peakVO_2, anaerobic threshold (AT), work readiness profile (WRp), as well as the cross sectional area of type I and II skeletal muscle fibers significantly increased after the trial (Tzanis et al., 2014). VE/VCO_2 slope decreased and there was a rising trend on the allocating of fatigue resistant type I muscle fibers (Tzanis et al., 2014). Another clinical trial with combined interval training and strength in which a considerable number of patients (72 out of 100) participated, showed more drastic changes in left ventricular diastolic function and peakVO_2 (Chyroshoou et al., 2013). In another trial, with a smaller number of participants, it was similarly shown that interval training when combined with strength training can be more effective as regards the vascular reactivity (Anagnostaku et al., 2011).

The meta-analysis, of Haykowesky et al. (2013), concludes on a significantly higher peakVO_2 in interval training. The findings of Smart et al. (2011) meta-analysis agree with that of Haykowsky et al. (2013) with the only difference that it refers to a combined intermittent aerobic exercise with strength training, (Haykowsky et al., 2013; Smart et al., 2013). Ismail et al. (2013) state that high-intensity interval exercise training if compared to other exercise intensities seems superior as it produces significant improvements in peakVO_2 and systolic heart function (Ismail et al., 2013). Cornelis et al. (2016), additionally claim that evidence supports the superiority of interval training over the left ventricular ejection fraction (LVEF) and left ventricular end diastolic diameter (LVEDD) improvement (Cornelis et al., 2016). Furthermore, Piepoli et al. refer to the fact that interval training has been suggested as an effective method which can better increase exercise ability compared to the continuous aerobic CR programs (Piepoli et al., 2011).

On the contrary, there are some trials which suggest that interval training is not more advantageous than continuous as regards the left ventricular remodeling, aerobic capacity and feasibility, a fact that leads to the conclusion that further investigation is needed for more precise results (Ellingen et al., 2017). Meyer et al. in their review agree that high intensity training is superior to the improvements in peakVO_2, however underline that the variety of interval training protocols as well as the patients' condition and the lack of adequate trials with careful methodological design (such as the double-blinded trials) may influence the results (Meyer et al., 2013). More clinical trials should be conducted with CHF patients who simultaneously suffer from cachexia, sarcopenia, and/or frailty to ensure the effectiveness and safety of such programs.

There is a debate on the effects of other types of training combined or alone, similar advantages (peakVO_2 improvement and ventricular remodeling) are not proven strength training alone or combined aerobic and strength training programs according to Haykowsky et al meta-analysis (Haykowsky et al., 2007). However, the review of Cornellis et al 2016 demonstrate that combined strength training with endurance improved exercise tolerance (of submaximal exercise level) reinforcing functional ability and QoL (Cornellis et al., 2016).

Calisthenics

Another common form of exercise-based CR which is often chosen for CHF patients is the calisthenics. The calisthenics is more or less considered as a type of aerobic training (Adsett and Mullins, 2010). Some scientists present calisthenics as a form of exercise which can be adopted during the mobilisation phase. Cachectic or sarcopenic and/or frail CHF patients should start the exercise-based CR in even more gradual and moderate way than the other CHF patients. This "gentle individualized gradual mobilisation" is often called calisthenics and is proposed as a preferable form of exercise-based CR for such patients to start with (Piepoli et al., 2011, p.p. 2/11). Specific recommendations regarding the number and choice of exercises and the programs are scarce, nevertheless precautions, such as arm movements up to the body level and execution in sitting position, can be taken to avoid any increase in the pre-load or after-load which may be hazardous for heart patients (Working group report, 2001). Every program should be individualised to the clinical condition and needs of every patient. In more innovative programs water calisthenics are investigated, yet there is lack of adequate information and in particular regarding the type of patients which this review is oriented towards.

Strength training

Muscle strength is a predictor of long term survival (Hulsmann et al., 2003; Braith and Beck, 2008). Taking into consideration that usually in CHF muscle mass and function are depleted, strength/resistance training can reasonably be incorporated into an exercise-based CR program. It is stated that muscular strength and mass determine the exercise capacity of CHF patients (Ebner, Elsner, Springer & von Haehling, 2014). Obviously, lean mass is highly related to sarcopenia and cachexia, or even frailty. It is stated that, decreased physical functional performance, which is quite prevalent amongst the elderly, could be associated to sarcopenia (Evans, 2018). "Resistance/strength training (RST) is a muscle contraction performed against a specific opposing force thereby generating resistance, such as lifting weights." (Piepoli et al., 2011)

There is a gradual development of resistance fitness programs in CR and treatment of CHF. Guidelines and position statements have been published shedding light on resistance training for CHF patients (Fletcher et al., 2014). Strength training can be beneficial, yet, there are no specified programs to be prescribed for frailty, sarcopenia, cachexia. It is admitted that, in the treatment and CR of CHF patients the implementation of exercise programs is developing (Fletcher et al., 2014). In the years between 2004-2014 official guidelines by the American College of Sports Medicine, the American Heart Association, the European Society of Cardiology, the Exercise and Sports Science Australia, and other institutions, with specific position statements referring to the implementation of resistance training exercise prescription have been published, and resistance training exercises are recognised as part of CHF exercise-based CR (Fletcher et al., 2014).

Nowadays, resistance training, besides some dissenting voices, is considered as a safe and effective intervention (Williams et al., 2007; Volakis and Tokmakidis, 2005; Meyer et al., 2013). Nevertheless, the execution of strength training with caution is of paramount importance. The majority of scientists emphasise the benefit of resistance training on muscle strength. Seo et al. (2014) in a trial with 102 participants analyse the difficulty CHF patients face maintaining muscle strength and its influence on the management of the symptoms; and underline that reduced muscle strength of quadriceps has high correlation to dyspnea and exercise intolerance (Seo et al., 2014). The correlation of low knee extensor muscle mass and fatigue was not statistically significant; nevertheless this clinical trial consisted of mainly NYHA IV patients, fact which could have influenced the outcome of its results. Another study assessed the isokinetic strength testing of the knee extensor and flexor muscles of (initially 122 patients) and respiratory gas exchange through bicycle ergo-meter as regards their relevance to death and event-free survival. It was figured out that the isokinetic strength of the knee flexors has a correlation with exercise performance mortality and morbidity (Hulsmann et al., 2004). Scientific evidence suggests that specified strength training programs are not only safe, but also effective in inducing “significant histochemical, metabolic and functional adaptations” in skeletal muscles (Volakis and Tokmakides, 2005). After resistance training, alone or combined with aerobic exercise changes in muscle composition, alterations of muscle metabolism, muscular mass increase, muscular endurance and strength have been reported (Volakis and Tokmakidis, 2005). Moreover, exercise tolerance and peakVO_2 seem to be increased in most studies (Volakis and Tokmakidis, 2005).

Downing and Balady in their state-of-the-art paper on the role of exercise training in CHF, refer to ten different resistance training studies the majority of them concluding on improvement on muscle strength, and, in a few cases, exercise capacity (Downing and Balady, 2011). Guiliano et al. (2017), demonstrate in their review the significance of resistance training in muscle strength, exercise capacity and QoL (Guiliano et al., 2017). Moreover, in this meta-analysis it is clarified that even one “single intervention” can improve muscle strength, aerobic capacity and QoL in patients with CHF; in this way strength training could be an “alternative approach”, especially for the patients who are not able to take part in aerobic training (Guiliano et al., 2017). Gasiorowski and Dutkiewiecz review that strength training increases strength and muscular endurance, peakVO_2, anaerobic threshold, and reduces dyspnea symptoms, and induces advantageous adaptations to the body of CHF patients such as lower blood pressure, wellbeing and function (Gasiorowski and Durkiewiecz, 2013).

Moreover, Meyer et al. (2013) in their review admit the beneficial impact of resistance training on the preservation of muscular strength, the percentage of muscle fiber, as well as insulin resistance and inflammation (Meyer et al., 2013). If the aim is to produce muscle adaptations into periphery, resistance training may be preferred (Braith and Beck, 2008). Braith and Beck demonstrated the muscle adaptations that occur with resistance training can improve the muscle phenotype. These facts suggest that resistance training could play a major role in the treatment of muscle weakness and specific myopathy which is common in CHF. Piepoli et al. (2011), underline in their position statement that resistance training except for toning and strengthening of skeletal muscles increases bone density and has been recommended as “an anabolic intervention”, suitable for the elderly CHF patients, which assists the wasting syndrome (Piepoli et al., 2011). It is assumed that sarcopenic, cachectic, or even frail CHF patients could benefit from resistance training as part of exercise-based CR and further trials should be conducted regarding the specific category of CHF patients (Volakis and Tokmakidis, 2005).

However, some researchers express their doubts regarding the strength training CR of CHF patients, which could be due to limited existence of information (Meyer et al., 2013; Braith and Beck, 2008). For example, there is a disagreement on the negative consequences strength training may have on left ventricular remodeling and left ventricular function, due to the increased after-load (Piepoli et al., 2011). The diversity of resistance training methods, modes and intensities may have lead to ambiguity as regards the answer of this question. In the meantime, Piepoli et al., refer to the controversy which exists regarding some negative consequences on left ventricular remodeling of the eccentric phase of resistance training, and the probable superiority of endurance training at some cardiovascular benefits; concluding that endurance training is still “the mainstay” (Piepoli et al., 2011). They additionally suggest that resistance training should complement and not substitute aerobic training (Piepoli et al., 2011). This suggestion seems quite reasonable as different types of exercise produce different adaptations in the body. Fletcher et al. (2014), referred to some concerns of strength training regarding the substantial pressure loads as well as the left ventricular structure and function and revealed some parameters that influence these factors (Fletcher et al., 2014). Braith and Beck (2008) explain that resistance training should be conducted in low intensities as it is considered the safest option. Body weight, ECG and blood pressure should be frequently monitored, especially four to six weeks after initiation to ensure the safety and efficacy of the CR program (Braith and Beck, 2008). They also explain that due to lack of enough evidence resistant training should be avoided in NYHA IV patients.

Prescription of resistance training and exercise modes

There is a vast variety of protocols resistance training can be applied:

Isotonic/dynamic exercises which involve concentric and eccentric contraction could be considered as the most common form of strength training. These exercises can be conducted with the body weight or with the assistance of strengthening equipment which are plentiful, such as free weights, weight machines, and elastic bands. This type of strength training could successfully be adopted by CHF patients who are sarcopenic, cachectic or frail due to the positive muscular alterations that it offers; hopefully in the future specific trails will be conducted regarding the issue.

Isometric exercises are not recommended for patients with CHF; such exercises are not functional reflecting daily activities, do not work the neuromuscular system from all angles and mainly can be risky for CHF patients. It is known that isometric exercises cause excessive hemodynamic changes, increasing both systolic and left ventricular end-diastolic pressure, mean arterial pressure, as well as the after-load, and decreasing cardiac output, stroke volume and ejection fraction (EF), causing wall motion abnormalities, mitral regurgitation and arrhythmias (Volakis and Tokmakidis, 2005).

On the other hand, few researches included isometric exercise protocols of low intensity 30-50% and small muscle groups, for 3-5 minutes each exercise (Volakis and Tokmakidis, 2005). It would be interesting to figure out whether such low intensities are safe and beneficial for sarcopenic, cachectic or frail CHF patients. Besides the increased after-load which could possibly be better managed with controlled breathing, isometric exercises could offer a solution to CHF patients who have balance issues due to frailty.

Isokinetic exercises can only be conducted with the assistance of specific equipment. It is known to have some benefits, such as the homogenous development of the muscles, nevertheless, more evidence is needed to justify their role on CHF rehabilitation (Volakis and Tokmakidis, 2005). The question remains as regards the effectiveness of isokinetic exercise training and sarcopenia, frailty or cachexia, this type of physical training could potentially benefit from such training as it possibly could offer an alternative to patients with movement limitations who are prone to injury.

Fletcher et al. (2014), explain that besides the primal part of aerobic exercise in CHF there is growing acceptance of dynamic ST that should be included in CR of CHF, as complementary exercise, according to CHF guidelines; and refer to some precautions that should be taken when ST is executed by CHF patients in general:

1. Patients should be clinically stable and have proven aerobic exercise tolerance before starting resistance training (RT)
2. The intensity of RT should be based on each individual needs
3. The training should slowly and moderately start and gradually progress
4. Blood pressure, perceived exertion, and body weight should be monitored through ECG
5. Be aware of possible symptoms that may indicate a change of severity of CHF (Fletcher et al., 2014)

Resistant training is usually contraindicated for CHF patients in NYHA Class IV Except of the types of strength training (ST); the overall workload of ST seems to be related to the exercise adaptations. For optimal results, strength training should be designed to have specific exercises, repetitions, sets, time of performance, time of rest, intensity, total duration of each session, frequency of sessions during the week, according to the individual needs of every patient. The magnitude of cardiovascular stress has to do with the percentage of resistance of one repetition maximum (1-RM), the duration of the contraction, the size of the working muscle mass, and the duration of time of rest between the sets (Piepoli et al., 2011). Although, there is a wide range of protocols, there are no specific guidelines for the type of patients who are investigated in this research. Fletcher et al., as mentioned above, reveal some specific factors that influence some risk parameters of CHF patients, these are:

- The “magnitude of workload of 1RM”
- The “number of repetitions relative to a multiple repetition maximum” the closer to fatigue the repetitions lead, the greater the pressure load to the heart will be

- The “volume of contracting muscle mass”, muscles that contract simultaneously produce higher pressure than one muscle alone, bilateral limb exercises increase the pressure load more than the unilateral ones
- “The duration of muscle contraction” regarding the time of rest between sets and repetitions, the shorter the resting period the greater the pressure loads which are accumulated (Fletcher et al., 2014)

Lately, low or moderate resistance exercise protocols, which minimize the heart pressure load and are well tolerated, have been proposed for CHF patients (Fletcher et al., 2014). Piepoli et al. (2011), state that strength training can be introduced, after the establishment of aerobic exercise tolerance. Strength training for CHF patients is divided into three different phases: the “instruction phase” to mainly establish neuromuscular co-ordination with low intensities below 30% RM, the “endurance phase” 15-25 repetitions and low intensity 30-40%, the “strength phase” 8-15 repetitions 40-60% 1-RM for muscular strength (Piepoli et al., 2011). These phases highlight the importance of the progressive increase of the workload. The “Borg scale” is a useful tool to assess the exercise workload and fatigue which should range between: 10 to 13, of the “6-20 Borg scale” (see table IV). Additionally, a rate pressure product (RPP) which causes symptoms should be avoided (Piepoli et al., 2011). Fletcher et al. (2014) refer to three periods of training and how long they should last: “the instruction period” one to two weeks, the “resistance/muscle endurance period” two to four weeks, and the “strength period” starting after the other two. Training should be conducted two to three times a week, lasting for around 10 minutes in total according to the tolerance of the patients (Fletcher et al., 2014). The exercises as part of CR for CHF patients, in most of the researches, target at the upper or lower body, or both (Fletcher et al., 2014). There can also be differences among protocols that aim at muscle endurance to those at muscle strength. Protocols range depending on the desired outcome, if the focus is on muscular endurance the weight is low and the repetitions are 12 to 15, if, however, it is on muscular strength, the weight is heavier and the repetitions are less with an adequate resting period. Fletcher et al. propose 6 to 15 repetitions of unilateral dynamic exercises without strain at the beginning of training sessions, once to twice a week; followed by between 11-15 repetitions once exercise tolerance is established (Fletcher et al., 2014). Large and small muscle groups, up to 10 repetitions, of maximum 70% intensity Volakis and Tokmakidis recommend. (Volakis and Tokmakides, 2005) While, smaller muscle groups are preferred by Maeyer et al. (Maeyer et al., 2013). It is suggested that resistance training can be performed with safety when firstly small muscle groups are worked (Piepoli et al., 2011). Fletcher et al. (2014) emphasise that rest between sets is recommended for CHF patients. Short sessions with an adjusted number of repetitions (Piepoli et al., 2011); time should have a minimum 1:2 ratio between work and resting period (Piepoli et al., 2011; Fletcher et al., 2014).

Braith and Beck propose resistance training programs for NYHA I-III HF patients, with bilateral and/or bilateral exercises of 40-60% 1-RM intensity, with contraction speed 6 seconds, (3 seconds each concentric or eccentric phase), with 1:2 work/recovery ration (60 seconds/60 second or more) 2-3 times a week, for 12-30 minutes in total and 4-9 sets of 6-10 repetitions according to the goal and depending on the NYHA stage (Braith and Beck, 2008). For NYHA IV intensity and exercise duration is reduced; highlighting the importance of adjusting the program in each patient's individual needs (Braith and Beck, 2008). Some scientists propose that strength training in NYHA IV should be avoided.

As regards the pace of execution, literature reveals that muscle strength only increases during slow, and not fast explosive execution, "of 60 and 180°/s^{-1}", of resistance exercises, this fact may change the perspective of strength training in the future, as it was believed that the elderly who were unable to move their muscles rapidly had high risk of falls (Guiliano et al., 2017). This may have a scientific value for patients with frailty, sarcopenia and cachexia who are lacking muscle mass, face difficulty in walking and maintaining their balance.

The Gasiorowski and Dutkiewicz review, included aerobic and strength training programs to underline the safety and efficacy of such programs which could possibly be superior than aerobic training alone in reversing muscular weakness, increasing exercise performance and improving the function of the periphery (Gasiorowski and Dutkiewicz, 2013). There is growing evidence that exercise tolerance and improvement of muscle structure and function are achieved with the combination of aerobic and dynamic strength training (Volakis and Tokmakidis, 2005). The "Cohrane" review of Taylor et al. (2014) refer to researches which include mixed aerobic and strength training protocols with different outcomes on mortality, morbidity, cost effectiveness and QoL. It seems well justified that patients can differently benefit from several types of exercise and the combination may offer more advantages that a single intervention alone. There should additionally be clarified whether aerobic and strength training should be applied at the same day or in different days and which one should be conducted first.

Respiratory muscles training

The respiratory muscles, too, must not be disregarded. So far, scientific evidence strongly suggests that dyspnea, poor exercise tolerance and poor functional status in patients with CHF is associated with poor inspiratory muscle performance (Cahalin et al., 2013). These patients suffer from muscle weakness, inhibition, phenotype changes, inflammation, decreased mitochondrial oxidative function equally as the other skeletal muscles. For those patients, according to some scientists, respiratory training could be added into the usual exercise-based CR program and improve respiratory muscle strength and endurance, dyspnea, functional capacity and QoL, even peakVO_2 (Fu et al., 2014; Laoutaris et al., 2004; Smart et al., 2013; Maeyer, Beckers, Vrints, Conraads, 2013) Smart et al. (2013), though explain how respiratory muscle training could be used as a plausible alternative for the HF patients who are more severely de-conditioned (Smart et al., 2013). Such patients may start with respiratory muscle training until being prepared for the conventional training (Smart et al., 2013). For this purpose, a variety of protocols and devices can be used in a clinical or even home-based setting (Piepoli et al., 2011). Three to five sessions per week 20-30 minutes of training per day is recommended (Piepoli et al., 2011). The intensity of maximal inspiratory mouth pressure (PImax) is suggested to increase from 30% to gradually 60% (Piepoli et al., 2011). On the other hand, Johnson et al. (1998) it was proved that respiratory training did not bring significant increase in respiratory muscle strength; it must be noted though that the number of patients was limited and the training intensity was relatively low (30% PImax) (Johnson et al., 1998). Further research with larger populations is required to define the exact role of inspiratory muscle training in CHF rehabilitation (Cahalin et al., 2013). There is no evidence regarding the effect of inspiratory muscle training when frailty, sarcopenia and cachexia coexist with CHF.

Alternatives to the conventional exercise training for CR

Besides the importance of aerobic training and resistance training, other types of training such neuromuscular electrical stimulation are known to increase muscle mass, a fact which is of great interest especially when CHF is accompanied with frailty, sarcopenia, cachexia.

Neuromuscular electrical stimulation

Neuromuscular electrical stimulation (NMS) is another CR method for patients with CHF (Dobsak et al., 2012; Dobsak et al., 2006; Bouchla, Karatzanos, Gerovasili, Zerva, Nanas, 2019). Muscles are stimulated artificially with the presence of electrodes and electrical currents (Bouchla et al., 2019). It is considered as a safe and effective exercise option for the patients who are critically ill and usually unable to perform any other form of exercise (Dobsak et al., 2006). Despite the wide prevalence of NMES in CHF, there is a limited number of studies as regards the issue. Parameters such as the endurance, duration and intensity have not been investigated enough to conclude on the most effective program. Usually, a NMES program lasts 30-60 min and intensity could be 30-50 Hz in a pace 20s stimulation and 20s rest, from three to seven days a week (Dobsak et al., 2006; Dobsak et al., 2012; Bouchla et al., 2019). Low frequency electrical stimulation (LFES) is considered to be around 60 mA or 25 Hz, and is often preferred to high frequency electrical stimulation (HFES) as it possibly better matches the criteria of CHF patients (Dobsak et al., 2006). The benefits of NMES are shown in the Ploesteanu et al. review: improvement in muscle mass, endurance, functional capacity, vascular and endothelial function, aerobic enzyme activity and QoL (Ploesteanu et al., 2018). Inflammatory factors seem to be reduced in some trials, in some other results prove that the conventional CHF rehabilitation training is prior to this alternative (Bouchla et al., 2019). Similar are the results of a pilot study conducted by Parissis et al. as it showed that except for the improvement of psychological parameters such as the emotional stress, there were improvements in QoL and the endothelial function after a 6-week program with CHF patients (Parissis et al., 2015). Optimistic are the findings of Kadoglou et al. who experimented on NMS in a study with 120 elderly CHF participants. The 6-week protocol showed a plunge in hospitalisation which is related to HF, but there was no effect in mortality (Kadoglou et al., 2017). NMES seems of great interest especially when it comes to the type of patients this thesis focuses on. More intensive research is required with large numbers of participants and better methodological structure to figure out more about NMES programs and their benefits, according to the related studies (Bouchla et al., 2019; Parissis et al., 2015; Kadoglou et al., 2017). The role of NMES in CHF accompanied by cachexia, frailty or sarcopenia is not identified yet. Future research should be conducted, on whether CHF patients could benefit from taking part in NMES sessions so as to improve muscular mass, function, reduce inflammatory factors, especially when patients are also cachectic, frail or sarcopenic and the chances of conventional exercise-based CR are sometimes limited.

Other alternatives (i.e. Hydrotherapy, Yoga)

Hydrotherapy

There are other types of exercise that could be applied for CHF patients such as hydrotherapy and swimming. During water immersion physiological adaptations and hemodynamics differ to the types of exercise outside water. More research should be conducted with large and homogenous sample to prove whether aqua therapy and exercise is a safe and effective option. (Meyer and Bucking, 2004)

Schmid et al. (2007) who compared 10 healthy controls with CHF patients with 10 intensely reduced EF and peakVO_2 less than 15 ml/kg/min participants figured out that swimming in thermo-neutral temperature and water immersion was tolerated by both groups (Schmid et al., 2007). Meyer and Leblanc (2008) suggest aquatic therapies as a form of exercise-based CR, swimming at a slow pace (20-25m/min), warm water immersion up to a certain level are proposals for experimentation and research (Meyer and Leblanc, 2008). Adsett and Mullins refer to swimming for CHF patients and explain how water immersion changes hemodynamic parameters, such as the stroke volume and pulmonary arterial pressure, suggesting that a specific position there must be found that does not excessively raise pulmonary arterial pressure (Adsett and Mullins, 2010). If water immersion is up to the level of the diaphragm, for example, central venous pressure is around 10-15mmHg (Adsett and Mullins, 2010). Sarcopenia, frailty and cachexia are not taken into consideration in these studies which propose alternative forms of exercise-based rehabilitation. It would be interesting to assess the benefits of hydrotherapy and swimming in sarcopenic, cachectic, or frail CHF patients, as water immersion offers many advantages such as reduced possibility of injury especially for the frail patients who have a lack of balance and more drastic improvements in the neuro-muscular and cardio-respiratory system.

Tai chi

The Chinese martial arts' sport "tai chi" is also proposed as a method to resolve balance issues while enjoying the physiological benefits of this moderate form of exercise (Adsett and Mullins, 2010). Except of the cardio-respiratory, self efficacy and QoL improvements, Tai Chi seems to increase muscle strength which possibly seems promising for cachectic, sarcopenic or frail CHF patients (Adsett and Mullins, 2010).

Yoga

Yoga through exercise postures (asanas) may be another way to treat CHF patients. The main advantages of yoga to general population are already known. This type of exercise improves motor kinetic ability for those with mobility limitations. Moreover, it can positively affect psychology, improving sleep, metabolic syndrome, insulin sensitivity, releasing stress, increasing self-awareness, reducing anxiety and depression, while offering beneficial physiological adaptations (Pullen, Seffens & Thompson, 2018). The plethora of benefits are also analysed in a 2018 review highlighting the better sympathetic - parasympathetic balance, reduction of blood pressure, hormonal improvement in baroreflex sensitivity, hemodynamics (i.e. increased HRV) and decreased catecholamine levels as a response to hypoxia and hypercapnia, inflammation agents and vascular reactivity, as well as QoL (Pullen et al., 2018). A randomised controlled study which compared hydrotherapy and yoga as a form of CR for CHF patients, applied 45-60 minutes of yoga or hydrotherapy and; found both types of exercise having an equal impact on exercise capacity and psychological symptoms of anxiety and depression (Hägglund, Hagerman, Dencker & Strömberg, 2017). Nevertheless, in this small but rather pioneering research, the group which followed hydrotherapy showed significantly improved lower limb muscle strength compared to yoga; indirectly suggesting that as regards sarcopenia, cachexia and frailty muscle waste, hydrotherapy could be more drastic in increasing muscle mass (Hägglund et al., 2017). The clinical picture, and assessment of each individual needs are currently used to plan the appropriate exercise intervention with incorporated asanas. Furthermore, QoL seems to be improved with yoga. There is a wide range of yoga programs, such as haltha yoga, kundalini yoga and other; the meditation part should not be disregarded. More studies with specific and consistent long term yoga exercise programs need to be developed with specified exercise type and dosage targeting at frail, sarcopenic, cachectic elderly CHF patients.

Quality of life

Cardiac rehabilitation is seen as an option that does not only improve some physiological parameters, but also QoL. This parameter is measured with questionnaires and scales that could be prone to patients' subjective opinions; nevertheless, as such patients have limited options to make their lives better, what they believe about their condition and how life-changing exercise-based CR could be is of paramount importance. It must be mentioned that QoL is as independent predictor of mortality and CHF admissions to hospital (Fletcher et al., 2014). The majority of published research agrees that exercise-based CR improves CHF patients' QoL.

Belandrinelli (2012) measured QoL with the "Minnesota Living with Heart Failure Questionnaire", which is a patient self-assessment measure (Belandrinelli et al., 2012). It was concluded that QoL was significantly increased (Belandrinelli et al, 2012). Resistance training seems to improve QoL too (Braith and Beck, 2008). In another review, aerobic interval training with combined aerobic interval and strength, continuous aerobic versus combined aerobic continuous and strength, interval versus continuous aerobic and continuous with strength training were compared, and proved that any mode of exercise can positively affect QoL (Cornelis et al., 2016). Moreover, optimistic are the findings of the Tablet et al. (2009) review, as QoL was improved regardless to the type of exercise, intensity or duration of exercise program both in old and young CHF patients. More results referring to QoL are given in the section below, where QoL is combined with the other two closely related parameters (morbidity and mortality).

Morbidity (hospitalisations; days of stay), mortality and quality of life

It is evident that, body weight reduction and muscle fiber decrease are related to frailty, lack of efficacy, poor prognosis, and higher risk of death, even for people who do not suffer from CHF (Ali and Garcia, 2014). If one combines sarcopenia or cachexia with this frailty, as well as CHF, the situation can get even more serious and threaten patients' not only QoL, but life itself. Morbidity and mortality are two separated indices that usually proceed in accordance. Taking into consideration the studies which were used for this research, CR may prevent or even reverse the situation. There is an overall trend towards statistically significant reduction of morbidity in different types of exercise-based CR programs. Mortality is a more complicated index and there is not a clear answer regarding its decrease. Gasiorowski and Dutkiewicz, in their review article highlight that physical exercise can be beneficial in reducing mortality and frequency rates of heart diseases (Gasiorowski and Dutkiewicz, 2013). There has been reference of both morbidity and mortality in studies including different types of exercise training. Even if there cannot be a solid conclusion because most studies show high heterogeneity, it is considered worthwhile to indicatively mention some of them.

Belandrinelli et al. showed the benefits of long term exercise training in CHF patients, where after 10 years of calisthenics, stretching with aerobic training, patients' mortality and morbidity were significantly decreased, however this randomised controlled trial consisted of no more than 123 people (Belandrinelli et al., 2012). Hulsmann et al. (2004), in their trial with 122 patients, found that knee flexor isokinetic strength is related to long-term survival (a parameter more valuable than peakVO2 and workload) (Hulsmann et al., 2004). Gianuzzi et al., in their 90 participants' trial, which was designed with 30s of aerobic training 3 times per week and then home-based program with everyday vigorous walking and calisthenics, assessed QoL with a different measuring instrument, the "modified Likert questionnaires" and discovered that long-term moderate exercise training can increase exercise capacity, QoL and even reverse the hazardous heart remodeling (Gianuzzi et al., 2013)

O'Connor through HF-ACTION trial focused on aerobic exercise, and in 2009 showed no statistically significant reductions and with some adjustments finally the results turned to a slight statistically significant decrease of all-cause mortality and hospitalisations. (O'Connor et al., 2009). Kateyian et al. (2012), with a participation of 959 CHF patients, attempted to expand the results of O'Connor HF-ACTION project, and highlighted the importance of exercise volume in CHF rehabilitation and its relation to mortality and morbidity (Keteyian et al., 2012). It was shown that only moderate volume (3-7 METs) offered such benefits (Keteyian et al., 2012). These findings shed light into a part of CR that still requires research.

A Cochrane review (2010) on exercise-based CR of CHF patients concluded on improved QoL and significantly reduced hospital admissions as well as insignificant decrease in mortality (Davies et al., 2010). Another Cohrane review, which included studies with aerobic exercise interventions and some resistance training, resulted in significantly better QoL; the variety of trials with different modes of exercise may have influenced the consistency of the findings, yet they may remind scientists that any type of physical exercise could possibly improve QoL and morbidity (Sagar et al., 2015). This fact is reinforced by a meta-analysis which found that QoL as well as the overall and HF related hospitalisations were significantly improved. Regarding mortality, besides its tendency to decrease, there was no statistically significant outcome (Sagar et al., 2015).

Smart el al, in their review on morbidity and mortality, compared 81 different trials, aerobic, strength training or a combination (Smart et al., 2004). The outcome was that exercise-based CR can substantially reduce the risk of adverse health-related events, but more research was required to conclude on mortality and its relationship with exercise-based CR. In 2014, the Cohrane review of Taylor et al. (Taylor et al., 2014), which included a number of combined aerobic and resistance training programs for CHF, found mixed results on mortality improvement as there was no significant reduction of mortality in some trials and increase in some other with longer term follow up. At the same time, hospitalisation was decreased and QoL was improved (Taylor et al., 2014). This review included trials with patients with both reduced and preserved ejection fraction (EF), which may have influenced the outcome of exercise-based CR.

Gasiorowski and Dutkiewicz in their review which included aerobic and strength training trials found reduced mortality by 35% and increased QoL (Gasiorowski and Dutkiewicz, 2013). In the same review, exercise capacity ascended up to 15% offering an improvement in NYHA class too (Gasiorowski and Dutkiewicz, 2013). Fletcher et al. (2014), examined the influence of aerobic and strength training program and concluded in the preservation of physical ability, reduction of HF events and increase in QoL (assessed with Minnesota Living with Heart Failure Questionnaire) (Fletcher et al., 2014). What is important to be mentioned in this review is that as it seems, the greater the duration or intensity of exercise is, the better the benefits in QoL are (Fletcher et al., 2014). Promising are the results of another review article, which underlines the effect of exercise in the significant enhancement of QoL, as well as the drop of hospitalisations, including health-care costs and mortality rate (Fu et al., 2014). A meta-analysis, which included trials with aerobic, interval and strength training programs, found statistically significant improvements in QoL and exercise ability (van Tol et al., 2006). Giallauria et al. (2018) findings agree with the previous ones as regards the exercise capacity and QoL improvements (Giallauria et al., 2018). Outstanding are the results of a meta-analysis revealing that strength training CR program alone can increase aerobic ability and QoL of CHF patients (Guiliano et al., 2017).

Regarding the inspiratory exercises as part of exercise-based CR in CHF it is evident that they improve QoL (Smart et al, 2013); as far as the mortality and morbidity rates there are no optimistic conclusions, but it must be considered that this type of exercise is not much investigated and there are no data regarding frail, sarcopenic and cachectic CHF patients. Generally, as regards the various alternative types of exercise, research is still in its infancy and there cannot be a clear answer about these two vitally important parameters. Besides the optimistic scientific results of various studies, a consistent conclusion is not possible to be drawn. This may be due to the lack of enough research on the effect of CHF exercise-based CR in the long run. Lloyd-Williams et al., had distinctively addressed this issue since 2002 by highlighting the need for a change of focus of the studies on the long-term instead of the short-term effects of physical exercise when it comes to mortality and morbidity (Williams, F., Mair, S. & Leitner, M., 2002). In “table V” reviews and meta-analyses are displayed with their results regarding morbidity, mortality and QoL.

It must be mentioned that, the most reliable meta-analyses are the “ExTraMATCH” which are also the first studies which expressed the ambiguity amongst the results on exercise based CR in CHF. In the “ExTraMATCH letter to the editor”, it is highlighted that the results of exercise-based CR on mortality are not precise, as the data provided in various researches are not convincing enough (Smart et al., 2018). In another “ExtraMATCH” meta-analysis of trials, on exercise-based rehabilitation, the results show that mortality rate was significantly reduced after exercise-based CR intervention (ExTraMATCH, 2004). Nevertheless, as distinctively stated, even if mortality is shown to be reduced, when “all –cause” mortality is measured there cannot be evidence that one single parameter produces this outcome, as mortality could be caused by any reason; therefore the results could be doubted (ExTraMATCH), 2004). Furthermore, remarkable are the results of two recent meta-analyses of Taylor et al., the first study focuses on the effect of exercise-based CR on mortality as well as hospitalisation, and highlights that both parameters were not significantly reduced and that there cannot be a solid conclusion due to the inconsistency of statistical data (Taylor et al., 2018). While, the second one, underlines that even if exercise-based CR has a advantageous impact on health-related quality of life (HRQoL) and exercise capacity, still the effect on different HF patient categories are uncertain (Taylor et al., 2019). Taking this idea a step further, sarcopenia, cachexia, and frailty are common co-morbidities that may influence the results of meta-analyses and should also be taken into consideration.

Limitations

As regards the topic, there is not enough research being conducted from scientists. There is some evidence related to some variables of this topic such as sarcopenia alone, and few studies on sarcopenia and cachexia, or frailty with CHF. The need to clearly define cachexia, sarcopenia and frailty through the description of a specific clinical picture of the patients, through the assistance of specified and relevant scales to measure them, has become evident. The majority of already existing studies on exercise-based CR have small sample sizes and in some cases are not representative of the broadly existing frail, sarcopenic and cachectic CHF population. No matter how closely related these terms are, no research combining sarcopenia, and cachexia and frailty with CHF has been found yet, therefore the bibliography used for this research included exercise-based CR with CHF and in some cases combined with either frailty, or sarcopenia, or cachexia. Additionally, there is not homogeneity amongst the samples of related trials and exercise protocols which were used. Many researches do not examine the long-term effect of exercise-based CR, others are sex biased, or their exercise interventions are not properly designed based on the condition and the disease progress of each patient. Furthermore, the existing studies on exercise-based CR vary according to the patients' stage of CHF, type of exercise, intensity, duration, and instruments to measure the outcome of the exercise. The participants of different trials may have other co-morbidities influencing their condition, or their ability to exercise, and in many cases the sample was not consistent. There was an attempt to adjust the results so as to produce some answers in the area of focus; nevertheless comparing non-equivalent values cannot bring safe and fruitful results, for this reason the variables used in this work were qualitative.

Future directions

Based on the existing literature and its limitations more research should be conducted with large samples and meticulous design with a view to finding results that could drastically change the approach of CR in patients with CHF. The element of frailty, sarcopenia and cachexia needs to be added as it is a common phenomenon and reflects the true picture of the elderly CHF patients' condition.

Conclusion

The number of the elderly amongst the population is critically rising and CHF patients are increasing worldwide. Such patients commonly appear to suffer from sarcopenia, cardiac cachexia and/or frailty, terms that are often closely related. This is often a typical picture of an aged CHF patient which may lead to a deadlock. The impact on both the patients and their families is serious, as the negative consequences of the combination of CHF with sarcopenia, frailty, cachexia bring except of the unfavourable symptoms (dyspnea, weakness, inflammation, muscle waste , fatigue and other), frequent hospital admissions, morbidity, mortality, lack of self-efficacy, poor QoL and other.

Identifying these cases is one of the first steps of tackling the issue. Different measuring instruments are used to define and assess sarcopenia, frailty and cardiac cachexia, nevertheless there is no specific officially agreed method to detect them. Scientists and health practitioners are applying different strategies and methods on CHF as well as cachexia, sarcopenia and frailty alone, while seeking to diagnose and treat the particular patients. Exercise-based CR is nowadays gaining more and more ground as a safe and effective way to treat CHF. However, there is no official CR plan for the triplet (of sarcopenia, cachexia and frailty) which frequently appears with CHF.

Aerobic exercise is known to reduce fatigue, inflammation, produce anabolism, and improve the cardiovascular function, the balance of the nervous system, muscular adaptations and other positive results to CHF patients. Strength training plays a drastic role in some beneficial adaptations of the muscular system, such as the increase of muscle mass and strength, promoting anabolism or even reducing dyspnea, facts that seem promising for sarcopenic/cachectic/frail patients. Both strength and aerobic training have been investigated to an extent that their benefits are mostly accepted by the scientific community. The inspiratory muscles training as well as other alternative types of exercise-based CR such as hydrotherapy, yoga, tai chi, swimming, neuromuscular stimulation, could more or less complement and assist CR; yet there is not enough evidence to support such postulations. Different exercise protocols are shown to increase QoL. There is no clear answer regarding morbidity and mortality even if the results seem optimistic. Nevertheless, CR programs for CHF patients so far are not orientated in sarcopenia, cardiac cachexia and frailty. More answers are needed regarding the type of exercise, the methods, and other parameters of exercise training which play a leading role in the result exercise-based CR may have. Moreover, there is no solid CR plan which brings a complete solution to CHF patients' issues which constitute a daily reality for them. A holistic approach, such as the one that exercise-based CR offers, is one of the best ways to manage the multi-compound situation the old CHF patients are facing; as sometimes is considered to constitute the only approachable solution. Seeing CHF patient's picture as a whole, taking into consideration sarcopenia, frailty, cachexia and other co-morbidities is of paramount importance. Exercise-based CR when methodically applied may be a powerful way to drastically and optimistically change people's lives.

APPENDIX-TABLE I

Recommendations for designing resistance training programs for patients with CHF

	NYHA class I	NYHA class II–III
Frequency	2–3 days/week	1–2 days/week
Duration	15–30 min	12–15 min
Intensity	50–60% 1RM	40–50% 1RM
Contraction speed	6 s (3 concentric + 3 eccentric)	6 s (3 concentric + 3 eccentric)
Work: rest ratio (duration)	60 s or longer (work: rest ‡ 1:2)	60 s or longer (work: rest ‡ 1:2)
Number of exercise stations	4–9	3–4
Number of sets per station	2–3	1–2
Number or repetitions per set	6–15	4–10
Involved muscle mass	Unilateral and/or bilateral	Unilateral and/or bilateral
Mode of training	Segmental training during the introductory phase (first months) whole body training rarely when tolerated	Segmental training mainly, then whole body training as tolerated
Flexibility/balance training	Daily as tolerated	Daily as tolerated

(Braith and Beck, 2008)

TABLE II

New York heart association symptoms classification

Class	Patient Symptoms
I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea (shortness of breath).
II	Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea (shortness of breath).
III	Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, or dyspnea.
IV	Unable to carry on any physical activity without discomfort. Symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases.

Class	Objective Assessment
A	No objective evidence of cardiovascular disease. No symptoms and no limitation in ordinary physical activity.
B	Objective evidence of minimal cardiovascular disease. Mild symptoms and slight limitation during ordinary activity. Comfortable at rest.
C	Objective evidence of moderately severe cardiovascular disease. Marked limitation in activity due to symptoms, even during less-than-ordinary activity. Comfortable only at rest.
D	Objective evidence of severe cardiovascular disease. Severe limitations. Experiences symptoms even while at rest.

(https://www.heart.org/en/health-topics/heart-failure/what-is-heart-failure/classes-of-heart-failure)

TABLE III

Summary of contraindications to exercise testing and training (A), exercise training (B), and increased risk for exercise training (C)

(A) Contraindications to exercise testing and training
1. Early phase after acute coronary syndrome (up to 2 days)
2. Untreated life-threatening cardiac arrhythmias
3. Acute heart failure (during the initial period of haemodynamic instability)
4. Uncontrolled hypertension
5. Advanced atrioventricular block
6. Acute myocarditis and pericarditis
7. Symptomatic aortic stenosis
8. Severe hypertrophic obstructive cardiomyopathy
9. Acute systemic illness
10. Intracardiac thrombus

(B) Contraindications to exercise training
1. Progressive worsening of exercise tolerance or dyspnoea at rest over previous 3–5 days
2. Significant ischaemia during low-intensity exercise (,2 METs,50 W)
3. Uncontrolled diabetes
4. Recent embolism
5. Thrombophlebitis

New-onset atrial fibrillation/atrial flutter

(C) Increased risk for exercise training
1. .1.8 kg increase in body mass over the previous 1–3 days
2. Concurrent, continuous, or intermittent dobutamine therapy
3. Decrease in systolic blood pressure with exercise
4. NYHA functional class IV
5. Complex ventricular arrhythmia at rest or appearing with exertion
6. Supine resting heart rate .100 b.p.m.
7. Pre-existing co-morbidities limiting exercise tolerance

(Piepoli et al., 2011)

TABLE IV

Rating of Perceived Exertion (RPE) and Pain Category Scale

6

7 Very, very light

8

9 Very light

10

11 Fairly light

12

13 Somewhat hard

14

15 Hard

16

17 Very hard

18

19 Very, very hard

20

(Borg, 1998, p.p. 30/38)

TABLE V

Author(s)	Year	Type of exercise	Scale	Results
Taylor et al Meta-analysis	2019	Not specified	MLwHFQ, KCCQ, Guyatt CHF scale	↑HRQoL ↑Exercise capacity
Gialauria et al. Review	2018	Aerobic (High intensity)/ Resistance/Inspiratory	—	↑QoL
Taylor et al. Meta-analysis	2018	Not specified	—	All-cause mortality HF-specific mortality? All-cause hospitalisation HF-specific hospitalisation (Non statistically significant evidence)
Guliano et al. Review, Meta-analysis	2017	Resistance training	—	↑QoL
Cornelis et al. Review, Meta-analysis	2016	Aerobic-strength: IT vs ST, IT vs CT, CT vs CTST, CT vs ST	MLwHFQ	↑QoL
Sagar et al. Review, Meta-analysis	2015	Exercise-based CR not specified	MLwHFQ and KCCQ	↑QoL ↓Hospitalisations ↓Mortality?
Taylor et al. Review	2014	Not specified	MLwHFQ	↑QoL ↓Hospitalisations
Fletcher et al. Review	2014	Aerobic, resistance and flexibility training	MLwHFQ	↑QoL ↓Hospitalisations ↓Mortality
Gasiorowski & Dutkiwewicz Review	2013	Aerobic and ST	—	↑QoL ↓Morbidity ↓Mortality
Davies et al. Review	2010	Mix of aerobic and resistance training	MLwHFQ	↑QoL ↓Hospitalisations ↓Mortality
Tablet et al. Review	2009	Aerobic (The majority of studies: low-moderate interval aerobic training)	KCCQ	↑QoL ↑Exercise capacity
Braith & Beck Review	2008	Resistance training	—	↑QoL ↑Strength ↑Functional Ability
Van Tol et al. Meta-analysis	2006	Not specified	MLwHFQ	↑QoL
Smart et al.	2004	Aerobic and strength	MLwHFQ and KCCQ	↓Risk of morbidity

Review		training		↓Mortality?
ExtraMatch collaborative Meta-analysis	2004	Aerobic	—	↓Mortality ↓ Hospitalisations

↑=Statistically significant increase; ↓=Statistically significant decrease; ?=not significant

MLwHFQ=Minnesota Living with Heart Failure Questionnaire; KCCQ=Kansas City Cardiomyopathy Questionnaire;

IT=Aerobic interval training; ST=Strength/Resistance training; CT=Aerobic continuous training, CHF=Chronic Heart Failure

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