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Functional characterization of respiratory muscles and effects of rehabilitation in chronic heart failure patients

Zahra Sadek

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de l'Université Libanaise

par

Zahra SADEK

pour obtenir le grade de Docteur de l'Université de Picardie Jules Verne

Caractérisation fonctionnelle des muscles respiratoires et effets de la réadaptation chez les sujets qui souffrent d'une insuffisance cardiaque chronique stable

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Submitted Articles

- Recommendations for Best protocol of aerobic training: type, intensity, frequency and duration in chronic heart failure patients. A Systematic review and meta-analysis. : Zahra SADEK, Wiam RAMADAN, Ali SALAMI, Ghina AJOUZ, Wissam H JOUMAA, Said AHMAIDI. Submitted to Respiratory Care Journal, September 2018, Impact Factor: 2.
- Inspiratory muscle training combined to aerobic interval training improves pulmonary responses, exercise capacity and quality of life in patients with chronic heart failure: Randomized controlled trial. Zahra SADEK, Ali SALAMI, Mahmoud YOUNESS, Charifa AWADA, Pierre NASSAR, Wissam H JOUMAA, Wiam RAMADAN, Said AHMAIDI. Submitted to Respiratory Care Journal, September 2018, Impact Factor: 2.
- Combining Aerobic Interval Training and Inspiratory Muscle Training improves cardiac and skeletal Function in Chronic Heart Failure Patients with inspiratory muscle weakness. Zahra SADEK, Said AHMAIDI, Mahmoud YOUNESS, Ali SALAMI, Charifa AWADA, Pierre NASSAR, Wissam H JOUMAA, Wiam RAMADAN. Submitted to European Journal of Preventive Cardiology, October 2018, Impact Factor: 4,5.

Prepared Articles

- Combined resistance, aerobic and inspiratory muscle training against resistance training in chronic heart failure-Additional benefits of resistance exercise: A randomized controlled trial.

COMMUNICATIONS

Oral Presentations

- Strength training- induced left ventricular remodeling in heart failure patients. Zahra SADEK, Wissam JOUMAA, Ali SALAMI, Charifa AWADA, Said AHMAIDI, Wiam RAMADAN. 11th Edition of the international Congress of the Order of Physiotherapists in Lebanon, Octobre 2018, Lebanon.
- Impact of resistance training in patients with chronic heart failure. Zahra SADEK, Wissam JOUMAA, Ali SALAMI, Charifa AWADA, Said AHMAIDI, Wiam RAMADAN. Global Health Congress, Athens, November 2018.
- Effects of Aerobic Training Combined to Inspiratory Muscle Training on Cardiopulmonary and Skeletal Muscle Function, Dyspnea and Quality of Life in Patients with Chronic Heart Failure. Zahra SADEK, Wissam JOUMAA, Fadia Shebbo, Mahmoud Youness, Said AHMAIDI, Wiam RAMADAN. Global Health Congress, Barcelona, Spain, April 2017.
- Effects of combined Aerobic and Inspiratory Muscle Training on Cardiopulmonary Function, Dyspnea and Quality of Life in Patients with Chronic Heart Failure. Zahra SADEK, Mahmoud YOUNES, Pierre NASSAR, Hassan MANSSOUR, Heba BAYDOUN, Wissam JOUMAA, Said AHMAIDI, Wiam RAMADAN. Lebanese Researcher Forum, Psychiatric Hospital of the Cross, Lebanon, April 2017.
- Effects of localized specific rehabilitation program of inspiratory muscles against a resistive load alone or combined with aerobic interval training on skeletal and pulmonary muscle function, dyspnea and exercise capacity in heart failure patient. Zahra SADEK, Wiam RAMADAN, Wissam JOUMAA, Said Ahmaidi. 23th LAAS International Science Conference, April 2017, Beirut, Lebanon.

Communications

- Functional characterization of respiratory muscles and effects of training in heart failure. Zahra SADEK, Wiam RAMADAN, Wissam JOUMAA, Said Ahmaidi. 10th Edition of the international Congress of the Order of Physiotherapists in Lebanon. Physio Beirut, September 2016, Lebanon.
- Caractérisation fonctionnelle des muscles respiratoires et effets de la réadaptation chez les insuffisants cardiaques chroniques stables. Zahra SADEK, Wiam RAMADAN, Wissam JOUMAA, Said Ahmaidi. XVIIIe journées d'études Francophones en Activités Physiques Adaptées. AFAPA-Amiens 2016, mai 2016, France.

Poster Presentations

- Combined aerobic, resistance and inspiratory training improves cardiopulmonary responses and muscle function in patients with chronic heart failure: A randomized controlled trial. Zahra SADEK, Ali Salami, Wissam JOUMAA, Fadia Chebbo, Said AHMAIDI, Wiam RAMADAN. 24th LAAS International Science Conference, May 2018, Beirut, Lebanon.
- Addition of inspiratory muscle training to aerobic training improves cardio-respiratory responses, exercise capacity and skeletal muscle function in heart failure. Zahra SADEK, Wiam RAMADAN, Wissam JOUMAA, Said Ahmaidi. World confederation for Physical therapy Congress, July 2017, Cape Town, South Africa

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LIST OF ABBREVIATIONS

6MWT	6 Minutes' Walk Test
ACE-I	Angiotensin Converting Enzyme Inhibitor
AIT	Aerobic Interval Training
ARB	Angiotensin II Receptor Blocker
ASIS	Anterior Superior Iliac Spine
AT	Aerobic Training
BMI	Body Mass Index
BNP	Brain Natriuretic Peptide
BP	Blood Pressure
CAD	Coronary Artery Disease
CHD	Coronary Heart Disease
CHF	Chronic Heart Failure
CO	Cardiac Output
CT	Continuous Training
EF	Ejection Fraction
FEV1	Forced Expiratory Volume in 1 second
FVC	Forced Volume Capacity
HF	Heart Failure
HIIT	High Intensity Interval Training
HIT	High Intensity Training
HR	Heart Rate
IMT	Inspiratory Muscle Training
IMW	Inspiratory Muscle Weakness
IPAQ	International Physical Activity Questionnaire
LV	Left Ventricle
LVEDD	Left Ventricle End Diastolic Diameter
LVEDV	Left Ventricle End Diastolic Volume
LVEF	Left Ventricle Ejection Fraction
LVESD	Left Ventricle End Systolic Diameter

LVESV	Left Ventricle End Systolic Volume
MCT	Moderate Continuous Training
MEP	Maximal Expiratory Pressure
METS	Metabolic Equivalent of a Tasks
MF	Median Frequency
MI	Myocardial Infraction
MIP	Maximal Inspiratory Pressure
MLWHFQ	Minnesota Living with Heart Failure Questionnaire
MT	Maintain Time
MVIF	Maximal Voluntary Isometric Force
NIH	National Institute of Health
NSAIDS	Non-Steroidal Anti-inflammatory Drugs
NYHA	New York Heart Association
QoL	Quality of Life
RF	Rectus Femoralis
RM	Maximal Resistance
RMS	Root Mean Square
RT	Resistance Training
SD	Standard Deviation
SEMG	Surface Electromyography
SMIP	Sustained Maximal Inspiratory Pressure
SNS	Sympathic Nervous System
TLC	Total Lung Capacity
VL	Vastus Lateralis
VM	Vastus Medialis
Vo2	Peak Oxygen Consumption

ABSTRACT

AIM: The present study shed lights on the non-pharmacological management in patients with heart failure (HF), with special focus on exercise training by its different modalities.

The aim of this study is to evaluate the effect of a combined program of two or three modalities: aerobic interval training (AIT), inspiratory muscle training (IMT), and resistance training (RT), on several outcomes such as: cardiopulmonary and skeletal muscle function, dyspnea and quality of life (QoL). Moreover, this study aims to find the best training exercise that could have additional benefits on measured parameters, thus providing a novel application in cardiac rehabilitation programs.

METHODS: 60 patients with HF (New York Heart Association, NYHA \leq 45) and inspiratory muscle weakness (IMW) were randomly assigned to one of the six following groups (n=10, for each group): Control, AIT, IMT, RT, AIT+IMT and AIT+IMT+RT. AIT was performed at 60% of maximum heart rate (MHR), IMT at 60% of maximal inspiratory pressure (MIP) and RT at 60% of 1 repetition maximum (1RM). The control group patients had no training at all. The training regimens were performed 3 times per week for 12 weeks. At the beginning and the end of the study, patients underwent pulmonary function test, respiratory muscle function test, echocardiography (Left Ventricular Ejection Fraction; LVEF, Left Ventricular End Systolic Diameter; LVESD, Left Ventricular End Diastolic Diameter LVEDD), exercise test, skeletal muscle function test, 6- minute walk test (6MWT) and were evaluated for their QoL using the Minnesota living with heart failure questionnaire (MLWHFQ)

RESULTS: No changes were detected in the control group. All groups showed significant positive effects on almost all the measured parameters. However, the combination of IMT to AIT and the addition of RT to IMT and AIT were the most powerful modalities and resulted in additional benefits over all training modalities. In fact, the double and triple combined groups, when compared to AIT, IMT and RT respectively, resulted in additional significant improvement in several parameters.

CONCLUSION: This study verified that, in patients with CHF and IMW, any exercise training, whether it is AIT, IMT or RT, improves the inspiratory muscle function, QoL, exercise performance and dyspnea. Moreover, the combination of the AIT and the IMT resulted in an additional improvement in the measured parameters. However, the addition of RT to AIT and IMT resulted in additional benefits in some of the measured parameters over the double combined group and all training modalities, which make the combination of two or more exercise training the most recommended protocol in cardiac rehabilitation programs.

ClinicalTrials.gov Identifier or Trial Registration number: NCT03538249.**Ethics committee:** Beirut cardiac institute IRB, OTLY- P- 38F- 16.

RESUME

OBJECTIF: Cette étude se concentre sur la prise en charge non pharmacologique des patients atteints d'insuffisance cardiaque (HF), en mettant l'accent sur l'entraînement physique selon ses différentes modalités. L'objectif de cette thèse est d'une part, d'évaluer l'effet d'un programme combiné de deux ou trois modalités: entraînement aérobie en intervalles (AIT), entraînement musculaire inspiratoire (IMT) et entraînement contre résistance (RT) sur plusieurs paramètres tels que: la fonction des muscles cardiopulmonaire et squelettique, la dyspnée et la qualité de vie. Et d'autres part, de chercher le meilleur type d'entraînement qui pourrait avoir des avantages supplémentaires sur les paramètres mesurés, fournissant ainsi une nouvelle application dans les programmes de réadaptation cardiaque.

METHODES: 60 patients atteints d'HF (New York Heart Association; NYHA \leq 45) et de faiblesse musculaire inspiratoire (IMW) ont été répartis par randomisation dans l'un des 6 groupes suivants pour n=10 pour chacun: Control, AIT, IMT, RT, AIT+ IMT et AIT + IMT + RT. AIT a été réalisé à 60% de la fréquence cardiaque maximale (HR max), IMT à 60% de la pression inspiratoire maximale (MIP) et RT à 60% de 1 maximum de répétition (1RM). Les patients du groupe control ne subissent aucun entraînement. Les protocoles d'entraînements ont été effectués 3 fois par semaine pendant 12 semaines. Au début et à la fin de l'étude, les patients ont subi un test de fonction pulmonaire, un test de la fonction des muscles respiratoires, une échocardiographie (Fraction d'Ejection du Ventriculaire gauche; LVEF, Diamètre Systolique du Ventriculaire gauche; LVESD, Diamètre Diastolique du Ventriculaire gauche LVEDD), le temps de l'exercice, un test de la fonction musculaire squelettique, un test de 6 minutes, de même ils ont été évalués par leur qualité de vie en utilisant le questionnaire Minnesota chez les patients souffrant de l'insuffisance cardiaque (MLWHFQ).

RESULTATS: Aucun changement n'a été détecté dans le groupe control. Tous les groupes ont montré des effets positifs significatifs sur presque tous les paramètres mesurés. Cependant, la combinaison de l'IMT à l'AIT et l'ajout de RT à l'IMT et à l'AIT étaient les modalités les plus efficaces et ont entraîné des avantages supplémentaires par rapport à toutes les modalités

Résumé

d'entraînement. En fait, les groupes de combinaison double et triple, comparés respectivement à l'AIT, à l'IMT et à l'RT, ont entraîné une amélioration significative de plusieurs paramètres.

CONCLUSION: Cette étude a permis de vérifier que, chez les patients avec HF et IMW, tout entraînement, qu'il s'agisse d'AIT, d'IMT ou d'RT, améliore la fonction musculaire inspiratoire, la qualité de vie, la performance physique et la dyspnée. De plus, la combinaison de l'AIT et de l'IMT a entraîné une amélioration supplémentaire des paramètres mesurés. Mais l'ajout de l'RT à l'AIT et à l'IMT a eu des avantages bénéfiques supplémentaires sur certains des paramètres mesurés par rapport au groupe combiné de deux modalités et à toutes les modalités d'entraînement, ce qui fait de la combinaison de deux modalités ou plus, le protocole le plus recommandé dans les programmes de réadaptation cardiaque.

ClinicalTrials.gov Identifier or Trial Registration number: NCT03538249.

Ethics committee: Beirut cardiac institute IRB, OTLY- P- 38F- 16.

RÉSUMÉ GÉNÉRALE

Introduction

L'insuffisance cardiaque chronique (CHF) est la dernière étape commune aux maladies cardiaques. Les patients atteints d'insuffisance cardiaque (HF) développent des symptômes qui limitent leurs activités quotidiennes; une manifestation importante est l'intolérance à l'exercice qui est caractérisée par la dyspnée et la fatigue (Clark, Poole-Wilson, and Coats 1996). La diminution du débit cardiaque (CO) est considérée comme le principal facteur de la pathogenèse de HF. Néanmoins, l'amélioration des facteurs hémodynamiques centraux ne permet toujours pas de réduire le niveau d'intolérance à l'exercice (Wilson, Mancini, and Dunkman 1993). En effet, des travaux ont montré que les patients atteints de CHF ont parallèlement un dysfonctionnement musculaire squelettique (Drexler et al. 1992) et une faiblesse musculaire inspiratoire (IMW) (Clark, Poole-Wilson, and Coats 1996). Ces altérations ont été montrées comme des facteurs contribuant à la genèse de la fatigue et à l'augmentation de la dyspnée chez cette population. Les anomalies des muscles squelettiques sont principalement caractérisées par des changements occasionnés au niveau des fibres musculaires. En effet, une atrophie des fibres accompagnée d'une fonte musculaire, ainsi qu'une réduction de la densité mitochondriale et de la capacité aérobie ont été observées (Sullivan, Green, and Cobb 1991; Drexler et al. 1992). Des altérations similaires; à l'exception du changement de type de fibres, ont été observées au niveau des muscles respiratoires. Le changement semble être en faveur des fibres de type II b pour les muscles squelettiques périphériques, alors qu'il est en faveur des fibres de type I au niveau des muscles respiratoires (Clark, Poole-Wilson, and Coats 1996).

A présent l'intérêt de l'entraînement physique dans la réduction des dysfonctionnements musculaires en améliorant le métabolisme musculaire et la capacité fonctionnelle n'est plus à démontrer. Parallèlement, des améliorations des muscles inspiratoires et de la fonction pulmonaire suite à l'entraînement physique ont été également rapportées. Le but de l'entraînement physique est d'améliorer la capacité fonctionnelle et la qualité de vie (QoL) chez les patients atteints de CHF et d'inverser les altérations intrinsèques musculaires. L'entraînement Aérobie (AT), l'entraînement des muscles inspiratoires (IMT) et l'entraînement contre résistance

(RT) se sont révélés sûrs et avec des bénéfices complémentaires chez les patients atteints de CHF. L'AT est l'exercice le plus couramment utilisé et est fortement recommandé à la fois par la Société Européenne de Cardiologie (Ponikowski et al. 2016) et l'American College of Cardiology / American Heart Association Guidelines (Yancy et al. 2013). Ce type d'entraînement s'est montré capable d'augmenter la capacité d'oxydation des muscles et avait un effet sur l'inversion du changement de type de fibre des muscles périphériques ainsi que sur l'amélioration de la capacité fonctionnelle et de la qualité de vie. Néanmoins, d'autres dysfonctionnements musculaires rencontrés chez les sujets atteints de CHF n'ont pas été directement améliorés par l'AT, tels que la force des muscles respiratoires et les caractéristiques histologiques et métaboliques des muscles squelettiques (Delagardelle et al. 2002).

Les études de la littérature rapportent que l'entraînement RT permet d'améliorer le métabolisme du muscle squelettique et l'angiogenèse, augmenter la densité capillaire et le flux sanguin dans le muscle squelettique, favoriser la synthèse et la libération d'oxyde nitrique et réduire le stress oxydatif (Gasiorowski and Dutkiewicz 2013). L'efficacité de RT et AT dans la réhabilitation de l'CHF est bien documentée (Delagardelle et al. 2002; A. Maiorana et al. 2000). Cependant, l'IMT est une prise en charge spécifique relativement nouvelle dans le domaine de CHF et mérite d'être considérée comme une intervention complémentaire pour les patients atteints de CHF. Les avantages comprennent l'augmentation de la force et de l'endurance des muscles inspiratoires, une capacité d'exercice améliorée, une dyspnée réduite et probablement une meilleure qualité de vie (Lin et al. 2012). La combinaison d'IMT ou de RT à l'entraînement aérobic avait permis d'inverser en partie les altérations des muscles respiratoires et squelettiques (Winkelmann et al. 2009). Comparativement à l'entraînement AT seul, des avantages supplémentaires pour la fonction des muscles respiratoires ont été démontrés suite à la combinaison de l'AT et de l'IMT. Ces bénéfices se résument essentiellement dans l'efficacité ventilatoire, la diminution de la dyspnée et l'amélioration de la qualité de vie (Winkelmann et al. 2009; Adamopoulos et al. 2014). En outre, la combinaison d'AT et de RT a également eu des avantages supplémentaires sur AT seul. Ces avantages comprenaient des améliorations de la capacité d'effort, de la force musculaire, de la capacité fonctionnelle, de l'efficacité du ventilateur et du métabolisme ont été montrées (Beckers et al. 2008; Gary et al. 2011; Georgantas et al. 2014). Laoutaris et al. (Laoutaris et al. 2013) ont étudié les effets de la combinaison de la RT et de l'IMT à l'AT chez des patients atteints de CHF et ont démontré que ce type d'entraînement qui

se réalise en toute sécurité permet d'apporter des améliorations importantes au niveau des réponses cardio-pulmonaires à l'exercice, ainsi qu'une augmentation de la fonction du muscle squelettique et de la qualité de vie comparativement à un AT seul.

À notre connaissance, il n'existe pas dans la littérature des études randomisées, contrôlées, en double ou simple aveugle qui comparent les différentes modalités d'entraînement chez les patients atteints de CHF. En outre, on ne sait pas-à présent quelle est la combinaison la plus efficace et les modalités d'entraînement les plus sécurisantes, et s'il existe des avantages supplémentaires en combinant plusieurs modalités d'entraînement.

L'hypothèse principale de notre travail est d'examiner l'efficacité d'un programme combiné de 3 types d'entraînement : aérobie, résistance et entraînement inspiratoire sur la fonction pulmonaire et cardiaque, la fonction musculaire squelettique et respiratoire, la capacité fonctionnelle, la dyspnée et la qualité de vie chez les patients qui souffrent de CHF stable.

Ainsi, l'objectif principal de la présente thèse est, d'une part, de caractériser les fonctions physiologiques impliquées dans la genèse de l'intolérance à l'effort et de la dyspnée, plus particulièrement les fonctions musculaires (respiratoires et squelettiques) et cardiorespiratoires chez les patients atteints de CHF, et d'autre part, d'étudier et de comparer les effets de la combinaison de différents programmes d'entraînement.

La première hypothèse serait d'étudier les bénéfices supplémentaires apportés lors de la combinaison de l'IMT à l'AIT sur la fonction musculaire cardio-pulmonaire et squelettique, la dyspnée et la qualité de vie par rapport à l'IMT seul, aérobie seul ou le groupe contrôle. Deux études récentes ont confirmé les effets supplémentaires de la combinaison de l'IMT à l'AIT chez les patients atteints de CHF par rapport à l'entraînement aérobie seul (Winkelmann et al. 2009; Adamopoulos et al. 2014); Mais les deux études ont utilisé l'entraînement aérobie continu, n'ont pas évalué les bénéfices obtenus au niveau de la fonction du muscle squelettique et ne comparaient pas leurs patients du groupe combiné au groupe IMT seul ou à un groupe témoin. Par conséquent, le premier objectif de cette étude était de déterminer les effets de l'entraînement combiné sur la fonction musculaire squelettique et respiratoire, la capacité d'exercice, le remodelage ventriculaire gauche, la dyspnée et la qualité de vie en CHF. Le deuxième objectif

était d'objectiver le type d'entraînement qui pourrait avoir des avantages supplémentaires sur les paramètres mesurés.

La seconde hypothèse serait d'étudier l'impact d'un entraînement contre résistance et de vérifier si ces effets sont cumulatifs aux effets d'un entraînement combiné de type aérobie et inspiratoire. Une étude a confirmé des améliorations importantes des réponses cardio-pulmonaires à l'exercice, ainsi qu'une augmentation de la fonction du muscle squelettique et de la qualité de vie (Laoutaris et al. 2013). Cependant, l'entraînement combiné de 3 modalités n'a pas montré des bénéfices supplémentaires au niveau de la fonction cardiaque en le comparant à AT seul, à l'exception du diamètre diastolique du ventricule gauche (LVEDD) qui a été amélioré seulement par l'entraînement combiné. L'utilisation de l'AT en mode continu à la place de l'entraînement aérobie intermittent (AIT) dans leur étude pourrait expliquer l'absence de différence significative en faveur du groupe combiné. Récemment, il a été déjà montré que l'AIT est plus bénéfique que l'AT en mode continu pour inverser le remodelage ventriculaire et améliorer la fonction endothéliale (Wisløff et al. 2007). En outre, Laoutaris et al. n'ont pas comparé les bénéfices de l'entraînement combiné à la RT seul chez la même population de patients avec un groupe contrôle. Par conséquent, le but de ce travail était d'étudier les effets supplémentaires de l'entraînement combiné : aérobie, respiratoire et résistance en le comparant à l'entraînement contre résistance et un groupe contrôle chez les patients atteints de CHF.

La troisième hypothèse serait d'étudier si l'amélioration de la force et de l'endurance des muscles squelettiques dans les différents types d'entraînement reflète la fonction neuromusculaire des unités motrices et réduit le seuil de fatigue chez les patients atteints de HF. À notre connaissance, aucune étude ne compare les différents types d'entraînement par électromyographie de surface. Par conséquent, l'objectif de cette étude est d'étudier et de comparer les effets de différents programmes d'entraînement sur la fonction du muscle squelettique en utilisant l'électromyographie de surface chez les patients atteints de CHF.

Matériels et méthodes

Forme de l'étude et participants

Une étude randomisée, en simple aveugle, contrôlée a été réalisée chez des patients qui ont été diagnostiqués avec une pathologie de type CHF stable et un déficit des muscles inspiratoires (IMW) [Pression Inspiratoire Maximale (MIP) <70% valeur prédictive]. La randomisation a été réalisée à l'aide d'un site Web de recherche sur la randomisation (Scott Plous et Jeff Breil, Lancaster, Pennsylvanie). Les sujets ont été recrutés à l'Institut Cardiaque de Beyrouth. Les sujets éligibles [Fraction d'éjection (FE) \leq 45%, NYHA classe II ou III, diagnostiquée avec CHF pendant plus de 6 mois, sans aucune admission à l'hôpital ou tout changement de médicaments au cours des 3 mois précédents et ont un style de vie sédentaire selon le questionnaire de l'activité physique (IPAQ)] ont été randomisés en bloc avec 1:1 à différents groupes d'entraînement. Les sujets exclus souffraient d'une limitation pulmonaire [volume expiratoire maximal (VEMS) et / ou capacité vitale <60% valeur prédictive], maladie orthopédique ou neurologique, avaient des antécédents d'arythmie cardiaque significative, des antécédents d'infarctus du myocarde ou une chirurgie cardiaque au cours des 6 derniers mois, une pression artérielle mal contrôlée, non échogène, instable, et / ou en phase terminale de HF.

Une fiche de consentement éclairé a été signée et obtenue de tous les sujets participants. Tous recevaient le même traitement médical comprenant principalement des bêtabloquants, des inhibiteurs de l'enzyme de conversion de l'angiotensine (ACE-I) ou des antagonistes des récepteurs de l'angiotensine II (ARB) et des diurétiques. Tous les patients ont été supervisés par des nutritionnistes et des professionnels afin de mener une vie saine et sans fumée.

En outre, une approbation du protocole expérimental a été obtenue auprès du Comité d'Ethique dans la Recherche de l'Institut Cardiaque de Beyrouth, IRB, OTLY-P-38-F-16. De même, le protocole expérimental a été enregistré dans clinical trial.gov sous ce code NCT03538249.

Protocole

60 sujets ont été répartis entre différents groupes ayant différentes modalités d'entraînement d'exercice. Six groupes ont été constitués (n=10 pour chaque groupe) : le groupe

AIT, le groupe IMT, le groupe RT, le groupe combiné de 2 modalités [AIT & IMT], le groupe combiné de 3 modalités [AIT & IMT & RT], et le groupe contrôle. Tous les groupes d'entraînement ont complété 3 séances d'exercices supervisées et non consécutives par semaine pour une durée de 12 semaines, pour un total de 36 séances. Les patients du groupe contrôle ont maintenu leur mode habituel et n'avaient effectué aucun programme d'entraînement. Les évaluations de la fonction pulmonaire, la fonction musculaire respiratoire, l'épreuve d'effort, la fonction cardiaque par échocardiographie au repos, la fonction musculaire squelettique, le test de 6 minutes de marche (6MWT), la dyspnée et la qualité de vie ont été réalisés avant et après la période d'entraînement. Les patients du groupe combiné ont subi les mêmes protocoles d'entraînement inspiratoire, aérobie et résistance mentionnés ci-dessous, avec 5 minutes de repos entre chaque modalité. La saturation en oxygène et la fréquence cardiaque ont été contrôlées en utilisant l'oxymétrie pulsée VIAMED et la pression artérielle a été mesurée en utilisant un sphygmomanomètre avant et à la fin de chaque séance d'exercice.

Les outils de mesures

Test de la fonction pulmonaire

Digital Spiromètre est le test de la fonction pulmonaire standard utilisé pour évaluer la fonction pulmonaire de chaque patient. L'analyse des données a été effectuée en utilisant un programme expliqué précédemment par NHANES II en 1990. Un technicien a pris en charge d'expliquer la procédure de respiration diaphragmatique. La manœuvre a été effectuée trois fois de suite et la plus grande valeur enregistrée a été utilisée dans l'analyse. La capacité vitale forcée (FVC) et le volume musculaire expiratoire forcé en une seconde (FEV1) ont été mesurés pendant que le patient était assis en position verticale.

Fonction des muscles respiratoires

Pour évaluer la force musculaire respiratoire, la pression inspiratoire [MIP] et la pression expiratoire maximale [MEP] ont été enregistrés à l'aide d'un transducteur de pression électrique [MicroRPM care fusion], connecté à un logiciel PC PUMA qui offre des fonctionnalités uniques et avancées sur la force des muscles inspiratoires et expiratoires. En outre, la pression inspiratoire maximale soutenue [SMIP] a été utilisée pour évaluer l'endurance des muscles inspiratoires où le temps a été enregistré pendant la période durant laquelle un patient peut

maintenir 70% de MIP. Les encouragements verbaux aidaient les patients à faire leur mieux. Ce test a été répété 3 fois, avec 2 minutes de repos entre chaque essai et la plus grande valeur obtenue a été enregistrée lors de l'analyse.

Fonction des muscles squelettique

La force du muscle squelettique a été évaluée en utilisant un appareil isocinétique (Manual Muscle Tester Lafayette 01165). La force isométrique maximale volontaire (MVIF) du quadriceps a été mesurée sur l'appareil isocinétique; le patient était assis et positionné avec un genou à 60° et une angulation de hanche à 120° (Johnson, Cowley, and Kinnear 1998). Trois séries de trois répétitions chacune ont été réalisées afin d'obtenir une force maximale pour 3 secondes avec 2 mn de repos entre les séries.

L'évaluation de l'endurance du muscle squelettique : le temps d'endurance isométrique (MT) a également été mesuré lorsque les sujets maintenaient une contraction isométrique à 50% du MVIF rapporté. Des encouragements verbaux ont été donnés aux sujets pour maintenir la charge aussi longtemps qu'ils le pouvaient (Johnson, Cowley, and Kinnear 1998). La manœuvre a été répétée trois fois pour garantir une performance maximale avec 5 minutes de repos entre chaque essai.

Pendant l'évaluation de force et d'endurance, les activités d'électromyographie de surface (SEMG) ont été enregistrées à partir de la vaste latérale (VL), du droit antérieur (RF) et du vaste interne (VM). Des électrodes en forme de disque ont été placées sur le VL sur un quart de distance proximal du condyle tibial latéral sur une ligne reliant celle-ci et l'épine iliaque antérieure-supérieure-iliaque (ASIS). Pour la RF, des électrodes étaient placées à mi-distance le long de la ligne reliant l'ASIS à l'aspect supérieur de la rotule. Pour VM, les électrodes étaient placées à 20% de la distance le long d'une ligne reliant l'espace médial du genou à l'ASIS. Avant l'application des électrodes, la peau a été nettoyée. Les signaux de 3 muscles : VL, RF et VM ont été acquis et stockés grâce à l'utilisation de LabVIEW (32 bits). Root mean square (RMS) et fréquence médiane (MF) ont été calculés par le programme Matlab. La valeur moyenne de RMS et MF ont été calculés pour chaque muscle (Gayda et al. 2005).

Fonction et structure cardiaque

Le dysfonctionnement cardiaque au repos a été confirmé par la méthode d'échocardiographie, avec l'aide de deux cardiologues expérimentés. Les sujets ont été examinés au repos dans la position couchée latérale gauche en utilisant un échocardiographe Vivid S6, General Electric Healthcare, fournitures GEMs. La méthode de Biplane Simpson (vue apicale à quatre chambres) a été utilisée pour l'estimation des mesures échocardiographiques. Les paramètres évalués au cours de l'échocardiographie étaient les suivants: fraction d'éjection ventriculaire gauche (LVEF); Diamètre and volume systolique et diastolique de l'extrémité ventriculaire gauche (LVESD, LVEDD, LVESV, LVEDV).

Test d'effort

Pour évaluer la capacité de tolérance à l'exercice, le test d'effort sur tapis roulant avec protocole de Bruce (Bruce et al, 1973) a été utilisé. En fait, il s'agit d'un test d'effort maximal où le patient travaille jusqu'à l'épuisement complet lorsque la vitesse et l'inclinaison du tapis roulant augmentent toutes les trois minutes. L'intensité de l'exercice était représentée par la pente (%), le temps d'exercice par secondes et l'équivalent métabolique d'une tâche (METs).

Capacité fonctionnelle et Dyspnée

La capacité fonctionnelle estimée a été évaluée à l'aide de la distance maximale parcourue par le test de 6 minutes de marche (6MWT) (Weiner et al. 1999). Le test a été réalisé dans un couloir de 60 m sous la supervision d'un examinateur. Un chronomètre a été utilisé pour enregistrer le temps écoulé. Le test a répété 3 fois avec 5 minutes de repos entre chaque essai. Les patients a été libre de diminuer leur vitesse et de s'arrêter si nécessaire. De plus, la fréquence cardiaque et la pression artérielle ont été mesurées au début et à la fin du test et la dyspnée a été évaluée selon l'échelle de Borg pendant le test d'effort et le 6MWT (Grant et al. 1999).

Qualité de vie

La qualité de vie a été évaluée à l'aide du Minnesota Living with Heart Failure Questionnaire (MLWHF) (Dall'Ago et al. 2006). Le MLWHFQ, instrument spécifique pour évaluer la qualité de vie chez les patients de HF, évalue la perception d'un patient à la maladie de HF et à l'impact du traitement sur les aspects physiques, psychologiques et sociaux de la vie. Il comprend 21 questions, un score total global et deux dimensions : physique et émotionnel. Les patients ont été invités à répondre, en utilisant une échelle de Likert à 6 points (0-5), à quel point

chacune des 21 facettes les empêchait de vivre comme ils le souhaitaient. Les articles sont totalisés pour donner un score de qualité de vie lié à la santé.

Interventions

Entraînement aérobic alternatif (AIT)

Les patients suivent un entraînement aérobic de 30 minutes en 4 blocs en utilisant un tapis roulant, 4 mn de travail à une intensité de 60% de la fréquence cardiaque maximale (HRmax) déjà mesuré pour chaque patient a part lors du test d'effort, et 2 mn de récupération à une intensité de 50% de l'intensité du travail effectué d'une manière alternative (Wisløff et al. 2007). Les périodes d'échauffement et de refroidissement à faible intensité progressive durent trois minutes chacune.

Pour assurer la surcharge progressive appropriée, l'intensité modérée de l'exercice aérobic a été ajustée toutes les deux semaines avec une augmentation de 5% de la fréquence cardiaque afin d'atteindre 90% à la fin du traitement.

Afin de contrôler l'intensité de l'entraînement, nous avons sélectionné lors du stress test la vitesse correspondant à 60% de la MHR. En outre, tous les patients ont été surveillés à l'aide d'une électrocardiographie pour observer en permanence leur fréquence cardiaque. Pendant l'entraînement, la fréquence cardiaque, la pression cardiaque, et les signes fonctionnels d'alerte ont été systématiquement contrôlés en permanence.

Entraînement des muscles inspiratoire (IMT)

L'entraînement des muscles inspiratoires consiste à un entraînement d'endurance de moyenne intensité à 60% de MIP de 20 minutes (Dall'Ago et al. 2006). La MIP a été calculé individuellement à chaque session d'entraînement. L'entraînement des muscles inspiratoires a été assuré par l'utilisation de valves de type Power Breathe. Durant l'entraînement, il est demandé au patient de maintenir une respiration diaphragmatique normale de 15 à 20 respirations par minute pendant 15 mn. Les périodes d'échauffement et de récupération sans résistance durent une minute chacune. La séance se divise en 4 blocs de 3mn de travail séparés par 20 s de repos.

Entraînement contre résistance (RT)

Le protocole d'entraînement comprenait des exercices de musculation ciblant les muscles des quadriceps, des ischio-jambiers et des muscles fessiers des membres inférieurs ; Biceps, Triceps, Deltoïde et Pectoral des membres supérieurs. Un total de sept exercices de force a été utilisé pour entraîner le haut du corps et six exercices de musculation pour entraîner les membres inférieurs du corps. Chaque entraînement était composé de 3 séries de 10 répétitions chacune, avec au moins 15 secondes de repos entre les séries. Au début de la période d'entraînement, les patients ont commencé à s'entraîner à 60% de la 1RM. Cette intensité a été évaluée toutes les deux semaines. Tous les patients ont commencé avec 3 séries de 5 répétitions chacune. Après la troisième session, tous les patients avaient terminé les 3 séries complètes avec 10 répétitions chacune. Le temps total d'entraînement était de 30 minutes. Les périodes d'échauffement et de récupération sans résistance dure une minute chacune.

Discussion

Les effets de l'entraînement physique touchent à la fois les éléments centraux et périphériques. Il est considéré ainsi comme une thérapie intéressante d'un point de vue physiopathologique. Selon Dafoe et Huston, l'exercice physique constitue l'ossature des programmes de réadaptation cardio-vasculaire (Dafoe and Huston 1997). En effet, 25 ans de recherche clinique ont démontré les nombreux bénéfices de l'entraînement physique qui se traduisent cliniquement par des effets anti-remodelage, une meilleure capacité fonctionnelle et QoL, et une réduction de la sensation de dyspnée et des taux de mortalité.

En conséquence, les guidelines de la Société Européenne de Cardiologie sur l'insuffisance cardiaque en 2016 (Ponikowski et al. 2016) recommandent fortement la pratique régulière d'exercices physiques pour les patients souffrant de HF. Des recherches sont ainsi nécessaires pour déterminer l'exercice type et protocole optimale pour ces patients.

L'objectif global de cette thèse était d'étudier les effets de différentes modalités d'entraînement physique chez les patients atteints de CHF. Une combinaison AIT et IMT a été examinée afin d'établir l'influence de l'intervention sur les réponses cardiopulmonaires, la fonction des muscles squelettiques et la qualité de vie chez les patients atteints de CHF avec

IMW. En suite une combinaison RT, AIT et IMT a été étudiée afin de caractériser les avantages supplémentaires de RT chez les patients atteints de CHF.

Ce travail de recherche avait deux principaux objectifs : premièrement, examiner les bénéfices de chacune des cinq modalités d'exercice : aérobie, inspiratoire, résistance, aérobie + inspiratoire et aérobie + inspiratoire + résistance, et ensuite déterminer la meilleure modalité d'exercice à suivre afin d'aborder les recommandations pratiques dans la réhabilitation cardiaque pour les patients souffrant de CHF.

Le résultat le plus important obtenu à partir des données collectées se manifeste par le bénéfice supplémentaire et cumulatif résultant de la combinaison de deux modalités d'entraînement ou plus. L'amélioration de la fonction des muscles inspiratoire, de la capacité fonctionnelle, de la dyspnée et de la qualité de vie dans les groupes combinés était supérieure à l'amélioration obtenue dans chaque modalité seule. En outre, les groupes combinés semblent être non seulement faciles et bien tolérés en pratique clinique, mais également sécurisants pour les patients souffrant d'CHF.

Fonction Pulmonaire

Aucun changement significatif n'a été détecté au niveau de la FVC, FEV1 or FEV1/FVC dans tous les groupes, à l'exception du groupe IMT + AIT où une amélioration de 10,3% de FVC a été notée. Ces résultats confirment les résultats observés par Adamopoulos (Adamopoulos et al. 2014) qui n'a trouvé aucun changement significatif dans les paramètres de la fonction pulmonaire. Une explication possible de ce résultat serait liée au fait que tous les patients inclus avaient une fonction pulmonaire normale. De plus, les changements non significatifs détectés pour ces paramètres étaient en accord avec la variabilité du poids chez certains patients.

En effet, la taille, le sexe et le poids ont été utilisés dans les équations de référence pour les paramètres de la fonction pulmonaire et en particulier, le gain de poids chez certains patients est significativement lié au dysfonctionnement pulmonaire, affectant ainsi les paramètres respiratoires.

Fonction des muscles respiratoires

La combinaison de l'AIT et de l'IMT était sécurisante et a entraîné des bénéfices supplémentaires par rapport à l'AIT et IMT seuls chez les patients atteints de CHF. AIT + IMT a

entraîné une augmentation de la moyenne de MIP et de MEP respectivement de 62,4% et de 40,6%, tandis que IMT a augmenté ces paramètres d'une moyenne de 25% et de 37,9%.

Pour IMT, ces résultats sont en accord avec ceux d'Alba Ramirez (Ramírez-Sarmiento et al. 2002) qui ont montré que les muscles intercostaux externes ont la capacité d'exprimer une réorganisation structurelle après un entraînement inspiratoire spécifique, ce qui pourrait se traduire par une meilleure ventilation et une augmentation de la force inspiratoire.

D'autre part, les bénéfices supplémentaires de l'AIT à l'IMT sont en accord avec l'étude d'Adamopoulos (Adamopoulos et al. 2014) et celle de Winkelmann (Winkelmann et al. 2009) qui ont rapporté respectivement une augmentation de MIP dans le groupe AT / SHAM et une augmentation de la MIP de 72% en moyenne. Ces améliorations peuvent être attribuées en partie à l'entraînement aérobic et peuvent s'expliquer par le fait que tous les patients sélectionnés dans notre étude avaient une IMW. Ainsi, tout entraînement physique, comme AIT, IMT ou RT peut être bénéfique pour améliorer la force musculaire respiratoire.

Les recherches menées par Smart et al. en 2011 (Smart and Steele 2011) et Nunes et al. 2013 (Nunes et al. 2013) montrent qu'en diminuant la quantité de cytokines en particulier le TNF- α , l'AIT peut augmenter la force des muscles inspiratoires, car il a été démontré que le TNF- α à forte dose stimule la perte de la myosine des muscles squelettiques et favorisent l'atrophie musculaire, contribuant ainsi à un dysfonctionnement des muscles respiratoires (Wong, Selig et Hare 2011).

En outre, une amélioration de manière significative à la fois de la MIP et la MEP de 14% et 25% a été notée respectivement. Ce résultat montre que l'entraînement contre résistance améliore la capacité fonctionnelle non seulement en améliorant la fonction du muscle squelettique, mais aussi en améliorant la fonction du muscle respiratoire.

En ce qui concerne le groupe combiné AIT, IMT et RT, des améliorations plus importantes de la fonction respiratoire ont été rapportées dans notre étude par rapport à celles de Laoutaris et al (Laoutaris et al. 2013), MIP (59,8% vs. 35%) et SMIP (71% vs. 33%). Une explication possible de ce résultat pourrait être due au fait que l'entraînement par intervalles, utilisé dans notre étude, s'est avéré être plus efficace pour améliorer les résultats respiratoires que l'entraînement continu de Laoutaris (Laoutaris et al. 2013).

Pour SMIP, une amélioration significative a été observée pour les 2 groupes combinés par rapport au groupe IMT, versus une amélioration non significative par rapport aux groupes AIT et RT, et cela est dû au fait que L'AIT et la RT n'avaient pas amélioré SMIP efficacement.

Ce résultat peut avoir été également affecté par l'intensité d'IMT appliquées. En fait, des études antérieures ont montré qu'un IMT sélective à 30% de MIP entraînait une amélioration de MIP mais pas de SMIP (Johnson, Cowley, and Kinnear 1998). À cet égard, l'intensité MIP de 60% appliquée dans notre étude permet l'amélioration de SMIP et améliore donc la capacité de travail et l'endurance des muscles respiratoires ainsi que la dyspnée qui donne des résultats positifs encourageants. Les mécanismes possibles pour améliorer l'endurance respiratoire pourraient inclure l'augmentation du métabolisme oxydatif aérobie des muscles respiratoires, ce qui peut entraîner une résistance accrue à la fatigue (Mancini et al. 1994). En outre, il est possible que l'augmentation du SMIP soit obtenue grâce à l'amélioration de l'entraînement contre résistance. En fait, les muscles plus forts exécutent n'importe quelle tâche à un pourcentage inférieur à leur capacité maximale; Donc, les muscles forts sont plus capables de soutenir une activité donnée pendant de plus longues périodes (McConnell et al. 2003).

Fonction des muscles squelettiques

La diminution de la force musculaire et la fatigue perçue sont souvent associées à l'intolérance à l'effort et peuvent être responsables de plusieurs limitations de CHF. Ainsi, l'évaluation de la force et de l'endurance des muscles squelettiques est très importante après l'entraînement.

Dans notre étude, tous les groupes ont montré des améliorations significatives de la force des muscles squelettiques, sauf pour le groupe IMT, et les avantages les plus importants ont été pour le groupe combiné de 3 modalités. L'amélioration observée dans les 2 groupes combinés a été attribuée à l'AIT et à RT puisque l'IMT seule n'a montré aucune amélioration significative. En effet, l'entraînement aérobie a permis d'améliorer le MVIF exercé par le muscle du quadriceps des membres inférieur gauche et droit d'environ 10%, ce qui n'est pas différent de l'amélioration de 11% du MVIF rapportée chez les patients du groupe AIT & IMT. Donc, l'IMT n'a eu aucun effet sur les muscles squelettiques périphériques et l'augmentation attribuée était due à l'entraînement aérobie. Et en ce qui concerne l'entraînement contre résistance, on remarque un

développement indicatif de la force musculaire puisque l'amélioration du MVIF dans les jambes gauche et droite était respectivement de 11% et 18%.

Une explication de ces résultats positifs pourrait être due au fait que l'entraînement aérobie et contre résistance inversent partiellement les anomalies musculaires squelettiques en réduisant l'état pro-oxydant, en améliorant l'homéostasie calcique et la fonction mitochondriale et en augmentant le rapport des fibres musculaires de type 1 et 2, qui donc, réduit à son tour la fatigabilité et améliore le métabolisme des muscles squelettiques (Brum et al. 2011).

Cependant, pour l'endurance, tous les groupes ont montré une amélioration significative sauf pour le groupe IMT et le groupe RT (pour MT de la jambe gauche). MT dans le groupe combiné de 3 modalités était sensiblement plus élevées que le groupe RT (41% et 47% versus 24% et une amélioration non significative concernant les jambes droite et gauche, respectivement). Cela pourrait souligner l'importance de l'entraînement aérobie par intervalles dans l'amélioration des activités sous-maximales, et la capacité de l'entraînement contre résistance à améliorer la force générée par les muscles squelettiques.

Électromyographie de surface

Il y a de plus en plus de preuves que les muscles squelettiques sont affectés négativement chez les patients CHF ce qui contribue fortement à la réduction de la capacité à l'effort. La fatigabilité des muscles squelettiques, en particulier, a été largement corrélée à la capacité d'exercice et à la progression de la maladie chez les patients CHF, mais il existe peu de données sur l'activité électrique des muscles avant et après l'exercice. Pour cela, cette étude a examiné l'utilisation de l'EMG dans le diagnostic clinique, chez les patients atteints d'insuffisance cardiaque, afin de surveiller la progression de l'activité neuromusculaire et de la fonction des muscles squelettiques. Nous avons évalué les activités électromyographies de trois muscles: le muscle vaste latéral (VL), le droit antérieur (FR) et le vaste médial (VM) du quadriceps et nous avons comparé les différents résultats entre six groupes: groupe contrôle, AIT, IMT, RT, AIT&IMT et AIT&IMT&RT. Nous avons d'abord démontré une augmentation significative de la RMS des trois muscles des groupes combinés de deux modalités pour le membre gauche et droit et seulement du membre gauche du groupe de trois modalités, lors des manipes de force et d'endurance. Mais étonnamment, l'avantage le plus élevé a été démontré pour le groupe de deux modalités et non pas de trois. En d'autres termes, l'ajout de RT sur le groupe à deux modalités ne

montre aucun effet additif. Il est possible que ce résultat soit dû au faible nombre de patients dans notre étude et puisse également être affecté par la durée totale de l'entraînement, qui devrait peut-être être plus longue, soit lié à la différence d'âge, d'indice de masse corporelle et la distribution entre mâle et femelle dans le groupe de 3 modalités. L'augmentation du RMS après l'entraînement est due à l'adaptation de la fibre musculaire, au recrutement d'un nombre accru d'unités motrices et à une augmentation de l'excitation de chaque unité. De plus, nous n'avons constaté aucune augmentation de la réponse des trois muscles du groupe IMT lors des manipes de force et d'endurance (à l'exception d'un muscle dans la manipe d'endurance). Ainsi, l'amélioration de l'entraînement combiné résultait de l'entraînement aérobique et non de l'entraînement inspiratoire. En ce qui concerne la MF, qui est un moyen optimal d'évaluer la fatigue musculaire, nous avons retenu les résultats de la manipe d'endurance et non de la force, car lors de la manipe de la force, la force ne dure que 3 secondes, ce qui nous empêche de détecter la fatigue musculaire. Il a été démontré que, pendant la manipe d'endurance, les entraînements aérobique, inspiratoire, résistance et en double combinaison avaient des effets positifs sur les indices de fatigue du muscle squelettique. Ce résultat peut être affecté par le recrutement plus élevé d'unités motrices et par l'accumulation des métabolites anaérobies tels que le lactate, les protons, l'ammonium (Gayda et al. 2005).

Test D'effort

L'analyse des variables mesurées lors du «Test d'effort» donne une évaluation importante de l'aptitude cardiovasculaire et de la capacité fonctionnelle des patients atteints de CHF.

Dans notre étude, le temps d'exercice, METS et la dyspnée se sont améliorées après l'intervention dans tous les groupes, avec des bénéfices supplémentaires pour le groupe combinant les 3 modalités.

En fait, le temps d'exercice s'est amélioré de 68,6% pour le groupe combiné de 3 modalités contre 62,3% pour le groupe combiné de 2 modalités. Ces résultats semblent confirmer les résultats de l'étude de Laoutaris (Laoutaris et al. 2013) qui montre une amélioration du temps d'exercice, mais seulement de 16%, et cela peut avoir été influencé par l'entraînement aérobique continu dans l'étude Laoutaris, en comparaison à un entraînement aérobique par intervalles dans notre étude.

L'avantage supplémentaire de l'entraînement par intervalles est dû à sa caractéristique d'altération entre les phases de travail et de récupération et à l'entraînement d'intensité élevée et modérée. Pendant les périodes de repos, le corps travaille à se rétablir et à reconstituer tout ce qu'il a dépensé (Meyer et al. 1990). Cela permet aux patients souffrant de HF d'achever de courtes périodes de travail avec une intensité plus élevée et d'utiliser plus intensément les muscles, ce qui se reflète sur l'habileté de pompage cardiaque dans un pourcentage plus élevé par rapport à l'entraînement continu, améliorant ainsi la résistance à la fatigue et le temps de l'exercice (Piepoli et al. 2011).

De même, le conditionnement des muscles inspiratoires dans le groupe IMT pourrait atténuer le métaboreflex inspiratoire qui pourrait alors améliorer la redistribution du flux sanguin vers les muscles squelettiques du corps. Cela améliore la performance à l'exercice en raison de la diminution de l'activité sympathique et de la vasoconstriction périphérique, conduisant à une perfusion accrue des muscles locomoteurs, ce qui retarde ainsi le temps de la fatigue et améliore la tolérance à l'effort (Ribeiro, Chiappa, and Callegaro 2012)

Les améliorations observées des deux autres variables du test d'effort (METS et Grade) confirment l'avantage supplémentaire de chaque modalité d'entraînement dans l'amélioration de la performance globale à l'exercice, et montrent également une supériorité du groupe combiné de 3 modalités.

Fonction Cardiaque

Il est largement reconnu que l'AT améliore la capacité de la pompe cardiaque (Brum et al. 2011). Cependant, les effets de l'AT sur la fonction cardiaque en HF sont encore controversés. Bien que certaines études n'aient pas amélioré la fonction cardiaque chez les patients atteints de HF (van Tol et al. 2013), d'autres études ont confirmé une augmentation significative de la contractilité et de la fonction cardiaque. Il est également important de souligner que, malgré ces données contradictoires, l'AT améliore réellement la réserve de flux sanguin myocardique indépendamment de l'amélioration de la fonction ventriculaire (Haykowsky et al. 2007).

Nos principaux résultats ont montré que les groupes AT, et les 2 groupes combinés, ont augmenté la LVEF respectivement de 14,1%, 16,6% et 12%, versus une légère amélioration de 5% après l'entraînement RT. Ces résultats ne corroborent pas les résultats de PU et al. (Pu et al.

2001) qui n'ont trouvé aucune amélioration de l'EF après l'entraînement contre résistance. Ce résultat peut être dû aux différents protocoles utilisés et / ou à la période plus courte d'intervention (10 semaines vs. 12 semaines). De même, Jankowska et al. (Jankowska et al. 2008) n'a pas observé d'amélioration significative de l'EF ventriculaire gauche ou des dimensions du ventricule gauche après un entraînement contre résistance. Cette différence observée entre notre étude et le protocole de Jankowska et al. peut être liée au fait que ces auteurs se sont concentrés sur l'entraînement des membres inférieurs (c'est-à-dire le quadriceps) et pas sur les membres supérieurs. Ces données indiquent que l'entraînement aérobie et l'entraînement contre résistance, seuls ou combinés à l'IMT, sont efficaces pour améliorer la fraction d'éjection chez les patients atteints de CHF.

Par ailleurs, ces résultats ne semblent pas être cohérents avec d'autres études concernant les résultats de l'effet de l'AT sur la fonction cardiaque chez les patients atteints de HF. Certaines variables telles que l'intensité de l'entraînement et les méthodes utilisées pour évaluer la fonction cardiaque dans les études cliniques, peuvent avoir influencé les résultats observés. Haykowsky et al (Haykowsky et al. 2007) ont mené une méta-analyse de 14 études et ont constaté que l'intensité de l'exercice adopté pendant les séances d'entraînement joue un rôle important dans le degré d'adaptation cardiovasculaire chez les patients CHF. Ils ont constaté que les séances d'entraînement aérobie effectuées à des intensités supérieures à 60% de la fréquence cardiaque maximale (HRmax) sont plus appropriées, ce qui améliore la fonction cardiaque chez les patients atteints de HF. Wisloff et al. (Wisløff et al. 2007) ont suggéré que l'AIT (70-95% HRmax) améliorait la EF plus que l'entraînement continu modéré (70% HRmax) et conduisait à un remodelage du ventricule gauche.

L'AIT a apporté des améliorations significatives des paramètres centraux : LVEDD et LVESD. Cependant, des améliorations plus importantes ont été obtenues dans les 2 groupes combinés suggérant que l'ajout de AIT à IMT et RT avait un effet plus prononcé que l'entraînement aérobie seul. De plus, par rapport aux résultats de Laoutaris et al. (Laoutaris et al. 2013), une différence notable dans les dimensions du ventricule gauche a été rapportée en faveur de notre programme d'entraînement combinant les 3 modalités ; une diminution de 18% contre 2,7% dans le LVEDD et une diminution de 20% contre 0,7% dans le LVESD, respectivement. Cela pourrait être dû aux modes d'intensité intermittente utilisés dans notre étude.

Finalement, nos résultats ont montré la supériorité du groupe combiné de 3 modalités, qui s'est prouvé avoir un effet sur tous les paramètres discutés, conduisant ainsi à un remodelage inversé du cœur qui est détérioré en HF.

Capacité Fonctionnelle, Qualité de Vie et Dyspnée

Il a été démontré que toutes les modalités d'entraînement améliorent la capacité fonctionnelle, que ce soit pour les paramètres 6MWT, NYHA, MLWHFQ ou dyspnée. Tous ces effets ont été principalement enregistrés dans le groupe combinant les 3 modalités d'entraînement. Ce résultat est expliqué par l'effet cumulé des bénéfices de la combinaison de 3 modalités ensemble, à l'exception de l'indice de dyspnée où la forte amélioration a été démontrée dans le groupe combiné de 2 modalités. Ce dernier résultat serait lié à la différence d'âge et l'indice de masse corporelle (IMC) entre les 2 groupes combinés qui pourraient affecter les résultats (âge: 52 vs. 58, IMC: 28 vs. 32 pour les groupes combinés de 2 et de 3 modalités respectivement).

Cette étude confirme les résultats de Laoutaris qui montre que l'AIT peut partiellement inverser toutes les anomalies du muscle squelettique en améliorant le statut fonctionnel, la qualité de vie et peut-être les perspectives de survie (Laoutaris et al. 2013). D'autre part, l'amélioration de la capacité d'effort à l'exercice par l'IMT serait probablement liée à la réduction de la dyspnée. Ainsi, la moindre perception de dyspnée peut aider les patients à être plus indépendants dans les activités de la vie quotidienne, améliorant ainsi leur qualité de vie (Bosnak-Guclu et al. 2011).

La classification fonctionnelle de la NYHA est également un déterminant de la qualité de vie des patients atteints de CHF. Elle est souvent corroborée, aux symptômes et aux signes représentant un obstacle entravant souvent la vie des patients. Des améliorations ont été détectées après l'entraînement physique dans tous les groupes avec toujours les avantages supplémentaires pour le groupe combinant les 3 modalités. De façon similaire, Adamopoulos et al. (Adamopoulos et al. 2014) et Laoutaris et al. (Laoutaris et al. 2013) ont également montré une amélioration de la classe fonctionnelle de la NYHA chez leurs patients après l'entraînement. Néanmoins, l'amélioration observée dans notre étude était plus importante en raison de l'amélioration de la capacité fonctionnelle et de la performance des muscles squelettiques.

Conclusion

Notre étude montre que tout entraînement physique, AT, IMT ou RT, améliore la fonction musculaire inspiratoire, la qualité de vie, la performance physique et la dyspnée chez les patients avec CHF. Néanmoins, la combinaison de l'AIT et de l'IMT entraîne une amélioration supplémentaire de la fonction musculaire inspiratoire, de la performance musculaire squelettique, du temps d'exercice et de METs, de la capacité fonctionnelle, de la qualité de vie et de la dyspnée. Contrairement à l'IMT, l'AIT seul améliore la force et l'endurance des muscles squelettiques ainsi que la structure et la fonction cardiaque appréciée par LVEF, LVESD et le LVEDD.

L'ajout de RT à AIT et IMT a été le plus probant dans la mesure où il a entraîné des avantages supplémentaires par rapport au groupe combiné à 2 modalités et à toutes les modalités d'entraînement. En effet, ce bénéfice cumulé résulte de l'effet de la RT sur l'amélioration de la fonction du muscle respiratoire et de l'EF du ventricule gauche.

Nos résultats indiquent qu'il est indispensable d'évaluer l'activité électrique des muscles squelettiques au cours d'études ultérieures, car une augmentation de la réponse et le retard du seuil de la fatigabilité de ces muscles a été mis en évidence dans notre étude, en particulier dans le groupe de doubles modalités.

Compte tenu de nos résultats, nous recommandons fortement l'utilisation de l'entraînement combinée de 3 modalités (AIT + RT + IMT) chez les patients CHF avec IMW. La combinaison des 3 modalités est un traitement adjuvant efficace, sécurisant et peu coûteux, qui améliore l'efficacité des programmes de réadaptation cardiaque dans le système de santé publique. Il peut également être intégré dans la prise en charge globale pharmacologique et non pharmacologique chez les patients atteints d'insuffisance cardiaque congestive avec une faible fraction d'éjection.

Il est envisagé également la réalisation d'autres études avec un plus grand nombre de patients et l'ajout du groupe AIT + RT aux cinq groupes que nous avons pris. Des biomarqueurs cardiaques et des études au niveau cellulaire pourraient également être évalués afin de confirmer l'innocuité et l'efficacité des interventions. En outre, des biopsies du muscle squelettique

Résumé générale

pourraient donner un aperçu plus clair sur les adaptations potentielles du muscle squelettique après conditionnement physique.

INTRODUCTION

Chronic heart failure (CHF) is a common final pathway for several heart diseases. Patients with heart failure (HF) develop several symptoms that limit their daily life activities; which is an important manifestation in exercise intolerance (Clark, Poole-Wilson, and Coats 1996). The latter is characterized by dyspnea and fatigue sensation. A decrease in cardiac output (CO) is the main player in HF pathogenesis after its setting. However, the improvement in central hemodynamic factors was not able to reduce the level of exercise intolerance (Wilson, Mancini, and Dunkman 1993). Indeed, researchers have demonstrated that CHF patients do have skeletal muscle dysfunction (Drexler et al. 1992) and inspiratory muscle weakness (IMW) (Clark, Poole-Wilson, and Coats 1996). They found that these alterations contribute to fatigue and breathlessness in this population. Skeletal muscle abnormalities are mainly characterized by muscle fiber type switch, fiber atrophy and muscle wasting, as well as a reduction in mitochondrial volume density and mitochondrial aerobic capacity (Sullivan, Green, and Cobb 1991; Schaufelberger et al. 1995; Drexler et al. 1992). Similar alterations have been detected in the respiratory muscle, with the exception of fiber type switch. In the peripheral skeletal muscles, the switch appeared to be in favor of type IIb fibers, while respiratory muscles had a switch towards type I fibers (Clark, Poole-Wilson, and Coats 1996).

Exercise training has been shown to be helpful in reducing muscular dysfunction by enhancing muscular metabolism and functional capacity. In addition, improvements in inspiratory muscles and pulmonary function were also reported. The aim of exercise training was to improve the functional capacity and the quality of life (QoL) in patients with CHF and reverse to an extent, muscular intrinsic alterations. Aerobic training (AT), inspiratory muscle training (IMT) and resistance training (RT) have been shown to be safe and with complementary benefits in CHF. Moreover, AT has been the most commonly used exercise and is highly recommended by the European Society of Cardiology (Ponikowski et al. 2016) and the American College of Cardiology/American Heart Association guidelines (Yancy et al. 2013). This type of exercise was proven to be safe and beneficial. In fact, it was able to increase the oxidative capacity of the

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muscles and had an effect on reversing the fiber type shift in the peripheral muscles, as well as improving functional capacity and QoL. Nevertheless, other muscular dysfunctions encountered in CHF subjects were not directly improved by AT, such as respiratory muscle strength and skeletal muscle histological and metabolic features. Thus, RT can improve skeletal muscle metabolism and angiogenesis, increase capillary density and blood flow in skeletal muscles, promote the synthesis and the release of nitric oxide (NO), and reduce oxidative stress (Gasiorowski and Dutkiewicz 2013). The effectiveness of RT and AT in the rehabilitation of CHF has been well documented (Delagardelle et al. 2002; A. Maiorana et al. 2000). However, IMT is a relatively new technique in the field of CHF and deserves to be considered as an additional intervention for patients with CHF. Benefits include increased inspiratory muscle strength and endurance, improved exercise capacity, reduced dyspnea, and probably a better QoL (Lin et al. 2012). The addition of IMT or RT to aerobic exercise has reversed partially the alterations in the respiratory and skeletal muscles (Winkelmann et al. 2009). Additional benefits in the respiratory muscle function, ventilator efficiency, dyspnea and QoL, were demonstrated after the combination of AT and IMT (Winkelmann et al. 2009; Adamopoulos et al. 2014) compared to AT alone. Furthermore, the addition of AT to RT also had additional benefits over AT alone. Those benefits included improvements in exercise capacity, muscle strength, functional capacity, ventilator efficiency and metabolism (Beckers et al. 2008; Gary et al. 2011; Georgantas et al. 2014). Recently, Laoutaris et al. (Laoutaris et al. 2013) investigated the effects of adding RT and IMT to AT in CHF patients. In their study, they proved the safety of this triple combination, when compared to AT alone, and reported important improvements in cardiopulmonary responses to exercise, as well as an increased skeletal muscle function and a better QoL.

To our knowledge, there are no randomized, controlled, double or single blinded studies that compare different training modalities to each other and to a control group in the same population of CHF patients. Moreover, it is not known until now which is the most effective combination and safest training modality, and whether there are additional benefits by the combination of several training modalities.

The principal hypothesis in our study is to examine the effectiveness of a combined program of 3 modalities: aerobics, resistance, and inspiratory training on pulmonary and cardiac

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function, skeletal and respiratory muscle function, functional capacity, dyspnea and QoL by comparing it with other modalities in patients with stable CHF.

Thus, the principal objective of our project is to characterize the physiological functions involved in the genesis of exercise intolerance and dyspnea, more particularly muscular (respiratory and skeletal), and cardiorespiratory functions in patients with CHF and on the other hand, to study and compare the effects of different training programs and to prove the superiority of the program that combined the 3 modalities of training.

This manuscript is structured in four parts. The first part will make the state of art on CHF: Epidemiology, Etiology, Pathophysiology, Consequences, Pharmacological and Non pharmacological approaches, followed by 2 systematic review and meta-analyses to analyze the evidence based practice of aerobic training and inspiratory muscle training in HF patients by highlighting the different parameters from which practical recommendations are made. The second part will describe the common methodology and materials. The third part, deals briefly with the results by introducing our 3 studies of this work. Finally, the last part is a general discussion followed by some perspectives.

STATE OF ART

STATE OF ART

Chapter 1: Chronic Heart Failure

CHF is the end-stage of most Cardiac Diseases, whereby the heart is not capable of adequately pumping blood to meet the overall body needs (“American Heart Association. Heart Failure). According to the American college of cardiology and the European society of cardiology, HF is the consequence of any structural or functional deterioration that affects the working mode of systole and/or diastole (Yancy et al. 2013; Ponikowski et al. 2016). More than one etiology could be responsible for developing HF, and more than one alteration could contribute to its pathophysiology.

HF does not mean that your heart will stop at any time. However it means that your heart does not work as well as it should. It is a progressive disorder and not a disease. The heart “fails” not in the sense that it will stop beating (as occurs during cardiac arrest). But it weakens, usually in the months or years, so it is unable to pump all the blood that enters the chambers. Therefore, the fluids tend to accumulate in the lungs and tissues, which cause congestion. This is why HF is also sometimes referred to as “congestive heart failure” (Belardinelli 2007).

1.1- Epidemiological facts

Worldwide around 26 million people have HF (Roger 2013; Ambrosy et al. 2014), with an age mean of (70-75) \pm 15 years as a primary diagnosis age (Ambrosy et al. 2014). In the United States, it is estimated that from 2009 till 2012, around 5.7 million people (Mozaffarian et al. 2016) had HF, and this number is still increasing. This syndrome constitutes a global epidemic with around 870,000 cases diagnosed each year (Mozaffarian et al. 2016). In Europe and according to ESC, there are, at least, 10 million HF patients in the ESC represented countries (population >900 million). HF patients’ mass increase is related to an aging population, developments in the treatments available to different cardiac diseases (Pazos-López et al. 2011), or both.

The epidemiology of HF is relatively not well known in France, despite its considerable economic impact on the health care system. The number of patients with HF is about 500 000, there are 120 000 new cases each year. The incidence ranges are from 4% in men and 3% in

women in the population aged 55 to 64 years and from 50% in men and 85% in women in the population aged 85 to 94 years. The average age of onset of HF is 73.5 years; two-thirds of patients are over 70 years old (Hogg, Swedberg, and McMurray 2004).

1.2- Hospitalization

HF patients exhibit frequent hospitalization events (McDonagh et al. 2014; Pazos-López et al. 2011) associated with a huge load economically on healthcare expenditures. It accounts for 1 million hospitalizations each year with a rate found to be greater among women than in men (Roger 2013). In addition, it is estimated that readmission to the hospital is six months (Pazos-López et al. 2011). In France, there are approximately 3.5 million visits and 150,000 hospitalizations for HF per year and more than 32,000 annual deaths. Expenses related to HF represent more than 1% of total medical expenses. HF is a major public health problem. This should encourage us to treat our patients better, and to implement preventive measures (Hogg, Swedberg, and McMurray 2004). Nevertheless, rehospitalization is not a measure of prognosis for HF and it can occur due to other pitfalls (Pazos-López et al. 2011).

1.3- Morbidity

Exercise intolerance due to fatigue and breathlessness is considered the gold standard clinical manifestation of HF syndrome. Many complications are often accompanied by a deterioration of the patients' QoL and poor prognosis. The origin of these worsening events is the skeletal muscle weakening as a major cause of physical fatigue, and the shutdown of other body systems (Clark, Poole-Wilson, and Coats 1996). Pathophysiological mechanisms, along with reduced perfusion, initiate a vicious cycle, which leads to several malfunctioning systems as a response and adaptation to its pathophysiology (Wilson, Mancini, and Dunkman 1993). These include myocardial changes, skeletal muscles impairment, lungs and inspiratory muscle dysfunction, and other reflex responses to exercise. Accordingly, patients with HF end up possessing a sedentary lifestyle due to the lack of minimal physical activity which leads to exercise intolerance and dependability (Anker et al. 1997). This inactivity doubles the risk of cardiovascular disease, diabetes, obesity and increases the risk of colon cancer, high blood pressure (BP), osteoporosis, lipid disorders, depression and anxiety (Anker et al. 1997).

1.4- Mortality

CHF is known as a leading-for-death worldwide syndrome. Mortality is still considered high even in the presence of advanced treatment approaches (Barretto et al. 2008). Several studies have reported different mortality rates among HF patients. According to the National Health and Nutrition Examination Survey, it is estimated that a 10 year mortality rate is around 71.8% in men and 59.5% in women. In this study, lower rates were associated with younger subjects. It is estimated that a 10-year increase in age is associated with a 26% increase in mortality (Cowie et al. 2000).

In fact, mortality rates are high, even for fit patients with the best treatment available, thus, 50% of patients die within 5 years after diagnosis (Roger VL, Weston SA, Redfield MM 2004). Based on the Framingham Heart Study, mortality at 30 days was about 10%, mortality, at 1 year was 20-30%, and the 5-year mortality was 45-60%. In addition, all HF patients, even those who are considered asymptomatic (NYHA class I) or mildly symptomatic (NYHA class II), are at high risk of death (Daniel Levy et al. 2002). Additionally, Stewart and his colleagues suggested that HF was more malignant than cancer in a study of over 30,000 patients hospitalized for HF, myocardial infarction, or for common cancers in Scotland. With the exception of lung cancer, HF was associated with the worst 5-year adjusted mortality (Stewart et al. 2001).

1.5- Heart failure classification

New York Heart Association (NYHA) functional classification provides useful and supplemental information concerning the presence and severity of HF. NYHA classes focus on exercise capacity and the symptomatic status of the disease. These classes are progressive and inviolate; once a patient moves to a higher class, regression to an earlier one is not observed. Progression in HF classes is associated with reduced 5-year survival. The NYHA functional classification is an independent predictor of mortality. It is widely used in clinical practice and research and for determining the eligibility of patients for certain healthcare services (Ponikowski et al. 2016).

The stages of HF: Class I - No signs of physical activity limitation, no fatigue, no palpitation and/or no dyspnea under ordinary physical activity. Class II - Mild limitation upon

physical activity, but comfortable at rest associated with fatigue, palpitation and dyspnea caused by ordinary physical activity. Class III - Pronounced limitation of physical activity, but comfortable at rest associated with Fatigue, palpitation and dyspnea caused by less than ordinary physical activity. Class IV - Serious discomfort is a primary limitation of physical activity with marked symptoms of HF at rest.

1.6- Etiology of heart failure

HF causes (Figure 1) are described as any condition or event that leads to improper functioning of the myocardium (Kemp and Conte 2012; Pazos-López et al. 2011). Coronary artery disease, myocardial infarction, high BP, abnormalities in heart valves, cardiomyopathies, congenital heart defects, serious pulmonary illnesses, diabetes, high body mass index (KENCHIAIAH et al. 2002), and serious sleep disorders (Apnea) are time dependent variables (D Levy, Kannel, and Deedwania 1996) that contribute to the development of CHF with coronary artery disease (70% of cases) and hypertension being the most common causes of HF (Ghoerghiade and Bonow 1998; Pazos-López et al. 2011).

HF is associated with different signs and symptoms including (“National Heart, Lung, and Blood Institute. What Are the Signs and Symptoms of Heart Failure?"): Coughing and breathlessness, edema, fatigue, and other symptoms like confusion. An increase in the heart rate (HR) may also develop due to certain blood substance change and to compensate for the failing heart output respectively.

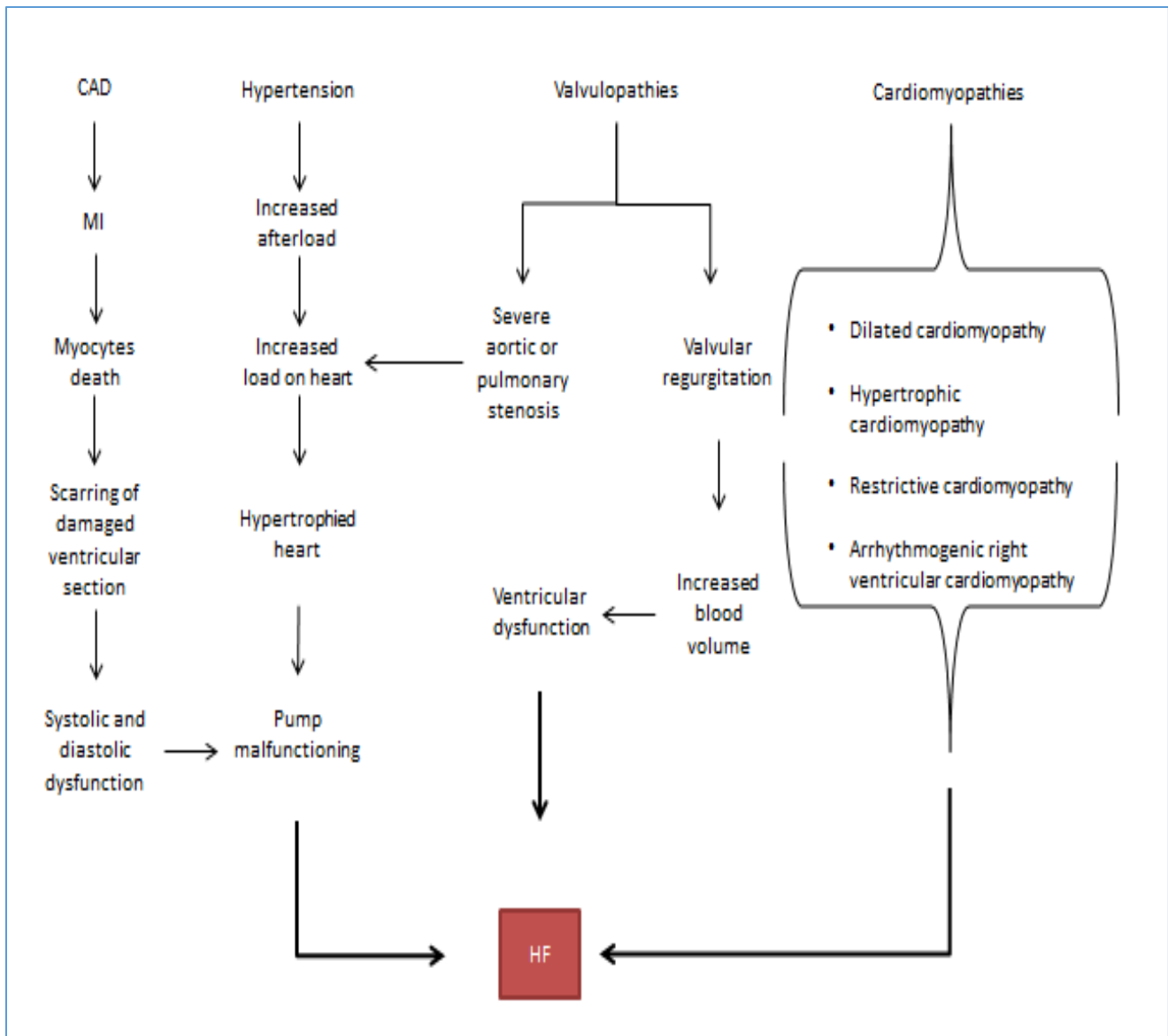


Figure 1 - Etiology of heart failure. CAD, coronary artery disease; HF, heart failure; MI, myocardial infarction.

CAD, if not early treated and managed, could lead to MI which consequently leads to a muscular pump dysfunction; Chronic hypertension, through increasing the afterload, places on the heart greater effort demands, and consequently the heart gets hypertrophies trying to compensate; Valvulopathies in either types leads to higher workloads on the heart and subsequently leading to pump dysfunction; Cardiomyopathies weakens the heart muscle to a point the heart can no more compensate for doing its work efficiently. The final common pathway is heart failure.

Chapter 2: Pathophysiology of heart failure

HF is a complex syndrome that can be maintained for a specific period of time, after which heart transplantation might be needed. HF is characterized by a multitude of clinical forms. We can use different criteria to classify HF. In our study we are concerned about patients with systolic HF. Inclusion criteria mentioned previously would make it clear about the patient's specifications in the study.

2.1- Type of Heart Failure

2.1.1- Left sided HF

The heart left ventricular compartment is not able to pump effectively or fill suitably due to contractile impairment or relaxation abnormality ("American Heart Association. Types of Heart Failure. Kemp and Conte 2012"). The former leads to reduced EF "Systolic dysfunction" and the latter to Preserved EF "Diastolic dysfunction".

In the systolic dysfunction, the heart fails to propel blood towards the body due to a loss in the contractility mechanism and/or increase in the afterload ("American Heart Association. Types of Heart Failure"). Patients with systolic dysfunction have an EF < 40% (Kemp and Conte 2012; P. Ponikowski et al. 2016). It can occur due to different etiologies like ischemic heart disease, prior infarct, valvular disease, hypertension or any disease that contributes to the loss of the effective pumping activity and leads to a decreased CO (Kemp and Conte 2012).

Diastolic dysfunction is described as impairment in the ventricular filling properties. The heart builds high filling pressures for the process to maintain the volume of blood ejected, thus higher end diastolic volume will be needed. It is the result of either a flexibility dysfunction of the myocardium or failure in relaxation process (Kemp and Conte 2012). Patients with HF may suffer of both systolic and diastolic impairment concurrently.

A common symptom between systolic and diastolic forms is pulmonary congestion due to backing up of fluid in the lungs (Kemp and Conte 2012; Pazos-López et al. 2011), clinically manifested by dyspnea.

2.1.2- Right ventricular dysfunction

Left ventricular dysfunction could end up with right ventricular failure as a result of increased pressure on the lungs and subsequently to the pulmonary arteries (“American Heart Association. Types of Heart Failure. Kemp and Conte 2012”). Therefore, the right side of the heart won’t be able to pump the deoxygenated blood to the pulmonary circulation effectively. The blood volume will eventually increase in the right ventricle, thus causing high pressures on both the heart’s right atrium and the venous system. Later, systemic congestion might occur leading to fluid retention in body tissues (e.g. abdomen, liver, ankles...) (“American Heart Association. Types of Heart Failure. Kemp and Conte 2012”; Pazos-López et al. 2011).

2.2- Pathogenesis

The development and progression of HF is complex. The main contributors to the pathogenesis of this syndrome are the compensatory mechanisms that get overwhelmed trying to compensate for the heart’s failure. Most of the mechanisms constitute a net where the result is the cause and vice versa. It is not clear where the process has been launched from, but the well-known key player is the drop in BP due to the decrease in CO (Fenton and Burch 2007; *Klabunde RE. Cardiovascular Physiology Concepts. 2nd Ed. Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins, 2012.*). See figure 2 for a summary of the most important pathophysiological processes.

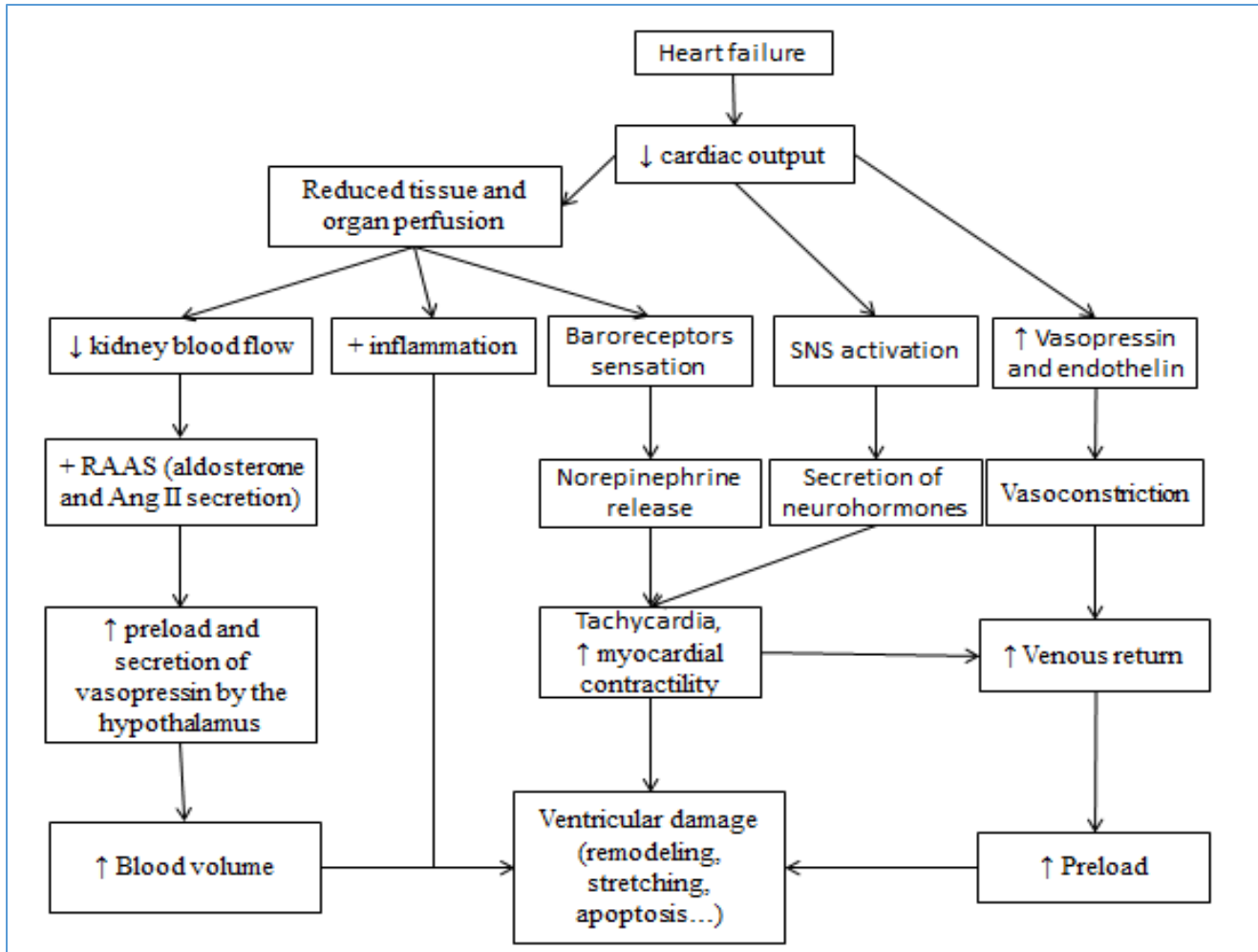


Figure 2 - Progression from adaptation to an overwhelmed system in heart failure.

2.3-Sympathetic nervous system activation

Sympathetic drive, initially, is essential in the compensatory mechanisms that respond to low CO. It becomes activated as a response to mechanoreceptors sensation to distortion and pressure on the heart (Fenton and Burch 2007). The induction of vasopressin release by hypothalamus accompanies this mechanism (Kemp and Conte 2012). This anti-diuretic hormone works on increasing the HR and the myocardial contractility to make up for the drop in CO. Neurohormones will be released due to sympathetic activation (epinephrine and norepinephrine mainly) and bind to receptors found on the heart and smooth muscles of the vascular system, i.e. alpha1, beta1 and beta2. The stimulation of these receptors leads to vasoconstriction, an increase in ventricular contraction, HR and relaxation rate (Chaggar et al. 2009; Fenton and Burch 2007).

Furthermore, an activation of the renin angiotensin aldosterone system (RAAS) takes place, members of this system increases vascular resistance and retention of sodium and water at the kidney level. Hence, an increase in blood volume results in increased ventricular filling pressure as an attempt to increase EF (Chaggar et al. 2009).

The above described is very helpful when the heart is working normally and needed to increase its work for sustaining blood distribution during a workout or any other activity. However, in the case of insufficiency, this will expose the heart to a greater load. The persistent stimulation of the SNS will lead to the desensitization of adrenergic receptors, tachycardia (to maintain CO), arrhythmias, ventricular wall thickening and an exaggerated load on the heart itself (Kemp and Conte 2012).

2.4- Frank starling mechanism

As mentioned above, decreased inotropy and increased blood volume leads to an increase in both atrial and ventricular pressure and volume. This will increase preload and subsequently leads to the stretching of the myocardium. A forceful contraction is followed to increase the fraction of blood ejected (Klabunde RE. *Cardiovascular Physiology Concepts. 2nd Ed. Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins, 2012*). The latter mechanism

follows the Frank-Starling law (Gill et al. 2006). Initially, this mechanism seems to be helpful, but with time, it will stop responding for the volume overload and therefore, the workload on the heart increases and contributes to the deterioration (Kemp and Conte 2012; Gill et al. 2006). Upon the increase in both volume and pressure placed on the left ventricle, pulmonary fluid accumulation will occur (Kemp and Conte 2012), thus leading to pulmonary congestion. Note that Frank-Starling mechanism is a physiological response to an increased ventricular filling and preload. In HF, this response reaches a point of overwhelming and can no more compensate (figure 3) (Klabunde RE. *Cardiovascular Physiology Concepts. 2nd Ed. Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins, 2012*).

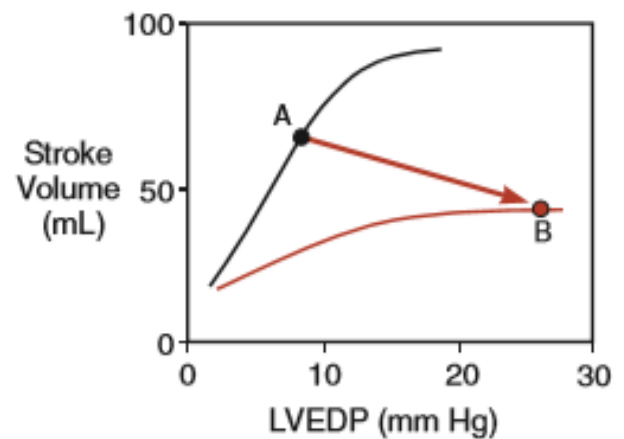


Figure 3 Frank starling mechanism in heart failure. LVEDP, left ventricular end-diastolic pressure

2.5- Renin angiotensin aldosterone system

Both the activation of sympathetic nervous system (SNS) and the decreased kidney perfusion trigger the release of renin and the reabsorption of sodium and water. Activation of RAAS causes a further stimulation of neurohormones release and further augments sympathetic nerves stimulation (Kemp and Conte 2012). The continuity of this system activation will end up in severe vasoconstriction and higher afterload on the heart. As a consequence, this cascade will result in remodeling and damage to the cardiac tissue (Kemp and Conte 2012).

2.6- Natriuretic peptides

Stress conditions, like preload and afterload, result in natriuretic peptide release from the heart (Krupicka, Janota, and Hradec 2013). Brain natriuretic peptide (BNP) and atrial natriuretic peptide (ANP) are produced by the ventricular and atrial cardiomyocytes respectively (Kemp and Conte 2012) mainly in response to stretching. Natriuretic peptides function as counter-regulatory neurohormones. They exert their effects i.e. vasodilation, diuresis, and inhibition of the secretion of RAAS components (Krupicka, Janota, and Hradec 2013; Kemp and Conte 2012), by binding to receptors almost found all over the body. Nevertheless, HF progression will lead to a decrease in receptors' number due to chronic release of natriuretic peptides (Krupicka, Janota, and Hradec 2013), and subsequently decrease their function and aggravate pathogenesis.

2.7- Inflammatory response

In 1996, in their review article, Seta et al. (Seta et al. 1996) related the patterned advance of HF to cytokine production along with the already well-known neurohumoral response. Most notably is TNF-alpha which its synthesis was demonstrated to be stimulated by myocardial stretching and pressure overload. Cytokines that elicit an inflammatory pathway are initially synthesized and released by the myocardium (Bradham et al. 2002), in order to maintain physiological equilibrium. Later on, it aids in the pathological setting-up of HF syndrome (Shirazi et al. 2017) through ventricular remodeling processes (Bradham et al. 2002). Cardiomyocytes dysfunction manifested by hypertrophy, fibrosis and remodeling and further myocyte injury are outcomes of the inflammatory cascades activation (Awad et al. 2009). Conversely, anti-inflammatory cytokines like IL-4 and IL-10 as well as others (Shirazi et al.

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2017) counteracts inflammation-related deleterious effects. However, the persistent underlying disorders and further recruitment of immune cells (macrophages, B and T lymphocytes mainly) identify the subset of cytokines. This process is like a sword of two edges and dominating mechanisms are yet not very clear (Shirazi et al. 2017).

Chapter 3: Consequences of heart failure

Pathophysiological mechanisms, along with reduced perfusion, initiate a vicious cycle. HF leads to several malfunctioning systems as a response and adaptation to its pathophysiology (Kemp and Conte 2012). The following describes how HF is affecting the heart itself, skeletal muscles, lungs, inspiratory muscles, and patient's QoL.

3.1- Myocardial changes

Compensatory mechanisms that lead to decompensation affect the ventricular wall structure and function and with time lead to pathological remodeling. This process ends in dilatation and/or fibrosis thus impeding functional contraction. First, the heart will compensate to greater blood volume by enlargement of the ventricular compartment; second the myocardium will thicken to improve its pumping ability (Kemp and Conte 2012), and reduce the stress on heart. Progressively, heart muscle cells won't be able to overcome the strain, the fact that will exaggerate heart impairment.

Increased afterload caused by compensatory mechanisms, most notably vasoconstriction, leads to pressure overload. Cardiac cells then adapt by enlarging and subsequently thicken and become hypertrophied. Abnormal heart rhythms might arise due to hypertrophy and are almost detrimental (Burchfield, Xie, and Hill 2013).

Cardiac cells are considered to be non-proliferative and terminally differentiated, so in HF the increased strain on heart and the persistent underlying diseases impair the ability of cells to adapt more. Thus, a pathogenic remodeling process occurs, associated with cellular apoptosis and oxygen debt (Burchfield, Xie, and Hill 2013).

3.2- Skeletal muscles impairment

Previously, it was known that skeletal muscles contribution to fatigue is due to decreased blood perfusion; however it was then shown that patients with HF and normal blood flow also complain about exercise intolerance (Wilson, Mancini, and Dunkman 1993). Thus, more important than hemodynamic factors are peripheral intrinsic changes. Several trials were done to confirm the existence of peripheral abnormalities in CHF patients.

Certain reflexes are exaggerated and are involved in the augmentation of fatigue and dyspnea sensation in CHF patients. Upon exercise, skeletal muscle ergo-receptors get sensitized, normally those afferents are present in muscles and do respond to metabolic alterations. In HF, metabolic abnormalities occur due to hemodynamic and muscular alterations (Manetos et al. 2011; P. P. Ponikowski et al. 2001) that their reasons are not yet very clear. Yet, the initiation of these changes is in part associated with low CO and hormonal imbalances, and in part to low activity of patients with HF. Proposed skeletal muscle changes that are considered as candidates for limiting exercise in CHF patients are as follows:

3.2.1- Muscle metabolism impairment

Impairment in the muscle metabolism is detected in CHF patients. Massie et al. (Massie et al. 1988) found that all CHF patients who were included in their exercise study, complained about muscle fatigue. They also reported an increased developed acidity in those patients' skeletal muscles and decreased phosphocreatine, and found no relation between the oxygen delivery via blood flow and the metabolic findings. Thereafter, Massie and colleagues showed that metabolic changes measured by ^{31}P NMR in CHF are associated with an increase in the glycolytic metabolism but also with a decrease in oxidative phosphorylation. This dependence on glycolytic metabolism was previously shown by the same authors.

3.2.2- Mitochondrial changes

Mitochondrial respiration was also discussed in studies in order to understand the muscle fatigue origins in CHF. Metabolic changes that were mentioned above, especially the decrease in oxidative phosphorylation (Massie et al. 1988) and the dependence on glycolytic metabolism, make it not surprising to find a decrease in the cellular oxidative enzymes (Sullivan, Green, and Cobb 1990) like cytochrome oxidase, other mitochondrial based enzymes (D. Mancini et al. 1989) and mitochondrial density. As well, Drexler et al. (Drexler et al. 1992) related this decrease in the capability of skeletal muscles to utilize the oxidative respiration with a decrease in mitochondrial characteristics (volume and cristae surface density as well as the activity of cytochrome oxidase).

3.2.3- Altered fibers distribution

A transition of fiber type is of an important predictor of early fatigue encountered by HF patients (Larsen et al. 2002). Studies have reported a decrease in the slow twitch type I fibers (Sullivan, Green, and Cobb 1990; Drexler et al. 1992) and an increase in the fast twitch type II fibers in skeletal muscles of HF patients (Sullivan, Green, and Cobb 1990; D. Mancini et al. 1989). Mancini et al. (D. Mancini et al. 1989) proposed that the substantially sedentary lifestyle of those patients may contribute to this damage of skeletal muscles.

Two contradicting reports by different studies describe the relation between skeletal pathology and exercise capacity in CHF. Sullivan et al. (Sullivan, Green, and Cobb 1991) and Schaufelberger et al. (Schaufelberger et al. 1995) attested a relation between exercise capacity and both skeletal fiber size and type I fibers distribution. Conversely, Larsen et al. (Larsen et al. 2002) showed no attribution of the skeletal muscle fibers characteristics to exercise capability in CHF patients and suggested that those opposing theories may be due to different patients' failure severity and different underlying pathologies and lifestyle.

3.2.4- Inflammation and muscle atrophy

Circulatory pro-inflammatory markers are found to be elevated in CHF patients, this was assessed initially by Levine et al. in 1990 (Levine et al. 1990). Inflammatory cytokines are activated mainly in response to injured and dying cells that can result from activation of the neurohormonal system, inadequate perfusion of the skeletal muscles and the activation of immune cells. It was shown that TNF-alpha has a role in free radicals production from the mitochondria and subsequently the trigger of mitochondrial damage (Schulze-Osthoff et al. 1992). This inflammatory setting is directly related to the augmentation of weakness and fatigue (Torre-Amione et al. 1996).

Another candidate in patients with CHF is atrophy of skeletal muscle (Pu et al. 2001; Lavine and Sierra 2017). It minimally contributes to the limitation in exercise capacity in CHF patients; this situation was demonstrated by correlating the patient's muscle metabolic profile and the functional capacity. This muscle atrophy was found to be related to muscle inflammation, in a way that inflammatory cytokines add on the damage caused by the persistent activation of neuroendocrine pathways (Seta et al. 1996).

The study conducted by Larsen et al. in 2001 showed that skeletal muscle inflammation and atrophy are interrelated in patients with CHF as well as the presence of a negative correlativity between the thickness of fibers and interleukin 6 levels (Larsen et al. 2002).

3.3- Lungs and inspiratory muscle dysfunction

HF syndrome, being very complex and almost affecting more than one system in the body do have major effects on the pulmonary system including both the lungs and the inspiratory muscles.

A main reason for HF patients to stop exercise at an earlier onset relative to normal people is dyspnea along with muscle fatigue (Apostolo et al. 2012). Dyspnea can even occur at rest in those with end-stage HF (Apostolo et al. 2012) mainly due to pulmonary congestion that impedes the lung's ability to expand. Known with deteriorated lung mechanics and gases exchange properties accredited to pulmonary congestion, HF patients may encounter restrictive pulmonary disease (50% of severe cases) (Agostoni et al. 2006) that was attributed to the enlargement of the heart (Olson, Beck, and Johnson 2007).

Moreover, HF patients exhibit IMW (van Hees et al. 2007; D M Mancini et al. 1992) and expiratory muscle weakness as well as reduced diaphragmatic endurance (Dall'Ago et al. 2006). As skeletal muscle changes contribute to peripheral fatigue, respiratory muscle changes might be another candidate for dyspnea sensation (D M Mancini et al. 1992) which was demonstrated by Mcparland et al. in 1992 (Mcparland et al. 1992). It is not very clear how alterations in inspiratory muscles are developing but known mechanisms can be summarized as follows:

There is a shift in fibers type towards type II (Sullivan, Green, and Cobb 1990; D. Mancini et al. 1989) in the skeletal muscles of HF patients; however a shift towards type I fibers is detected in the diaphragm of those patients. Such difference might be attributed to the fact that in HF, diaphragmatic work (D M Mancini et al. 1992) increases due to altered lungs' dispensability and increased ventilator drive (Apostolo et al. 2012). Since a higher content of type I fibers is predominantly found in the diaphragm, oxidative capacity will be highly reflected by the proportion of oxidative enzymes present.

Angiotensin II (Rezk et al. 2012) and inflammatory cytokines contribute to the weakness of the inspiratory muscles in CHF. An important role of Sphingomyelinase activity and ceramide accumulation was shown to be present in HF, and proposed to be one of the candidates

responsible for diaphragm dysfunction (Doehner et al. 2007). Functional capacity (Ribeiro, Chiappa, and Callegaro 2012) and maximal inspiratory pressure (MIP) are reduced in HF subjects. IMW contributes to the pathophysiology of HF by influencing both chemo- and metabo- reflexes and thus assists the limitation in exercise performance (Ribeiro, Chiappa, and Callegaro 2012) (Ribeiro et al. 2009).

It has been shown that there is an activation of inspiratory metaboreflex during exercise in a healthy population that enhances the sympathetic nervous activity and thus causing vasoconstriction to the skeletal muscles of the peripheries and contributing to fatigue. Thus, in HF associated with IMW, metaboreflex is exaggerated. This was partly proved by Chiappa et al. (Chiappa et al. 2008) who found that IMW amelioration enhanced the hemodynamic properties in HF patients, and inspiratory training reduced metaboreflex firing respectively.

3.4- Reflex response to exercise

During exercise, muscle contraction is initiated and normally metabolic changes will occur in the active muscles; a chain of events will simultaneously start in an attempt to maintain adequate circulation and ventilation. Ergoreflex (sensed by ergoreceptors that are activated by work) is one of these events. In HF, this reflex system is abnormally functioning and metabolic by-products can't be cleared off due to inadequate blood supply resulting in an overall increase in sympathetic stimulation and metabolites accumulation. Metabolic products trigger type II fibers present in muscles and launch a metaboreflex response, contemporaneously mechanoreceptor senses muscle contraction leading to concurrent mechanoreflex response. Ergoreflex activation includes the sensation of both mechanoreceptor and metaboreceptors. The early sensation of fatigue in HF patients could be due to early production of lactate and increased acidification (M F Piepoli et al. 2001). Beside fatigue, ergoreceptors activation is associated with an increase in ventilator drive and vasoconstriction (M F Piepoli et al. 2001).

3.5- Quality of life and functional capacity

QoL is defined as the global impact of a disease subjectively reported by the patient and includes physical assessment, social impacts and psychological effects (Heo, Seongkum., Lennie, Terry., Okoli, C., & Moser 2009). QoL is related to NYHA functional class of the patient, his/her peak oxygen consumption (VO_{2max}) and functional capacity (Coelho et al. 2005).

Despite the fact that changes in cardiac function and heart structure are the reasons for the deterioration in those patients, QoL wasn't related to the EF of the subject's left ventricle (Juenger et al. 2002). A qualitative study published in 2008 investigated the health status in 20 HF patients using QOL questionnaires and after collecting data from these patients, analysis showed that most of them were with a deteriorated life quality at all its dimensions (Heo, Seongkum., Lennie, Terry., Okoli, C., & Moser 2009). Junger et al. (Juenger et al. 2002) found that CHF patients have similar depression level as patients with major depression. Studies (Rumsfeld et al. 2003; Gottlieb et al. 2004) who used depression questionnaires with CHF subjects to assess their depression levels, reported misery and despair symptoms in 30%-40% of the patients, which was also observed by Westlake et al. in 2005 (Westlake et al. 2005).

QoL reflected the functional capacity which is considered to be a predictor of the disease condition level and death rates associated with CHF (Awotidebe et al. 2017). Studies have shown that CHF patients have a deteriorated functional capacity compared to healthy controls (Awotidebe et al. 2017), and reasons illustrated and explained elsewhere in this report confirms the relation between HF skeletal and inspiratory muscles' damage and contribution to limitation in performance in those with CHF.

It has been shown that bad sleep quality is associated with reduced QoL scores in HF patients. Awotidebe et al. (Awotidebe et al. 2017) who correlated sleep quality to functional fitness and compared it with healthy controls confirmed that sleep disorders are present in CHF patients with females being more vulnerable.

Breathing disorders and periodic limb movement are the main contributors to bad sleep quality in HF patients. Breathing disorders lead to serious consequences that affect the heart and the circulatory system, and limb movement leads to light sleep and tiredness.

Chapter 4: Pharmacological treatment

Treating HF is not treating a single disease or malfunction but managing a whole syndrome. Pharmacological approaches include regulation of BP and dyslipidemia, treating diabetes and arrhythmias as well as prescribing diuretics to help reduce sodium and water retention (Kemp and Conte 2012). The main focus in this report is on the treatments available for patients with systolic dysfunction.

In this aspect, treating HF is a multi-approach strategy. Combining three drug types is the conventional pharmacological therapy which is constituted of an Angiotensin converting enzyme inhibitor/Angiotensin II receptor blocker (ACE-I/ARB), a diuretic and a beta blocker. A fourth medication i.e. Digoxin, could be further added in case of exacerbated symptoms and arrhythmias development (Yancy et al. 2013). Most commonly prescribed are:

4.1- Angiotensin converting enzyme inhibitors

ACE-Is are drugs that slow the activity of the enzyme ACE that converts angiotensin I into angiotensin II, thereby blocking the production of angiotensin II from the body. Remember that angiotensin II is a hormone that circulates in the blood and its primary role is the constriction of blood vessels as well as cardiac remodeling and hypertrophic growth stimulation (Sweitzer 2003). Accordingly, blocking the production of this hormone with ACEI prevents the constriction of blood vessels and lowers BP. This low pressure makes it easier for the heart to pump blood and can improve his failing function (Sweitzer 2003).

Beneficial effects of inhibition of converting enzyme in HF comprise: 1) Reduced afterload, which enhances ventricular stroke volume and improves EF, 2) Reduced preload, which decreases pulmonary and systemic congestion and edema, 3) Reduced sympathetic activation, which has been shown to be deleterious in HF and 4) Prevent or reverse the hypertrophy of the heart and vessel walls.

The use of these medications has revolutionized the treatment of patients with CHF over the past 2 decades and has led to improved symptoms and survival rates (P. Ponikowski et al. 2016). But, on the other hand, ACE-Is might cause cough, due to its other action by preventing bradykinin degradation, hyperkalemia and hypotension.

More than one study was conducted to demonstrate the effect of ACE-Is in HF patients, and of these are the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS) and Studies of Left Ventricular Dysfunction (SOLVD). These trials showed that ACE-Is have benefits on survival and hospitalization (*“The CONSENSUS Trial Study Group. Effects of Enalapril on Mortality in Severe Congestive Heart Failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS)” 1987; SOLVD investigators 1991*), as well as on patient’s QoL, and on exercise tolerance. It is recommended that ACE-Is must be prescribed to patients with suitable renal function and normal levels of potassium.

4.2- Aldosterone antagonists

Aldosterone antagonists are used as a long-term therapy accompanied with other medications (Struthers 1995) to reduce aldosterone effects such as endothelial dysfunction, retaining of sodium, electrolyte imbalances and others; its efficiency was approved in the following studies, RALES, EPHESUS and EMPHASIS, that took into consideration the addition of aldosterone antagonists to ACE-Is in HF patients.

4.3- Angiotensin II receptor blockers

Patients who can’t tolerate ACE-Is (Granger et al. 2003) will be instructed to take ARBs instead and especially when developing cough or angioedema (Pazos-López et al. 2011). The efficiency of treatment with ARBs was proved before, and has been addressed in a meta-analysis done by Lee et al. (Lee et al. 2004). According to ESC guidelines, patients who are not responding efficiently to ACE-Is/ARBs and Beta-blockers must be treated using mineralocorticoid receptor antagonist that have good long-time impact opposite to other diuretics that have unwanted effects (Fenton and Burch 2007; Ponikowski et al. 2016).

4.4- Beta blockers

Beta-blockers act by reversible competitive antagonism of catecholamines (norepinephrine and epinephrine) at the beta-adrenergic receptors. The administration of beta-blockers is very efficient for controlling undesirable effects of sympathetic activation as they were reported to reduce both mortality and hospitalization in CHF adult patients and decrease

associated symptoms (Pazos-López et al. 2011; Ponikowski et al. 2016). Specifically, the nonselective beta-blocker “carvedilol” seems to improve symptoms and systolic function of the heart, prolong life by modifying the abnormal hemodynamic and protect the heart tissue. (Packer et al. 1996).

Actually, treating with beta blockers must be accompanied with an ACE inhibitor to complement each other’s action. Decreased HR, weakness and a drop in BP might occur as side effects of using beta blockers (Pazos-López et al. 2011).

4.5- Digoxin

Cardiac glycosides work on enhancing cardiac contraction. Their function is to inhibit the cardiac cellular membrane-bound Na^+/K^+ ATPase thus increasing intracellular sodium concentrations and subsequently increasing calcium pool for contracting fibers. Digoxin also attenuates the maladaptive sympathetic stimulation by decreasing renin and aldosterone (Covit et al. 1983).

4.6-Diuretics

In general, diuretics are the first to be used in HF patients with congestive HF and their primary use are for congestion relief (Pazos-López et al. 2011); Initially loop diuretics (Bumetamide, Furosemide, Torsemide) and/or thiazides are commonly used and well assigned for alleviating congestive edema consequences, but if symptoms persist, a higher dose is recommended or a combination of both is chosen (Ponikowski et al. 2016). Patients who have a more serious fluid retention can be treated intravenously. Non-Steroidal Anti-inflammatory Drugs (NSAIDs), if taken in patients on a diuretic medicament, reduce the diuretics effectiveness. Known and important to be considered, is cardiac arrhythmias that occurs as a result of cations exhaustion, potassium and magnesium; such depletion can be maintained via prescribing potassium and magnesium supplements (Pazos-López et al. 2011).

Chapter 5: Non-pharmacological approaches in heart failure

Exercise training in CHF is a beneficial non-pharmacological approach with promising and valuable effects especially in improving patient's QoL. Peripheral changes that are mentioned in this report are considered as predictors of mortality and morbidity in patients with CHF (Anker et al. 1997; Hülsmann et al. 2004). The exerted effects of this approach are manifested by improved functional capacity due to amelioration in peripheral dysfunction and not central adaptation (Jónsdóttir et al. 2006).

It had been known until 1980's that heart failure patients must avoid any exercise or physical activity. However, after the huge research done on utilizing different types of training on HF patients and especially after identifying the role of peripheral damage in the contribution to physical inactivity and exercise limitation, changes at the skeletal muscle level might be promising in improving functional capacity and life quality in those patients. Today it is highly recommended (Brum et al. 2011; Blair and Brodney 1999; Taylor et al. 2004; Massimo F. Piepoli et al. 2010) that stable HF patients, whose medical report do not mention any problem that would adversely affect them upon exercise, should be involved in cardiac rehabilitation programs, preferred to be supervised, as an adjunct therapy to the conventional pharmacological therapy.

It is vital to note that McDonald et al. (McDONALD, Burch, and Walsh 1965) have published an article under the title of "Prolonged bed rest in the treatment of idiopathic cardiomyopathy" where they recommended an activity-free lifestyle in cardiac patients. However after that, other researchers have revealed the importance of exercise in cardiac patients and further detrimental damage that might be caused by deconditioning, which is one of the risk factors for developing and/or further worsening the progression of cardiovascular and non-cardiovascular diseases (Blair and Brodney 1999). Later then, in their study, Coats et al. (Coats et al. 1990) contradicted the previously emerged reports about resting being beneficial for HF patients and revealed how important is to start exercise training programs to improve patients' life quality.

Exercise training had important and remarkable benefits at the level of skeletal muscle by increasing muscular bulk (Minotti et al. 1990; Tyni-Lenné et al. 1998), improving blood flow and oxygen delivery to the peripheries, as well as reducing vascular resistance (Sullivan, Higginbotham, and Cobb 1988). In addition, Hambrecht et al. (Hambrecht et al. 1997) showed that exercise training was able to decrease the levels of lactate at submaximal exercise. They also found a correlation between mitochondrial volume density and produced lactate at the level of femoral veins. Such correlation demonstrates that exercise limitation is related in part to aerobic metabolism capacity of the muscles. CHF patients suffer from muscle wasting, that have been shown to be a result of deregulated protein synthesis and protein degradation (Feiereisen et al. 2007), where the latter is mediated by proinflammatory cytokines. Exercise training was shown to improve muscle wasting profile by decreasing IL-6 levels and TNF-alpha levels in blood samples taken from CHF patients who undergone 40 sessions of different exercise training modalities with no superiority of any training (endurance, strength and combination of both) (Feiereisen et al. 2013). Meirelles et al. (Meirelles et al. 2013) also demonstrated that exercise training can ameliorate platelet aggregation and can reduce the risk of thrombotic events by exerting anti-oxidant and anti-inflammatory effects.

Other improvements that were seen after exercise training are as follows:

- Increased muscle fiber size (Belardinelli et al. 1995).
- Increased mitochondrial density (Belardinelli et al. 1995).
- Increased type I fiber, and decreased type II fibers (Hambrecht et al. 1997).
- Delayed lactate production and decreased anaerobic metabolism (Sullivan, Higginbotham, and Cobb 1988).
- Improved vasodilation (Maiorana et al. 2000).
- Reduced exaggerated ergoreflex responses to exercise (Piepoli et al. 2001).

Despite the recommendation for exercise as a core element of cardiac rehabilitation and the documented benefits of exercise-based cardiac rehabilitation, enrollment in these programs is generally low with turnout reaching only 15-30% of all eligible patients. Barriers to uptake of cardiac rehabilitation usually include lack of patient awareness for services, patient identity, perception of heart disease, and financial or professional constraints. Previously, the most commonly recommended form of exercise for both clinical and healthy populations was aerobic

training, five to seven days per week for at least 30 minutes a day. (Elliott, Bentley, and Aromataris 2013).

5.1- Aerobic training (AT)

AT is recommended to be used as a non-pharmacological intervention for management and monitoring of HF patients (Brum et al. 2011), (Ponikowski et al. 2016). AT targets large muscles in a way to improve the capacity of systems that produce aerobic energy (Piepoli et al. 2010), and it includes several exercises such as: treadmill walking or jogging, ergometer cycling and running. There are two approaches that can be used as protocols for AT, the continuous training and the interval training.

The former constitutes of a continuous exercise at a constant moderate to high intensity for 30-45 minutes. In the most deconditioned patients, it is recommended to start low and go slow (that is to say on low for 5-10 minutes twice a week). If well tolerated, training duration and the number of sessions per day are increased by 20-60 minutes on 3-5 days a week at a moderate to high intensity program with an indefinite duration (Piepoli et al. 2011).

However, interval training includes an intermittent aerobic exercise between low and moderate to high intensities, this method reduces time commitment required to meet the exercise guidelines and it shows significant benefits in healthy and diseased individuals (Piepoli et al. 2011). In fact, this is the best described and established training; because of its well demonstrated efficiency and safety thus; nowadays it is highly recommended in the guidelines. Over the past 15 years, a growing body of evidence suggests that high intensity exercise may be just as effective as low and moderate intensities, and in many cases it surpasses them in terms of treatment effects and risk reduction (Wisløff et al. 2007). What make interval training exciting are the interrupted bouts at different intensities; it includes high and low intensity intervals. High intensity is described as walking at 90% to 95% of peak HR, and low intensity is described as walking at 60% to 70% of peak HR. Intensities can be maintained according to the patient's capabilities and endurance. The interval training is found to be more efficient and recommended to be used instead of continuous endurance training in cardiac rehabilitation programs (Piepoli et al. 2011).

High intensity interval training (HIIT) program is an effective and time-efficient method to stimulate both the central and peripheral adaptations that can be linked to improved health

outcomes (Piepoli et al. 2011). A single weekly bout of HIIT (90% of maximum HR) gave a superior protection against premature death from all causes and cardiovascular mortality compared to several hours of moderate intensity training (MIT). Moreover, it has been consistently shown that exercise using HIIT is more effective compared to MIT on several important prognostic factors (ventricular function, endothelial function, ischemic heart disease, stroke, quality of life and certain types of cancer (Wisløff et al. 2007).

The preference of aerobic interval training (AIT) over continuous training is not by chance; but it is consistent with the results of other studies that have proven this theory.

Physical performance of coronary heart disease (CHD) patients was often reduced because they have stopped all physical activity remaining stretched in bed for long time. This reveals that these patients cannot, be exposed to HIIT because of their muscular weakness. However, after successful revascularization this should be possible. For that in 1990 *Meyer et al* examined the effects of the two methods (continuous versus interval) in order to determine the best revascularization method for CHD patients. Two groups of nine male patients were trained daily on a bicycle ergometer for 3.5 weeks, and the training session lasted for 20 minutes in both groups (interval and continuous); but what differs was that in the interval group on the first and second days, patients were trained for 15 minutes with 25 W; however from the third day the 15-min was carried out by alternating each minute between 0.33:0.66 W/kg (1st to 9th minute) and 0.33: 1.0 W/kg (10th to 15th minute). The training intensity was controlled according to a training HR of 86% of the maximum HR reached by each patient in the exercise ECG before training. Furthermore, many studies argue that the exercise intensity has a greater effect than the length on the physical performance of a patient. From this consideration, interval training method on an ergometer bike seems to be more suited to enhance physical performance and it was more effective in economizing the cardiac function. Due to its characteristic alteration between work and recovery phases and with high and moderate intensity training, the muscles that are under training are used more intensively during the working phases. This cannot be obtained by the continuous method (K. Meyer et al. 1990).

Rognmo also worked on patients with CHD in 2004 and examined the effects of the two methods. The results of this randomized controlled trial demonstrated that AIT is more effective compared to MCT in patients with stable CHD (Rognmo et al. 2004).

In addition, Wisloff et al. (Wisløff et al. 2007) conducted a randomized study to assess the preference between the two types of AT so they distributed their study subjects between two groups, either to aerobic continuous training or to aerobic interval training. As a result, they reported more improvements in target measures in favor of AIT revealing the role of high intensity bouts during endurance exercise; these improvements include an enhancement in aerobic capacity, a reverse in left ventricle remodeling explained by a decrease in end-diastolic and systolic volumes and dimensions, improvement in the endothelial function and QoL, and an increase in left ventricular ejection fraction (LVEF) and lateral vastus muscle mitochondrial function. The latter is indicated by taking a muscle biopsy to be analyzed and checked for mitochondrial biogenesis. Furthermore, patients in the AIT group appeared to be more enthusiastic and interested about the training, however, those enrolled to the continuous training found it boring due to the uninterrupted intensity. Interval training is favorable to be set at an intensity of 70-95% of HR peak (Brum et al. 2011).

Also, Wisloff et al. (Wisløff et al. 2007) showed that AIT is able to enhance the endothelial function of patients with HF. They assessed the flow mediated dilation (FMD) and the oxidative stress mediators after the training program; as a consequence, they found improvement in FMD, reduced oxidative stress and oxidized low-density lipoprotein (LDL). These authors suggested that this improved profile might be due to an increase in the NO bioavailability, since its amount in blood is vulnerable to reactive oxygen species (i.e. O_2^-) and to the level of oxidized LDL.

Considerable evidence is available to support the role of the HIIT as an effective and time efficient method. In clinical settings, HIIT usually refers to several shorter exercise periods (up to 4 minutes) at a high level of workload (85-95 % of HR peak). Each interval is separated by exerting active breaks at a lower workload. Interventions including HIIT typically range from 4 to 12 weeks in duration, with exercise sessions two to three times a week. In addition, a previous systematic review and meta-analysis that included more than 10,000 patients showed a significant reduction in cardiovascular and all-cause mortality, as well as reduced hospital admissions after a based exercise cardiac rehabilitation. In addition, there was also a trend toward an improvement in QoL scores in this population (Elliott, Bentley, and Aromataris 2013).

Previous studies have shown a greater effect of HIIT; they adopted relatively long high intensity training periods (3-4 min) followed by active periods of "rest" for 3 minutes at a current

of up to 70% of maximum HR. The performance of these long periods of high intensity exercise and / or resting periods to such vigorous intensity levels may not be possible for all patients with HF. In addition, most previous studies have applied a training frequency of three times per week, which takes time. Although training frequency of twice a week may be sufficient to induce a positive effect on fitness levels, no previous study has examined the effectiveness of HIIT with a low frequency of training .Therefore, *Benda* has explored the benefits of a workable HIT protocol with high intensity bouts of moderate duration (i.e., 1 min), active rest at a relatively low intensity (30% of maximal workload), and a training frequency of twice per week (Benda et al. 2015).

This above study examined whether 12 weeks of continuous training (CT) or high intensity bouts of moderate duration is effective and feasible for HF patients, and if that HIT protocol leads to greater effects on fitness, cardiovascular function and QoL by comparing it to CT. It was demonstrated that CT and HIT are both achievable in HF patients and induced a significant improvement in measures of (sub) maximum physical performance and fitness, with no significant difference between the two types of training exercise. Despite these changes in the physical condition, there was no improvement in cardiac resting and structure and vascular function. Therefore, Benda suggests that both types of exercise training successfully ameliorate physical fitness measures in 12 weeks, but not cardiovascular function at rest or QoL. Moreover, this study suggested that there is no evidence of the superiority of this HIT feasible protocol on traditional CT (Benda et al. 2015).

In 2016, *Anderson* also examined the effect of the two training methods. *Andersen* training protocol has been adapted from *Wisloff et al.* Patients randomized to HIIT and MCT exercised for 60 min (10 min of warming; 40 min MCT or HIIT and 10 minutes cooling). All patients were trained using a HR monitor and the speed and inclination of the treadmill were adjusted constantly to ensure that each training session was carried out at the assigned intensity throughout the study period. In addition, the Borg scale 0-10 was used to evaluate the subjective feelings of perceived exertion during and after each training session (Ulbrich et al. 2016).

As a summary, the main conclusion of these studies is that the AIT was superior to MCT in patients with post infarction HF with regard to the reversal of LV remodeling, aerobic capacity, endothelial function, and QoL (Wisløff et al. 2007). It is believed that for more than 2 billion of physically inactive adults worldwide, HIIT can be an effective way to improve health

and reduce mortality, particularly since the lack of time is the most commonly cited barrier for physical activity (Hallal et al. 2012). Due to the inverse dose-response relationship between vigorous activity and mortality, *Wisloff* claims that HIIT should play a central role in the guidelines of the health activities to maximize the benefits of physical activity in the worldwide (Wisloff et al. 2007).

The largest trial that have studied the effect of AT on HF patients is, “Heart failure: A Controlled Trial Investigating Outcomes of Exercise Training (HF-ACTION)”. It was conducted to test the efficacy and safety of exercising in HF (O’Connor et al. 2009). Patients recruited were randomized to either aerobic exercise training or usual care in this study. This large study demonstrated that AT is safe; it has also resulted in significant reductions in all-cause mortality and hospitalization after adjusting for prognostic factors. Furthermore, compared to usual care, patients in the exercise training group had additional improvements in functional capacity assessed by the six minute walk distance, exercise time, and aerobic capacity assessed by VO_{2max} . Thus, this huge trial does recommend and support the non-pharmacological approach as an adjunct therapy in the management of systolic heart failure.

5.2- Inspiratory muscle training (IMT)

IMT is a method being used to strengthen the inspiratory muscles and increase its durability. It is achieved by a step wise protocol (Charususin et al. 2013) that utilizes a cumulative increase in loading pressure to the inspiratory muscles as per improving the respiratory muscles (Bissett et al. 2015). To date, three IMT methods are used: the isocapnic hyperpnoea, the inspiratory resistive training, and the threshold loading.

Isocapnic hyperpnea (endurance): It is based on the assessment of maximum voluntary ventilation, and it is constituted of rapid breathing repetitions without any overload for a period of 15-20 minutes (Boutellier 1992).

Inspiratory resistive training and threshold loading (strength and endurance): The former uses a simple device placed through its small orifice on the inspiratory circuit. This type has some drawbacks, which include a poorly controlled charge and fluctuating inspiratory pressure upon varying inspiratory flow. However, the “threshold loading” device (Threshold IMT® Respiration®, power breathe®) governs an adjustable inspiratory valve which cannot open unless a predetermined pressure level is achieved. This device has the bonus of limitlessly setting

the pressure plate ranging from -7 to -40 cm H₂O, which is independent of the flow (Gosselink, Wagenaar, and Decramer 1996).

It is of great importance to target respiratory muscles in CHF patients because it is widely known and reported that several alterations in inspiratory muscles (Wong, Selig, and Hare 2011) contribute to exercise limitation and fatigue (Ribeiro et al. 2009; Ribeiro, Chiappa, and Callegaro 2012). Thus, lots of researchers who conducted studies that aim at improving HF patients' QoL used the IMT as an intervention to improve the performance and function of the inspiratory muscles (Cahalin et al. 2013; Wong, Selig, and Hare 2011).

Different studies used different protocols and different types of inspiratory training apparatus and reported slightly different measure outcomes. However, all trials worked on improving the muscular function of inspiratory muscle and patients' QoL.

Initially, Mancini was the first to demonstrate in 1995 the benefit of selective respiratory muscle training on exercise capacity in patients with CHF and it was the only study that administered a variety of breathing exercise (isocapnic hyperpnea, inspiratory strength training, and breathing calisthenics) in addition to Threshold IMT (Donna M. Mancini et al. 1995).

Then in 1998, Johnson conducted a study that despite achieving a significant increase in inspiratory muscle strength (increased MIP), the simple domiciliary IMT has not resulted in significant improvements in exercise tolerance and QoL owing to the fact that it may be that a higher percentage than 30% is required for these patients and also we must consider the possibility that the sham training performed by the control group actually have a training effect which causes no significant difference between the two groups (Johnson, Cowley, and Kinnear 1998).

In addition, we observed that two studies (Laoutaris et al. 2004; Dall'Ago et al. 2006) who had patients with IMW, and who performed IMT for 12 weeks, and had a control group that received placebo-IMT without load inspiratory showed marked improvements in peak VO₂ and greater gains from the distance in six minute walk test (6MWT). And this is may be due to the greater degree of impairment in patients in these trials and the longest duration of the intervention and with the fact that we have a comparison between the IMT group and the control group that received the placebo -IMT without inspiratory load.

Moreover, interestingly, in the study conducted by DallAgo, part of the effect on MIP and QoL was sustained after one year; although patients do not continue the training after four

months. These data provide the first evidence that the effects of IMT are consistent and are partially preserved after one year of follow-up (Dall'Ago et al. 2006).

The sample size for all studies was small and the mode of IMT in most studies was the Threshold inspiratory muscle trainer (Philips Respironics, Andover, MA, USA) at an intensity ranging from 20 to 60% of MIP, and the average duration was 30 minutes for 12 weeks, 7 days per week. The duration and progression of IMT varied in each study that utilized the Threshold inspiratory muscle training device, but usually maintained the same duration or increased it slightly, and maintained the training intensity at 30% to 40% of MIP by weekly reassessment of MIP. Two studies performed by the same investigators administered IMT using the Test of Incremental Respiratory Endurance (TIRE) via the TRAINAIR device (Project Electronics Ltd, Kent, UK) at 60% of MIP/sustained maximal inspiratory pressure (SMIP) with an increasing work to rest ratio for 20 to 30 minutes, 3 times per week. Each study has its own limitations and therefore we cannot conclude the best intensity to lead because we have different parameters.

Concerning the IMT training device, it is recommended to use the threshold IMT device (Cahalin et al. 2013) due to its convenience, easy-to-use strategy, and portability. Upon inhaling through this device, the patient must exert a pressure that overcomes the set spring tension which is placed in the central body of this hand-held device (Cahalin et al. 2013). The recommended intensity is 60% to 80% of MIP (Cahalin et al. 2013). This preferred intensity was previously approved by Laoutaris and his colleagues in 2007 (Laoutaris et al. 2007), after they had compared a high intensity IMT group to a low intensity group. They demonstrated that the high intensity training results in higher improvements in the inspiratory muscle strength and endurance, functional capacity, dyspnea, and pulmonary function.

Several studies (Cahalin, Semigran, and Dec 1997; Johnson, Cowley, and Kinnear 1998; Weiner et al. 1999; Martínez et al. 2001; Padula, Yeaw, and Mistry 2009; Bosnak-Guclu et al. 2011; Mello et al. 2012; Dall'Ago et al. 2006; I D Laoutaris et al. 2007; Chiappa et al. 2008) showed that IMT was able to increase MIP in CHF patients, and improve inspiratory muscle endurance (Cahalin, Semigran, and Dec 1997; Martínez et al. 2001; Dall'Ago et al. 2006; I D Laoutaris et al. 2007) as well as pulmonary function (Weiner et al. 1999)(I D Laoutaris et al. 2007). Dyspnea, functional capacity and QoL have been positively affected by the IMT (Padula, Yeaw, and Mistry 2009; Bosnak-Guclu et al. 2011; Mello et al. 2012). IMT improvements are not only confined to the above mentioned changes but also to increased quadriceps strength

(Bosnak-Guclu et al. 2011), blood flow to calf and forearm, and diaphragm thickness (Chiappa et al. 2008). Moreover, Chiappa et al. (Chiappa et al. 2008) found a correlation between inspiratory maximal pressure and change in the diaphragm thickness in CHF patients who performed IMT over a four week training regimen.

Metaboreflex associated with accumulating metabolites due to reduced diaphragm perfusion and increased work by inspiratory muscle, might be ameliorated by IMT (Chiappa et al. 2008) and subsequently causing a decrease in sympathetic-mediated vasoconstriction and an improvement in peripheral perfusion (Chiappa et al. 2008)(Ribeiro et al. 2009).

5.3- Resistance training (RT)

RT, also called strength training, is a type of exercise that increases muscle strength. It involves lifting light to medium weights (using dumbbells or a resistance exercise machine) using body weight or elastic bands as a source of resistance (Mitchell et al. 1974).

Actually it had been thought until 1990s that RT might impose danger in front of HF patients as a consequence of exaggerated left ventricular remodeling. Such theory was contradicted after proving the safety of resistance exercise on the heart (Mitchell et al. 1974; Katharina Meyer et al. 1999) and then it was indicated as a secondary prevention strategy in CHF (Braith and Stewart 2006). Indeed, since RT targets the muscles, it may have the capability of reversing the undesired feedback mechanisms that occur due to muscle dysfunction. Conraads et al. (Conraads et al. 2004) confirmed the safety of RT on cardiac function and left ventricular remodeling after they had detected a reduction in NT-proBNP levels in blood without any undesired effect on left ventricular parameters. In addition, benefits in NYHA functional class and aerobic capacity have been also confirmed in this study. In 2005, Levinger et al. (Levinger et al. 2005) also proved it safe on left ventricular structure and function. Thus, if RT is used wisely and under suitable supervision, the patient will be able to perform daily life activities without placing high load on the heart.

Reduced aerobic capacity and deteriorated muscle strength are characterized in CHF patients as determinants of physical disability. Several studies have been conducted to show the effectiveness of RT in CHF patients and to reveal the extra benefits by combining resistance exercises to aerobic exercise. Harrington et al. (Harrington et al. 1997) have previously confirmed the muscle dysfunction and reported a reduced muscular function both quantitatively

and qualitatively. Also, PU et al. (Pu et al. 2001) confirmed the role of peripheral dysfunction in limiting exercise capacity in CHF patients after they had compared women with CHF to normal age-matched peers. Besides, they have reported improvements in muscular strength and endurance, and functional capacity after a high-intensity progressive resistance exercise. They also assured that these improvements are related to peripheral characteristics and not to cardiac function. Palevo et al. (Palevo et al. 2009) showed that RT alone was able to elicit beneficial effects on both physical activity and LV function. The former was confirmed through the 6MWT and muscular strength assessment. Gary et al. (Gary et al. 2011) examined a 12-week home-based combined exercise program on CHF patients. They reported an improvement in both upper and lower body muscle strength and QoL, which was assessed by using the Minnesota living with heart failure questionnaire (MLWHFQ) and Epworth Sleepiness Scale.

Furthermore, Maiorana et al. (Maiorana et al. 2011) studied the effect of exercise training on the arterial remodeling in CHF patients. They also compared between resistance and AT with respect to several measures. They found that both AT and RT increased peak oxygen consumption and brachial artery diameter, however only RT decreased wall thickness and brachial wall to lumen ratio. Thus, RT is more favorable in affecting systemic vascular remodeling. This effect was considered as systemic since in their study, Maiorana and his colleagues assessed for brachial artery remodeling effect in patients who had their lower limbs preponderantly trained.

It is very interesting that strength training, after being examined on healthy subjects, have had beneficial effects on inspiratory muscle strength. It was shown to produce an increase in the trans-diaphragmatic pressure, a strengthening trigger for the diaphragm muscles.

Two recent meta-analysis have pooled the importance of RT execution in HF subjects on different levels, i.e. peak VO₂, QoL and 6MWT (Giuliano et al. 2016; Jewiss, Ostman, and Smart 2016) as well as improvement in skeletal muscle strength (Giuliano et al. 2016). RT is now highly recommended by guidelines (Bjarnason-Wehrens et al. 2004; Williams et al. 2007) to be used in patients with cardiac diseases. In addition, it has also been recommended by the U.S. Department of Health and Human Services since 2008. Note that it is not yet accepted to substitute AT with RT but it might be feasible to be used as an alternative in patients with limitations against aerobic exercise (Jankowska et al. 2008).

RT of the upper and lower extremities is more favorable, and each resistance/strength exercise must be performed slowly to have significant and desired effects (Giuliano et al. 2016). Several studies that supported strength exercise training and proved it safe in CHF, used different ways and percentages to determine the maximum training intensity (Pu et al. 2001; Levinger et al. 2005; Feiereisen et al. 2007; Beckers et al. 2008). Most importantly is taking into consideration the patient's capabilities at performing the exercise, but higher intensity percentages might have more improvements at the level of skeletal muscles.

5.4- Combined Aerobic and Inspiratory muscles Training

Both AIT and IMT have been proved efficient and safe for CHF patients. As mentioned previously in this report, many trials were done in order to prove this efficacy at different levels of cardiorespiratory and skeletal function as well as QoL. Researchers hypothesized that the combination of these two types of exercise might exert additional benefits. Thus, different trials were conducted to test the effect of this combination. A small clinical trial conducted by Winkelmann et al. (Winkelmann et al. 2009) has shown that a training period of 12 weeks of IMT combined with AIT produced additional improvements in maximal inspiratory pressure (110% vs. 72%), aerobic capacity VO₂peak (49% vs 21%), and ventilatory efficiency over AIT only. Also, the distance walked in 6MWT and QoL scores improved similarly in the 2 groups. The additional increment in the main outcome measure VO₂peak (about 19%) is important, given the fact that IMT was added to AIT as an effective intervention to improve peak exercise capacity (Winkelmann et al. 2009). Thus, the addition of IMT to AE results in improvement in cardiorespiratory responses to exercise in selected patients with CHF and IMW.

Another more recent study is the Vent-HeFT multicenter randomized trial that was conducted by Adamopoulos and his colleagues (Adamopoulos et al. 2014). They recruited 43 patients in 12 weeks of AT/Sham or a combined program AT/IMT. They showed that the addition of IMT to AIT elicited additional benefits in inspiratory muscle endurance, QoL and dyspnea sensation in CHF patients. They also found improvements in C-reactive protein and N-terminal-proBNP levels, which are considered serum biomarkers in CHF patients. These findings advocate for application of IMT in cardiac rehabilitation programs (Adamopoulos et al. 2014).

5.5- Combined Aerobic, Resistance and Inspiratory muscle Training

Considering all the benefits mentioned above and the additional effects of exercise combination, Laoutaris et al. (Laoutaris et al. 2013) were the first to study the effects of adding RT to AT and IMT. They included patients with CHF and examined a 12-week exercise training program constituted of two groups, and patients were allocated randomly to one of two groups; AT+IMT+RT (ARIS) against AT only. Both groups were proved safe. However, they didn't find any additional improvements in cardiac function and structure over the AT group. Compared to AT, ARIS resulted in much more improvements in inspiratory muscle endurance, exercise capacity, skeletal muscle function and patients' QoL. Accordingly, they proposed that the additional benefit in exercise capacity was attributed to the improved quadriceps and inspiratory muscle functions.

This was the only study that combined the three training modalities together, and compared it to aerobic training group without comparing it to a control group or resistance training group. In addition, Laoutaris and his colleagues used continuous AT, however, and as mentioned previously in this report, researchers have proved that AIT was better than continuous training (Wisløff et al. 2007).

Chapter 6: Review

As a result of the studies presented in the literature part, it came clear that a multimodal approach is required to treat chronic heart failure patients. This approach is a combination of non-pharmacological and pharmacological treatments.

In the following, we will focus on the non-pharmacological management, especially the inspiratory muscle training and aerobic interval training by summarizing the published research in order to find the best mode of training. For this purpose, we have conducted two systematic reviews and Meta-analyses to identify new recommendations for the best protocol in terms of: intensity, frequency, duration, and type of inspiratory and aerobic training in order to validate our intervention protocol.

Therefore, The exercise protocol training in our study was adapted after making a systematic Review and Meta-analyses to analyze the evidence based practice of IMT (Review 6.1) and AT (Review 6.2) in HF patients by highlighting the different parameters from which practical recommendations were concluded.

6.1- Best Mode of Inspiratory Muscle Training in Heart Failure Patients: A Systematic Review and Meta-Analysis

For updates

Review

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Best mode of inspiratory muscle training in heart failure patients: a systematic review and meta-analysis

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Abstract

Objectives: The objective of this study was to evaluate the effects of inspiratory muscle training on inspiratory muscle strength, functional capacity and dyspnoea for patients with chronic heart failure, by summarising the published research on the effects of inspiratory muscle training. To identify the best mode of intervention in terms of: the load of maximal inspiratory pressure; the frequency of sessions; and the total duration of intervention.

Methods: A relevant literature research using the PubMed database, Cochrane and references of published studies, from 1998 to 2016, was conducted. Out of 65 randomised controlled trials, seven were considered as potentially relevant and were retrieved for detailed analysis. The methodological quality of each randomised controlled trial was rated using the physiotherapy evidence database scale.

Results: The included seven studies contained data on 203 patients. Typical training protocols involved training three, six or seven times per week with intensity ranging from 30% to 60% and for a duration ranging from 6 to 12 weeks. Maximal inspiratory pressure, walking distance and dyspnoea were improved in all studies and especially in those who set a load of 60% in their maximal inspiratory pressure, and have trained patients six times per week for 12 weeks.

Conclusion: In chronic heart failure patients, inspiratory muscle training results in a marked improvement in inspiratory muscle strength, walking distance and dyspnoea, notably when training patients at 60% of maximal inspiratory pressure, six times per week and for 12 weeks. A small number of studies and heterogeneity among studies may limit the findings of the present study.

Keywords

Chronic heart failure, inspiratory muscle training, dyspnoea, quality of life, maximal inspiratory pressure

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Introduction

Chronic heart failure (CHF) patients often suffer from increased work of breathing and dyspnoea during physical activity.¹ First, the researchers considered haemodynamic disturbances as a major determinant of these symptoms, because of the well-known ability of the ineffective heart pump to increase pulmonary and systemic venous pressures, and to reduce cardiac output.

However, this hypothesis has been rejected and shifted towards the muscle hypothesis, which suggests abnormalities of skeletal muscle as the source of CHF symptoms,² due to the fact that the main contributor to exercise intolerance is musculoskeletal pathology,³ associated with an increased ergoreflex: a muscle reflex stimulated by work,⁴ mitochondrial

abnormalities, decreased oxidative enzyme activities, muscle atrophy, in addition to an increase in pro-inflammatory cytokines and markers of oxidative stress.

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It is therefore likely that these changes are not limited to the musculature of the lower limbs, but are widespread and may affect respiratory muscles. Observations showed a significantly lower percentage of type II and type IIa muscle fibres and a greater percentage of type I muscle fibres in the costal diaphragm, fibre atrophy and abnormalities in ventilation and/or perfusion.⁵

It has also been suggested that the symptoms of fatigue and dyspnoea usually reported in CHF patients may be partially attributed to decreased strength and endurance of the inspiratory muscles,⁶ assessed, respectively, by measuring maximal inspiratory pressure (PI_{max}) and by the ability to sustain pressure in time.^{7,8}

A multimodal approach is required to treat CHF patients; it involves a combination of non-pharmacological and pharmacological treatment.⁶ In this review, we will emphasise the non-pharmacological management and especially inspiratory muscle training (IMT) because it has been shown to benefit patients by an improvement in inspiratory muscle strength, inspiratory muscle endurance and quality of life, in addition to a greater sense of wellbeing, and a better functional capacity. From a therapeutic point of view, the beneficial effects of selective respiratory muscle training, in improving respiratory muscle strength and overall aerobic capacity in CHF, were first demonstrated by Mancini et al. with further data being published over the past decade.⁹

In fact, IMT uses progressive resistance to provide loading to the inspiratory muscles to achieve a strengthening effect.¹⁰ The devices used have evolved considerably, and they are: the resistive type of muscle trainer, the pressure threshold muscle trainer and the isocapnia hyperpnoea manoeuvre. Actually, the most commonly used is the second one, which is a commercially available spring-loaded threshold valve that can easily be adjusted to provide incremental resistance.¹¹

Moreover, all studies published used different protocols of training in terms of the load of PI_{max} and the duration of intervention. So we have variability in outcomes. So far, the best mode of training for CHF patients remains unclear.

Accordingly, the aim of this study was to shed light on the positive effect of IMT in patients with CHF by summarising the published research on the effects of IMT and subsequently to identify the best mode of intervention in terms of: (a) the load of PI_{max} ; (b) the frequency of sessions; and (c) the total duration of intervention.

Methods

Literature search

A literature search of published studies, from 1998 to 2016, was conducted. We used standard research

strategies involving the querying of two online databases (PubMed database and Cochrane), followed by evaluation of the bibliographies of published studies related to this subject for the identification of related relevant publications. We also use back-tracking to find earlier relevant sources, and forward-tracking in Web of Science to find the literature that refers to our subject. As a starting point for this study, we developed a series of key search terms in order to outline the scope of the literature to include in the review. So, we used the following research term categories in combination: 'congestive heart failure', 'cardiac failure', 'CHF', 'IMT', 'respiratory muscle training', 'exercise training' and 'maximal inspiratory pressure'. All clinical trials published in English were included. The second step for limiting and ameliorating the first research was to include only those articles on patients with 'heart failure' or 'congestive heart failure'.

We have screened all titles and abstracts and made decisions regarding potential eligibility after full-text review.

Eligibility criteria

We included all randomised controlled trials (RCTs) assessing IMT in the rehabilitation of CHF. We included studies that compared IMT to control groups (placebo IMT: the same regimen as the IMT group but with minimum inspiratory load or with no training effects or any other intervention such as an education programme) and that evaluate the following outcome measures: PI_{max} , distance walked in the 6-minute walking test (6MWT) or 12-minute walking test (12MWT) and dyspnoea.

Some studies were excluded based on the examination of the title or abstract, and other exclusion criteria were as follows: (a) studies that include subjects other than CHF patients; (b) studies that focus on general training and not IMT; (c) studies with the absence of a control group; (d) studies with intervention duration less than 6 weeks; and (e) non-randomised controlled trials and animal-based studies. Actually, seven studies were considered as potentially relevant and were retrieved for detailed analysis (Figure 1).

Data extraction

Demographic data such as age, gender, New York Heart Association (NYHA) functional class, and ejection fraction (EF) were recorded to characterise the trials and to determine the homogeneity of participants among groups and trials. The target intensity of PI_{max} , duration, frequency, the total period of time for the exercise training programme and the nature of the control group were also recorded.

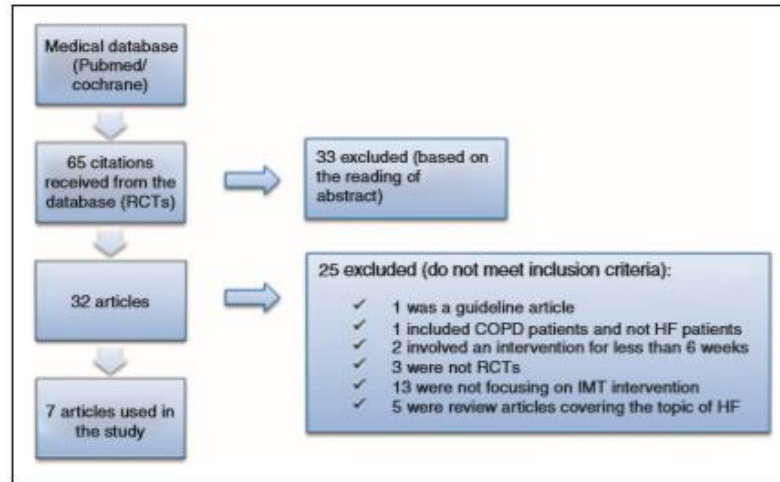


Figure 1. Flow chart for identifying eligible articles.

COPD: chronic obstructive pulmonary disease; HF: heart failure; RCT: randomised controlled trial; IMT: inspiratory muscle training.

Data analysis

To calculate the degree of the intervention effects, we determined the effect sizes for the following outcome variables: inspiratory muscle strength, walking test distance and dyspnoea. The effect size (d) of treatment (pre vs. post or experimental vs. control) was calculated using equation (1):

$$d = \frac{\mu_e - \mu_c}{S_p} \quad (1)$$

where d is Cohen's effect size, μ_e is the mean of the experimental group, μ_c is the mean of the control group, and S_p is the pooled estimate of variance calculated as follows:

$$S_{\text{pool}} = \sqrt{\frac{(n_1 - 1)S_1^2 + (n_2 - 1)S_2^2}{n_1 + n_2 - 2}} \quad (2)$$

where n_1 and n_2 are pre and post-intervention sample sizes, or experimental versus control group sample sizes; S_1 and S_2 are pre and post-intervention standard deviations, or experimental versus control group standard deviations. According to Cohen, an effect size of 0.2 represents a small effect, 0.5 represents a moderate effect and 0.8 represents a large effect.¹²

For meta-analysis, calculations were done using a random effect method. The level of significance was set at $P < 0.05$. Statistical heterogeneity of the treatment effects among studies was assessed using Cochran's Q test and the inconsistency I^2 test, in

which values above 25% and 50% were considered indicative of moderate and high heterogeneity, respectively.¹ All analyses were conducted using the software comprehensive meta-analysis 'V3'.

Methodological quality

The physiotherapy evidence database (PEDro) is used in order to estimate the value of the methodological quality of each RCT.¹³ It is an instrument utilised to assess the methodological quality of RCTs in physical therapy and exercise studies. Eleven items (see Table 1) on the PEDro scale were derived from a Delphi consensus procedure.¹⁴ Its scale scores can range from 0 to 10, with 10 associated with a better methodological quality. A total score is derived from the summation of responses to items 2–11, and item 1 relates to external validity. The reliability of this scale was evaluated with acceptable good results in interclass correlation coefficients 0.56–0.91.^{13,15}

Results

Methodological quality

PEDro scores ranged from 5 to 8 points, with a mean score of 6.14 (Table 1). A high quality of the chosen trials has been assured because all of the selected studies scored 5 or more. Moreover, all of the studies specified the eligibility criteria, and the subjects were randomly allocated to groups except in two;^{16,17} all were blinded to allocation and showed the similarities at baseline. In fact, one of

Table 1. Methodological classification of studies using the PEDro scale and clinical characteristics of patients randomised to training group (TG) or control group (CG) in the different selected studies.

First author	PEDro scale	N	Mean age	EF	NYHA	PI _{max} (cmH ₂ O)
Johnson, 1998 ¹⁸	6	TG = 8	70 ± 4.6		12 in II and 6 in III	70 ± 33
		CG = 8	63.4 ± 4.5			84 ± 18
Weiner, 1999 ²⁰	6	TG = 10	66 ± 4	24.7 ± 1.6	II–III	46.5 ± 4.7
		CG = 10	63 ± 4	22.9 ± 2.4		50.7 ± 4.2
Laoutaris, 2004 ¹⁶	5	TG = 20	57.6 ± 2.3	23.4 ± 1.5	60% II and 40% III	82.8 ± 5.7
		CG = 15	60 ± 2.6	25.7 ± 2.1		47% II and 53% III
Dall'Ago, 2006 ⁷	7	TG = 16	54 ± 33	39 ± 3		60.2 ± 9
		CG = 16	58 ± 2	38 ± 3		58.1 ± 1
Laoutaris, 2007 ¹⁷	5	TG = 15	53 ± 2	28 ± 3	10 in II and 5 in III	79.8 ± 4.7
		CG = 23	59 ± 2	27 ± 2		12 in II and 11 in III
Padula, 2009 ¹⁹	6	TG = 15	76 (51–89)	30	5 in II and 7 in III	48 ± 25
		CG = 17	73 (32–95)	33		9 in II and 6 in III
Bosnak-Guclu, 2011 ⁸	8	TG = 16	69.50 ± 7.96	33.43 ± 7.23	11 in II and 5 in III	62.00 ± 33.57
		CG = 14	65.71 ± 10.52	36.11 ± 7.62		9 in II and 5 in III

EF: ejection fraction; NYHA, New York Heart Association; PI_{max}: maximal inspiratory pressure.

the trials had blinded therapists: one of them had blinded participants⁵ and two had blinded assessors.^{4,5} All trials had retention rates of 85% or greater and none met the intention-to-treat analysis criteria. Statistical analysis was applied to group differences in all the studies as well as reporting point estimates and measurements of variability. None of the studies was excluded on the basis of their methodological quality.

The initial research yielded 65 RCTs. Of these, 33 studies were excluded based on the examination of the title or abstract, and 32 were considered as potentially relevant and retrieved for detailed analysis.

An additional 25 studies were excluded for different reasons (Figure 1). The results of each review have been favourable regarding many of the pathophysiological manifestations of CHF and the mechanisms and effects of IMT.

Overall, a total of seven articles with 203 patients were included in the systematic review.

The sample size for all studies was small, with an average of 29 and the mean age of subjects ranged from 53 to 76 years, which means that all studies focused on middle-aged and older adults because CHF affects older people in particular.

Concerning systolic dysfunction, EF was less than 40% and this is obvious as the main abnormality in CHF is impaired left ventricular function and a low cardiac output.

In addition, PI_{max} values ranged from 48 to 82 cmH₂O and this has been arbitrarily defined by respiratory muscle weakness that is prevalent in CHF patients.

IMT methods

In this study, two IMT methods were analysed: inspiratory resistive training and threshold loading. The pressure threshold device uses a spring-loaded one-way valve that places consistent resistance on the inspiratory muscles.

However, resistive training provides an endurance training effect as the patient is exercising at a percentage of sustained PI_{max} (SMIP) (pressure–time product).

The mode of IMT in most studies was threshold training (Philips Respironics, Andover, MA, USA) at an intensity ranging from 30% to 60% of PI_{max}, duration from 15 to 30 minutes for an average of 10–12 weeks and 6–7 days per week. In the literature, two studies performed by the same investigators^{16,17} had administered IMT using the test of incremental respiratory endurance (TIRE) by means of the TRAINAIR device (Project Electronics Ltd., Kent, UK) at 60% of PI_{max}/SMIP with an increasing work to rest ratio for 20 to 30 minutes, three times per week. TRAINAIR IMT was performed to the point of exhaustion.^{16,17}

Although all studies used different protocols of training in terms of PI_{max}, frequency and duration, statistically significant increases in PI_{max} values were detected in all studies. Almost all of them showed improvements in dyspnoea and walking test (Table 2).

Meta-analysis

Figures 2, 3 and 4 show that there was a significant improvement in PI_{max}, walking test and dyspnoea when comparing IMT versus all control groups

Table 2. Study measurements and outcomes of different studies of inspiratory muscle training in heart failure patients randomly assigned to training group (TG) or control group (CG).

First author	N	Load	Mode of the intervention (device, duration)	Study measurements	Study outcomes used for this review
Johnson, 1998 ¹⁸	TG = 8 CG = 8	30% P _I max 15% P _I max	Threshold for 8 weeks (15 min, 2 ^{*/} d, 7 ^{*/} wk)	P _I max, exercise duration, 100 m walking test, QOL	Treatment group: • P _I max (cmH ₂ O): +25.4 (11.2) • Treadmill test time: +152 s (144) [†]
Weiner, 1999 ²⁰	TG = 10 CG = 10	60% P _I max No load	Threshold for 12 weeks (30 min, 6 ^{*/} wk)	P _I max, PE _I max, IME, PFTs, peak VO ₂ , 12MWT, dyspnoea	Treatment group: • P _I max (cmH ₂ O): 46.5 (4.7) to 63.6 (4) [‡] • 12MWT (m): 458 (29) to 562 (32) [‡] • dyspnoea index: 1.7 (0.2) to 2.7 (0.2) [‡]
Laoutaris, 2004 ¹⁶	TG = 20 CG = 15	60% SMIP 15% SMIP	TRAINAIR for 10 weeks (3 ^{*/} wk for an uncertain duration/ training to exhaustion)	P _I max, SMIP, peak VO ₂ , 6MWT, dyspnoea, QOL	Treatment group: • P _I max (cm H ₂ O): 82.8 (5.7) to 111.9 (6.8) ^Δ • 6MWD (m): 367.1 (22.3) to 433.4 (16.9) ^Δ • Borg dyspnoea scale after 6-min walking test: 10.5 (0.7) to 9 (0.5) ^Δ
Dall'Ago, 2006 ⁷	TG = 16 CG = 16	30% P _I max No load	Threshold for 12 weeks (30 min, 7 ^{*/} wk)	P _I max, IME, 6MWT, dyspnoea, QOL, VO ₂	Treatment group: • P _I max (%P _I max): 57 (9) to 66 (7) [‡] • 6MWD (m): 449 (17) to 550 (17) [‡] • Dyspnoea during 6MWT: 3.7(2) to 1.5 (1.4) [‡] • VO ₂ : 17% increase
Laoutaris, 2007 ¹⁷	TG = 15 CG = 23	60% SMIP 15% SMIP	TRAINAIR for 10 weeks (3 ^{*/} wk for an uncertain duration/ training to exhaustion)	P _I max, SMIP, PFTs, peak VO ₂ , 6MWT, dyspnoea	High intensity group: • P _I max (cmH ₂ O): 79.8 (4.7) to 105.1(4.9) ^Δ • 6MWD (m): 378.2 (10.4) to 404.3 (11.9) [‡] • Dyspnoea: Borg scale 9.2 (0.4) to 8.0 (0.4) [‡]
Padula, 2009 ¹⁹	TG = 15 CG = 17	30% of P _I max Education on self-efficacy	Threshold for 12 weeks (10–20 min, 7 ^{*/} wk)	P _I max, dyspnoea, QOL	Treatment group: • P _I max (cmH ₂ O): 48 (25) to 78 (37) ^Δ • Decreased dyspnoea (Borg scale) [†]
Bosnak-Guculu, 2011 ⁸	TG = 16 CG = 14	40% P _I max 15% P _I max	Threshold for 6 weeks (30 min, 7 ^{*/} wk)	P _I max, PE _I max, 6MWT, dyspnoea, PFTs, depression, QOL	Treatment group: • P _I max (cmH ₂ O): 62 (33) to 97 (32) ^{‡*} • 6MWD(m): 418(123) to 478(131) ^{Δ*} • Δ Borg Dyspnoea scale: 2.42(1.7) to 1.42(1.3) [†]

[†]: < 0.05; [‡]: < 0.01; ^Δ: < 0.001; ^{*}: between groups; each value in the table was expressed as mean (standard deviation).

6MWT: 6-minute walking test; 6MWD: 6-minute walking distance; 12MWT: 12-minute walking test; HR: heart rate; IME: inspiratory muscle endurance; IMT: inspiratory muscle training; PE_Imax: maximal expiratory pressure; P_Imax: maximal inspiratory pressure; PFTs: pulmonary function tests; QOL: quality of life; SMIP: sustained maximal inspiratory pressure.

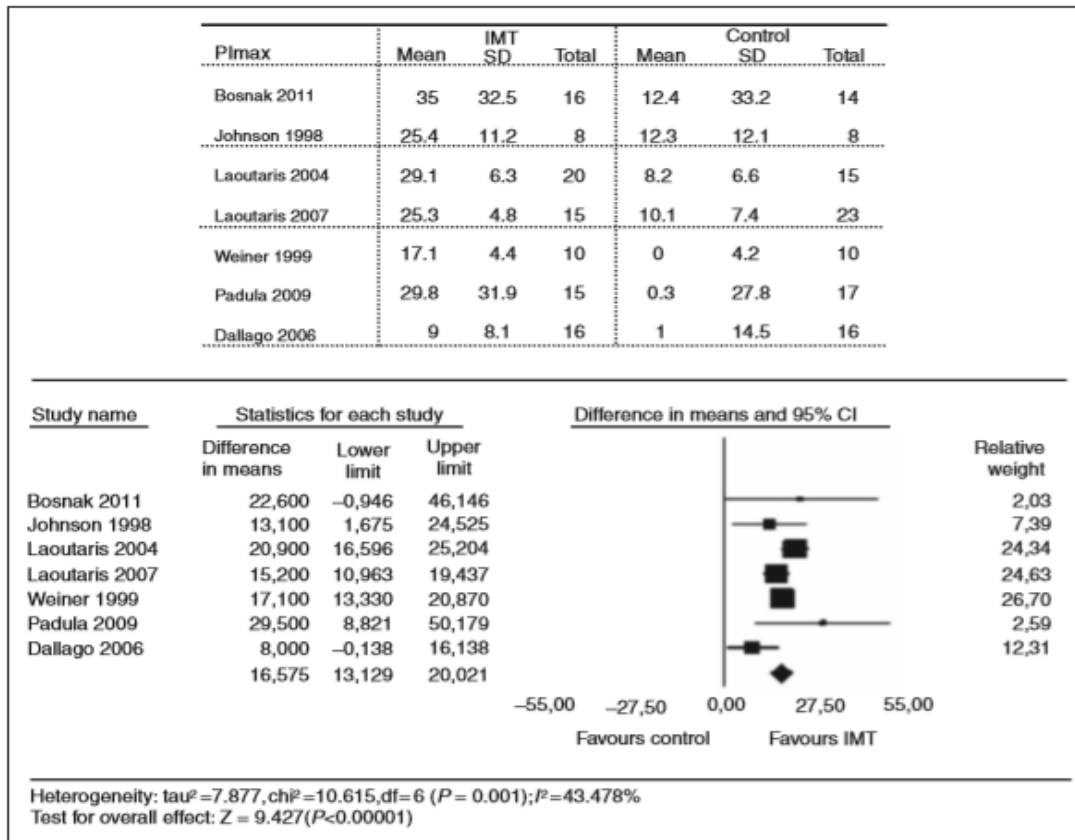


Figure 2. Maximal inspiratory pressure for treatment with inspiratory muscle training versus control groups. CI: confidence interval; IMT: inspiratory muscle training; SD: standard deviation.

($P < 0.00001$, $P = 0.001$ and $P < 0.00001$, respectively). The chi-square test for heterogeneity was significant for PI_{max} ($P = 0.001$) and for dyspnoea and Walking test ($P < 0.00001$). The I^2 value was approximately 43% for PI_{max}, 96% for the walking test and 85% for dyspnoea. These quantitative results suggest there was study variability (i.e. heterogeneity).

Outcomes of the different categories

We have divided the studies into four programmes according to their load of PI_{max} and duration.

In fact, we have considered a high intensity programme for those who provide training of more than 50% PI_{max}, and a low intensity programme for those who provide training of less than 50% PI_{max}. Moreover, low duration was attributed to 8 weeks maximum, and high duration to 12 weeks. And as for the 10 weeks training, it is considered as moderate duration

because it is performed only three times a week (Table 3).

PI_{max}

For PI_{max}, there was a remarkable improvement in all studies discussed when comparing IMT versus all control groups (not shown here). However, a greater benefit was shown for a high intensity-high duration programme (4.088 cmH₂O) when compared to the three other programmes (3.132 for high intensity-moderate duration, 0.929 for low intensity-high duration and 2.27 for low intensity-low duration) (Figure 5).

Dyspnoea

As for dyspnoea, the most marked improvement was also for the high intensity-high duration

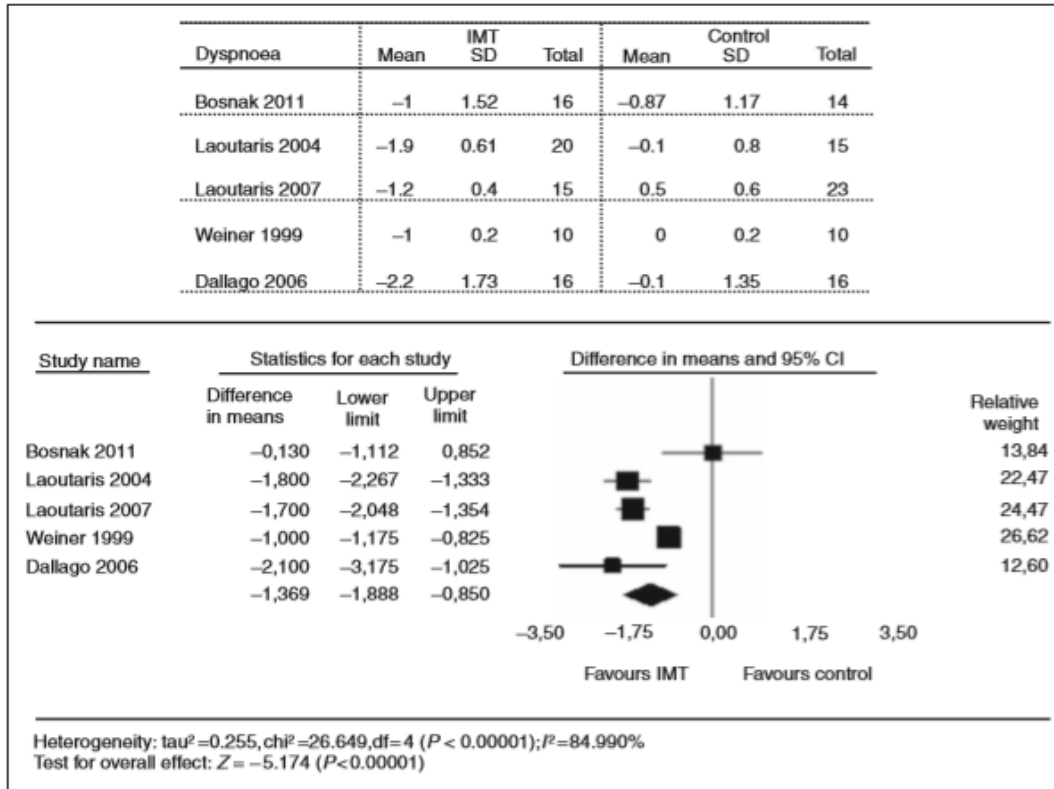


Figure 3. Dyspnoea with inspiratory muscle training versus control groups. CI: confidence interval; IMT: inspiratory muscle training; SD: standard deviation.

programme (-5) whereas less improvement was shown for the other programmes (-3.166 for high intensity-moderate duration, -1.427 for low intensity-high duration and -0.139 for low intensity-low duration) (Figure 6).

Walking tests

With respect to the distance covered in the walking tests (6MWT and 12MWT), it was improved in all studies but with additional benefits for the low intensity-high duration programme (4.514 m), while it was improved for 0.907 m in the high intensity-high duration programme, 3.217 m for the high intensity-moderate training programme and 0.36 m for the low intensity-low duration programme (Figure 7).

Discussion

Meta-analysis demonstrated that IMT results have marked an improvement in PI_{max} , dyspnoea and walking tests, but they were varying between studies

depending on the load of PI_{max} adjusted, the frequency, and the duration of the intervention.

Low intensity-low/high duration

Starting with the two low intensity programmes, in the studies by Johnson¹⁸ and Padula et al.,¹⁹ the improvement in PI_{max} was not important as much as it was in other studies because maybe a higher percentage than 30% was required for these patients. In addition, we must consider the possibility that the sham training performed by the control group had a training effect which caused no significant difference between both groups.¹⁸

According to the study by Bosnak-Guclu et al. (2011)⁸ (low intensity-low duration), the improvement in all parameters was small when compared to other studies, and this was due to the short duration of intervention and the low intensity of training.

Moreover, we noticed that Dall'Ago et al.,⁷ (low intensity-high duration) who had performed IMT on

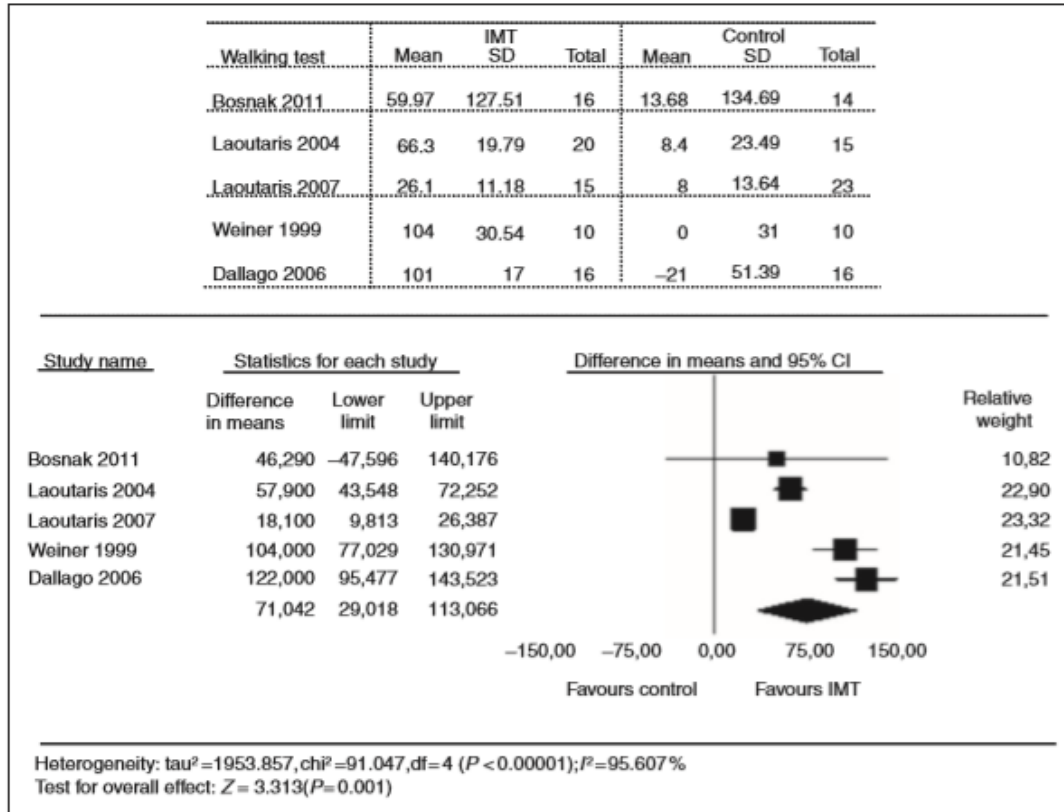


Figure 4. Distance walked in the walking test with inspiratory muscle training versus control groups. CI: confidence interval; IMT: inspiratory muscle training; SD: standard deviation.

Table 3. Distribution of the studies into different programmes.

Programme	First author	Load	Duration
High intensity–moderate duration	Laoutaris, 2004 ¹⁶ Laoutaris, 2007 ¹⁷	60%	10 weeks, 3 times/week
High intensity–high duration	Weiner, 1999 ²⁰	60%	12 weeks, 6 times/week
Low intensity–low duration	Johnson, 1998 ¹⁸ Bosnak-Guclu, 2011 ⁸	30% 40%	8 weeks, 7 times/week 6 weeks, 7 times/week
Low intensity–high duration	Dall’Ago, 2006 ⁷ Padula, 2009 ¹⁹	30%	12 weeks, 7 times/week

patients with inspiratory muscle weakness for 12 weeks, and had a control group that received placebo IMT without load inspiratory, showed greater gains from the distance in the 6MWT. This might be caused by the greater degree of impairment of the patients in these trials, the longer duration of the intervention, and the fact that we had a comparison between the IMT group and the control group that received the placebo IMT without inspiratory load.

High intensity–moderate/high duration

For those who have set a load of 60% PI_{max}, Weiner et al.²⁰ has shown the best results in terms of PI_{max} and dyspnoea, and this was related to the long duration of intervention and the frequency of sessions that the authors had taken.

However, Weiner et al.²⁰ did not find any increase in the aerobic capacity when compared to Laoutaris and

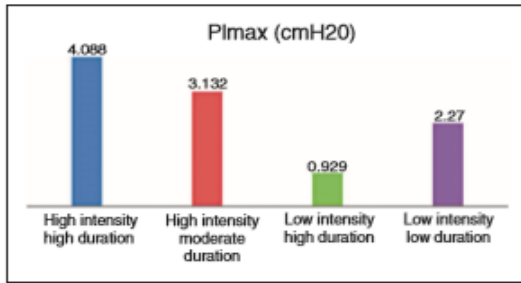


Figure 5. Improvement of maximal inspiratory pressure (cmH₂O) in the four programmes.

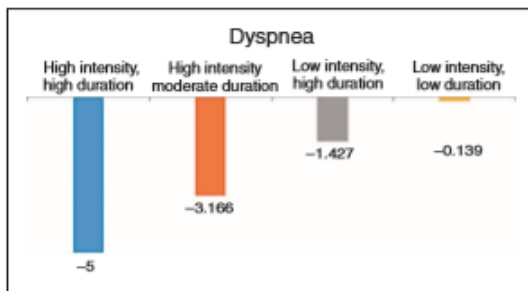


Figure 6. Improvement of dyspnoea (Borg scale 6–20) in the four programmes.

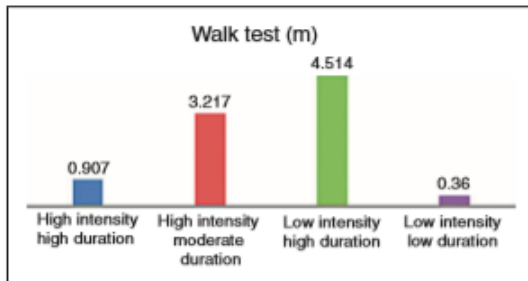


Figure 7. Improvement of the distance covered in the walking test (m) in the four programmes.

colleagues^{16,17} as evidenced by the unchanged peak oxygen consumption (17.3 ± 0.9 to 19.4 ± 0.4) ml/kg/minute versus (17.3 ± 0.9 to 19.4 ± 0.4) ml/kg/minute in Laoutaris and colleagues.^{16,17}

This may be related to the different training devices used. In fact, when IMT is performed using a mechanical pressure-threshold trainer (e.g. THRESHOLD), patients are required abruptly to develop a pressure above a fixed threshold value (%PI_{max}) and not to ‘sustain’ pressure in

time, because the opening valve closes at pressures below the set threshold usually at the mid to end inspiratory range, inhibiting patients from training at the full inspiratory range (especially at higher training intensities). However, IMT using electronic systems of resistive loading (e.g. TRAINAIR) with pressure-time profiles may provide training at %PI_{max}/SMIP, enabling patients to ‘sustain’ pressure in time and train to the end-inspiratory range even at high training intensities. So, increasing the endurance of respiratory muscles is equally if not more important than increasing the strength because SMIP was demonstrated to be more significantly depressed compared to PI_{max} in CHF.²¹

We observed that IMT carried out for 12 weeks improved PI_{max} more than training carried out for 6–8 weeks when compared to controls, and according to Weiner et al.,²⁰ six times per week of training was the most desirable.

Therefore, training for 12 weeks and six times per week was proved to be the best protocol.

Finally, the studies included samples of different sizes for short/long training duration, utilisation of relatively low/high intensity IMT, treated/untreated control groups, inclusion of patients with/without inspiratory muscle weakness, blinded/unblinded studies, etc., but despite the variety of studies, gains were higher in the high-intensity training group. So, we can consider that 60% is the best intensity to apply.

Overall, six sessions per week with an IMT set at 60% PI_{max}, for 30 minutes and for 12 weeks is the optimal programme so far.

Limitations

The improvement identified in the control group was the result of the training effect performed by the control group, because four studies have used the threshold loading of 15% PI_{max} as a sham therapy.

Thus, all studies should be designed in a way that the control group performs without any inspiratory load.

In addition, studies included a variety of patients, some of them suffered from inspiratory muscle weakness and the others did not. Therefore, this fact can contribute to a risk of bias because the weakness of respiratory muscles has contributed to exercise intolerance and could have influenced the results of the training.

Moreover, this review must include a greater number of RCTs in order to obtain a more generalised conclusion that covers the effect of IMT on several outcomes.

The heterogeneity found in this meta-analysis can be attributed to between-study differences in patient selection, study design, clinical setting and supervised and non-supervised IMT.

Despite these restrictions, it is still useful to explore sources of heterogeneity and incorporate it explicitly in

the analysis in order to explain it and remove it in further studies. Besides, selecting no workloads as a sham therapy will/would be better while investigating the effects of IMT to avoid the training effect.

Conclusion

In conclusion, this study has provided evidence that training the inspiratory muscles at 60% PI_{max} , six times per week for 12 weeks is the best protocol used in order to improve inspiratory muscle strength, walking distance and dyspnoea for patients with CHF. These positive effects advocate for application of IMT as a safe and effective intervention in cardiac rehabilitation programmes.

Moreover, healthcare professionals should receive more guidance in order to put a specific treatment programme for each single patient into practice, learn IMT theory and use it properly.

For this reason, a digital training and decision support system for exercise prescription in cardiovascular disease patients was recently developed: the European Association of Preventive Cardiology Exercise Prescription in Everyday Practice and Rehabilitative Training (EXPERT) tool.

Author contribution

Zahra Sadek and Charifa Awada contributed to the conception and design of the work. Ali Salami contributed to the analysis and interpretation of data for the work. Zahra Sadek and Charifa Awada drafted the manuscript. Wissam H Joumaa, Wiam Ramadan and Said Ahmaidi critically revised the manuscript. All authors gave final approval and agree to be accountable for all aspects of the work ensuring integrity and accuracy.

Declaration of conflicting interests

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6.2- Recommendations for Best protocol of aerobic training: type, intensity, frequency and duration in chronic heart failure patients. A Systematic review and meta-analysis

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ABSTRACT

Objective: The aim of this study is to determine whether aerobic exercise training: intensity, duration, and type (interval vs continuous) results in different VO₂ peak values, left ventricle dysfunction, and quality of life in patients with chronic heart failure .

Methods: A search was conducted on various electronic databases, including Cochrane database, Web of Science and reviews related to this subject (from 2002 till 2017) on exercise-based rehabilitation trials in heart failure, using the search terms “heart failure”, “continuous training versus interval training”, “effects of aerobic training”, “aerobic exercise” and “peak VO₂”.

Results: Seven studies reported ejection fraction, VO₂ peak consumption and quality of life data (n= 210); except for Wisloff et al., that didn't work on the patients' quality of life. All the trials have shown significant improvement after performing Aerobic exercise for limited duration (38 minutes), period (12 weeks), and specific intensity (high intensity: 95% of VO₂ peak) with the superiority of interval over continuous training with respect to the VO₂ peak data.

Conclusion: This systematic review suggested that Aerobic high interval training for a period of 12 weeks, 3 times per week and for 38 minutes each time, is the perfect protocol for chronic heart failure patient.

Key Words: Chronic heart failure, Aerobic training, Vo₂ PEAK, Quality of life, Ejection fraction

INTRODUCTION

It is generally recognized that heart failure (HF) incidence rates are still increasing on a large-scale, especially in an aging society (1). The clinical syndrome of HF is considered as a growing epidemic disease that causes a significant socio-economic burden all over the world (2). Despite considerable progress in the management of patients with HF, mortality and morbidity remain a major healthcare concern and frequent hospital admissions jeopardize daily life and social activities (2). Exercise intolerance and dyspnea are the major symptoms of patients with chronic heart failure (CHF), in association with the poor quality of life (QoL).

Prior to 1980, heart failure was a contraindication to exercise. This concept has been abandoned and many randomized studies have demonstrated that an adapted physical activity program leads to an improvement in exercise tolerance, which is an important prognosis marker for patients with HF (3). Therefore, exercise training is recommended for HF patients that may partially reverse these changes, improve or maintain functional capacity, restore QoL in patients with moderate to severe CHF and encompass a central component of cardiac rehabilitation (2) in addition to optimal medical treatment. Different training modalities are available to target the problems that face HF patients. It is essential to tailor the prescribed exercise regimen, so that both efficiency and safety are guaranteed (4). Current guidelines for the treatment and management of HF firmly recommend aerobic training for all stable outpatients with CHF (4). Previously, the most commonly recommended form of exercise for both clinical and healthy populations was the continuous aerobic training (CAT) for 30 minutes (mins) a day at least, prescribed five to seven days per week (5). However, the highly recommended form nowadays is the aerobic interval training (AIT) due to its demonstrated efficiency and safety. As such, recent data have already shown that AIT is superior to moderate continuous training, based on the improvements observed in HF patients (6).

Despite the availability of randomized trials examining AIT versus CAT exercise in patients with CHF, to date there are no systematic reviews available in this population comparing the positive effects of different exercise programs on cardiac function, quality of life and aerobic capacity in CHF patients. Indeed, it is not clear which modality is the best. Thus, in order to assess the effectiveness of different exercise training modalities, only the studies where HF had been defined as a systematic review were considered and meta-analysis was performed.

METHODS

Data Sources and Search Strategy

An extensive literature search on different electronic databases, including Cochrane database, Web of Science and reviews related to this subject (from 2002 till 2017), was performed in three phases. In the first phase, we introduce the search terms “heart failure”, “continuous training versus interval training”, “effects of aerobic training”, “aerobic exercise”, and “peak VO₂”. We extracted the theoretical framework that is used as the basis for the current review. In the second phase, our aim was to focus on the superiority of AIT over CAT, so we started removing the studies concentrating on the effects of aerobic exercise in general. Later, in the third phase, to be more accurate and to hit our goal directly, we excluded all the studies tackling intensities rather than comparing the different types of interventions; and to limit our review, we searched for articles using the following keywords and Medical Subject Headings: [(randomized controlled trial) AND (chronic heart failure) AND (aerobic exercise) OR (randomized controlled trial) AND (heart failure) AND (AIT versus CAT)].

This review will consider the studies that evaluate exercise programs, between four and 12 weeks in duration, applying the AIT, characterized by multiple, short bouts of exercise (up to four mins) at a high workload (85-95% of peak heart rate; (HR peak)) interspersed by periods of 3 min for recovery at low intensity. For the purposes of this review, AIT will be compared to traditional aerobic exercise training characterized by at least 30 mins of aerobic exercise, such as cycling, walking or running, performed at a moderate-intensity that is sustainable for the duration of the session (60-70% HR peak).

Eligibility Criteria

Based on the titles, abstracts and some parts of the articles (when needed), we screened the literature to select those articles meeting the inclusion criteria. We described all the studies that met the inclusion criteria according to the following:

Subjects: Heart failure patients including male and female adults, of all ages, having normal weight with no or slight myocardial infarction.

Medication: All patients have received beta blockers and angiotensin-converting enzyme for >12 months.

Study design: Original analysis of Randomized controlled trials (RCTs) citing some types of aerobic training intervention for the intervention group(s) (AIT and CAT) and the control group receiving no treatment and maintaining their habitual lifestyle.

Outcomes: Studies examine, as a primary outcome, the effects of the intervention on the domains of cardiac function, quality of life, and functional capacity. And all patients gave written informed consent to participate in the study, which was approved by the local Ethics Committee.

Exclusion Criteria: Patients should be free of physical or mental disabilities, which could limit the physical training. They were excluded if they presented unstable angina pectoris, uncompensated heart failure, primary pulmonary hypertension, pulmonary infections or active pulmonary thromboembolism, smoking, additional valvular disease, and prolonged healing of wounds.

Data Extraction

Data extraction was standardized according to the following terms: (i) Type of intervention (AIT versus CAT); (ii) Ejection fraction (EF<40%); (iii) New York Heart Association (class II or III); (iv) Intensity and duration of the intervention (60% to 90% and 30 min respectively); (v) Measurement tools (vi) Findings (superiority of AIT over CAT). Finally, ethical approval was noted for all the published papers included in this review.

Data Analysis

In order to calculate the degree of the intervention effects, we determined the effect sizes for the following outcome variables: VO₂ peak, ejection fraction, and quality of life. The effect size (d) of treatment (pre- vs. post- or experimental vs. control) was calculated using equation (1):

$$(1): d = \frac{\mu_e - \mu_c}{S_p}$$

Where d is Cohen's effect size, μ_e is the mean of the experimental group, μ_c is the mean of the control group, and S_p is the pooled estimate of variance calculated using equation (2):

$$(2): S_{pool} = \sqrt{\frac{(n_1-1)S_1^2 + (n_2-1)S_2^2}{n_1+n_2-2}}$$

Where n_1 , n_2 are pre- and post intervention sample sizes, or experimental vs. control group sample sizes; S_1 , S_2 are pre- and post-intervention standard deviations, or experimental vs.

control group standard deviations. According to Cohen, an effect size of 0.2 represents a small effect, 0.5 represents a moderate effect, and 0.8 represents a large effect (7).

As for Meta-Analysis, calculations were done using a random-effects method. The level of significance was set at $p < 0.05$. Statistical heterogeneity of the treatment effects among studies was assessed using Cochran's Q test and the inconsistency I^2 test, in which values above 25% and 50% were considered as indicatives of moderate and high heterogeneity, respectively (8). All the analyses were conducted using the software Comprehensive Meta-Analysis "V3".

Methodological Quality

The Physiotherapy Evidence Database (PEDro) is used in order to estimate the value of the methodological quality of each RCTs (9). It is an instrument utilized to assess the methodological quality in physical therapy and exercise studies. Eleven items (see Table 1) on the PEDro scale were derived from a Delphi consensus procedure (10). The scale scores can range from 0 to 10, noting that 10 is associated with a better methodological quality. A total score is derived from the summation of responses of the items 2 to 11, whereas the item 1 relates to external validity. The reliability of this scale was evaluated with acceptable good results in intraclass correlation coefficients 0.56–0.91 (10,11). Judgments by two independent raters were compared and, when necessary, discussed.

RESULTS

Methodological quality

PEDro scores ranged from 5 to 8 points, with a mean score of 6.85 (Table 1). A high quality of the chosen trials was assured since all of the selected studies (3,6,12–16) scored 5 or more. All the studies specified the eligibility criteria, and the subjects were randomly allocated into groups; five of them were blinded to allocation (3,12,13,15,17) and showed the similarities at baseline. None of the trials had blinded therapists; one of them had blinded participants and blinded assessors (18). All trials had retention rates of 85 % or greater (3,6,12–15,17), and none has met the intention-to-treat analysis criteria. Statistical analysis was applied to groups' differences in all the studies as well as the reporting point estimates and the measurements of variability (3,6,12–16). None of the studies was excluded on the basis of their methodological quality (see Table 1).

The database search identified 30 articles about heart failure and exercise treatments. After duplicate removal searching on specific types of intervention, 15 articles were considered potentially relevant and were screened for relevant content. 4 of these 15 articles were excluded on the basis of the abstract, and 11 were retrieved for full-text assessment of eligibility. In the next phase, 4 of the 9 full-text articles were excluded based on the inclusion criteria; two were focusing on the superiority of the high intensity interval training over moderate interval training and the other two proved the additional benefits of AIT versus CAT but in coronary artery disease patients and not in CHF patients. Finally, seven studies met the inclusion criteria and were included in this review (Fig. 1). All the studies specified the eligibility criteria and showed the similarities with respect to the medication and other activities at baseline. The subjects were randomly allocated into groups and only three studies had control group and all of them applied statistical analysis to group differences.

Participants and Study Characteristics

The included articles encompassed a sample of 210 HF patients with a mean age of 82.5 ± 4.3 years old. The patients were divided into three groups; 89 patients were included in AIT group, 93 in CAT group, and 28 in the control group. Two-dimensional echocardiography combined with Doppler using the Simpson's method (13) was applied to assess LVEF (%). The other studies used echocardiography with ultrasound to calculate LVEF (14,17). The QoL was described based on the data provided by the Minnesota Living with Heart Failure Questionnaire (MLwHFQ) (6,14) since it is a self-assessment measure of therapeutic response to interventions applied in HF. This Questionnaire contains 21 questions and the score can range from 0 to 105 with higher scores indicating greater perception of severity and intrusiveness of HF related symptoms. It contains physical and emotional dimension score (table 1).

Intervention Characteristics

The intervention characteristics are summarized in Table 2. The intervention lasted for approximately three months and the frequency of the training programs ranged from 2 to 3 times per week in almost all of the trials. All the authors reported the length of each session, ranging from 30 to 60 min. The Continuous aerobic training was typically performed at moderate to high exercise intensities (50 to 70%) as average, which allows the patient to perform prolonged training sessions. CAT training is well accepted since it is easily taught and performed by

patients, usually on a cycle ergometer or a treadmill (18). In more deconditioned patients, it is recommended to start low and go slow (i.e. at low intensity for 5–10 min twice a week) (13). However, the AIT had shown significant advantages in both healthy and diseased individuals (18) since it reduces the time commitment required for meeting exercise guidelines. Although all studies used different protocols of training in terms of VO₂, frequency and duration, significant increases in VO₂ values were statistically detected in all the studies, and almost all of them showed improvements in ejection fraction and quality of life.

Meta-Analysis

All the studies involved in this systematic meta-analysis review assessed VO₂ peak, and showed significant improvement when comparing between AIT and CAT groups ($P = 0.017$). The chi-square test for heterogeneity was significant at a level of 10% approximately and the I^2 value was around 44% (Figure 2). Five out of the seven studies assessed ejection fraction (12–15,17) and showed no significant improvement ($P = 0.203$). The chi-square test was significant at a level of 10% approximately and the I^2 value was around 48% (Figure 3). Regarding QoL, the four studies (14,17,18) 16 showed no significant improvement, comparing AIT versus CAT groups ($P = 0.616$), the I^2 value was 0% and the P-value for the test of heterogeneity was 0.984. All these quantitative results suggested the presence of statistical homogeneity among the samples estimated (Figure 4).

Outcomes of the different categories

We have divided the seven studies into four categories, according to the VO₂ peak intensity of the interval aerobic training. In fact, We have considered a high/moderate program for those who performed training more than 90% and 70%, a high/low program for those who performed training between 90% and less than 35%, a moderate/rest program for those who performed training at 70% as average and were asked to stay at rest, and finally a moderate/low program for those who performed training between 70% and less than 35% (Table 2).

VO₂ peak

For VO₂ peak, there was a remarkable improvement in all studies discussed when comparing the AIT to control groups (not shown here). However when it comes for comparing categories; a greater benefit was shown for category 1, the high/moderate intensity program (2.93 ml/kg/min),

compared to the other three programs (0.31 for category 2, high/low intensity; -0.02 for category 3 moderate/low; 0.74 for category 3, moderate/rest) (Figure 5).

Ejection Fraction

As for Ejection fraction, only categories 1 and 2 showed marked improvement with a greater benefit for category 1 (1.48 fractions and 0.69 fractions respectively), compared to the other two categories that didn't show any improvement, moreover there was a decline in EF of category 3 and 4 (-0.05 fractions and -0.28 fractions respectively) (Figure 6).

Quality Of Life

With respect to the quality of life, it was improved in all studies but with additional benefits for category 1; high/moderate intensity; (0.24), while it was improved for 0.07 in category 2; high/low intensity; 0.04 for category 3; moderate/low intensity; and 0.05 for category 4; moderate/rest intensity (Figure 7).

DISCUSSION

This systematic review and meta-analysis aimed to find recent evidence that examine the potential role of aerobic exercise interventions in chronic heart failure patients. In fact, it proved that aerobic exercise has positive effects on most of the outcome measurements included in this current revision; Such as functional capacity (VO₂ peak), quality of life (QOL) and left ventricle ejection fraction (LVEF).

There were, however, differences among the intervention groups, showing the superiority of interval training over continuous training. Most of the black squares (individual study point estimates the treatment effect) are on the same side of the line indicating the significant superiority for VO₂ peak only when comparing AIT versus CAT groups (P = 0.017); (Fig 2). However, there was no significant improvement in EF or in QOL (P = 0.203), (P = 0.616) respectively (Fig 3, 4) when comparing AIT vs CAT. A large number of black squares align on the vertical line, which means that there isn't wide difference between the two types of training (AIT or CAT) regarding EF and QOL. Actually, this was due to the large differences in the intervention strategies and not to the heterogeneity among studies, since these quantitative results suggest the presence of statistical homogeneity among the sample estimates.

In our study, we demonstrated that the duration of intervention, the time and the intensity were responsible for the significant changes observed in patients.

Moderate/ Low-Rest Intensity

Starting with the two moderate intensity programs (Category 3 and 4), in the studies Koufaki 2014 (15) and Neshwateh 2002 (12), which performed the moderate/low intensity program; the QoL improvement was not important as much as it was in the other studies. But the other two parameters, EF and VO₂ peak were declined in this category compared to others, maybe because there were a huge difference in the duration and frequency of training with respect to each other and with respect to category 1 and 2.

According to the studies of Freyssin 2012 (3) and Smart 2012 (14), which performed the moderate/rest intensity program, the improvement in QoL was small when compared to other studies in category 1 and 2, and with respect to EF these two studies didn't show any improvement; however there was a decline. But talking about aerobic capacity this category showed a remarkable improvement when compared to category 2 and 3. And here we can say that the time of intervention in these studies might be the cause of the difference in the parameters when compared to other categories, since this training program share the same duration in all the studies and there is no huge difference in the frequency of training with respect to each other and with respect to category 1 and 2.

In addition these small improvements and decline in the parameters of category 3 and 4 might be because of the moderate/low intensities, and intensity higher than 50% was required for these patients.

High/Moderate-Low Intensity

Talking about the high intensity programs (category 1 and 2). These two studies, Wisloff 2007 (13) and Andersen 2016 (6), which performed the high/moderate intensity program, have shown the best result regarding all the parameters, when compared to the other categories, and this was related to the increase in the intensities. In addition category 1 showed a significant improvement when compared to category 2, Benda 2015 (17) that performed the high/low intensity and this because of the appropriate duration and frequency of intervention, 3 times per week for 12 weeks.

Despite the variety of the studies, positive results were higher in the Interval Aerobic Training 4 mins at high intensity followed by 3 mins at moderate intensity so we can consider that the intensity 90% to 70% of VO₂ max is the best intensity to apply. Overall, 12 weeks of training, 3 sessions per week for 40 mins in average is the optimal program until now. Moreover, selecting

continuous training will/would be better than control while investigating the effects of training on VO₂ max. There isn't any difference between the 2 types of training regarding the EF and QoL.

CONCLUSION AND RECOMMENDATIONS

In conclusion, this systematic review showed that Aerobic training addressed to CHF patients could improve several parameters as long as it is performed in specific conditions. This study has provided evidence that exercising the Interval aerobic training for 12 weeks, 3 times per week, for 40 mins in average, divided into four intervals of 4 mins at a high intensity (90% of VO₂ peak) and 3 mins at a moderate intensity (70% of VO₂ peak), is the best protocol to follow in order to improve VO₂ peak, ejection fraction and quality of life. These positive effects advocate for the application of AIT as a safe and effective intervention in cardiac rehabilitation programs. Furthermore, healthcare professionals should receive more guidance in order to put the treatment program into practice, learn the AIT theory and use it properly.

LIMITATIONS

This systematic meta-analysis review is consisted of 7 articles, where 3 of them compare the intervention groups with a control group (12,13,17), while the other studies lack this comparison, which explains why we didn't mention any improvement in the control group.

In addition, studies include a variety of patients and thus a wide difference in ages. In other words, some of them suffer from elder diseases and others don't. Hence, this fact can contribute to exercise intolerance and can influence the results of the training. Moreover, this review must include a greater number of RCTs in order to obtain a more generalized conclusion that covers the effect of Aerobic Training on further outcomes such as left ventricle systolic and diastolic diameter (LVSD/LVDD). The heterogeneity found in this Meta-Analysis can be attributed to between-study differences in patient selection, study design, or clinical setting. Despite these restrictions, it is still useful to explore sources of heterogeneity and incorporate it explicitly in the analysis in order to explain it or remove it in further studies.

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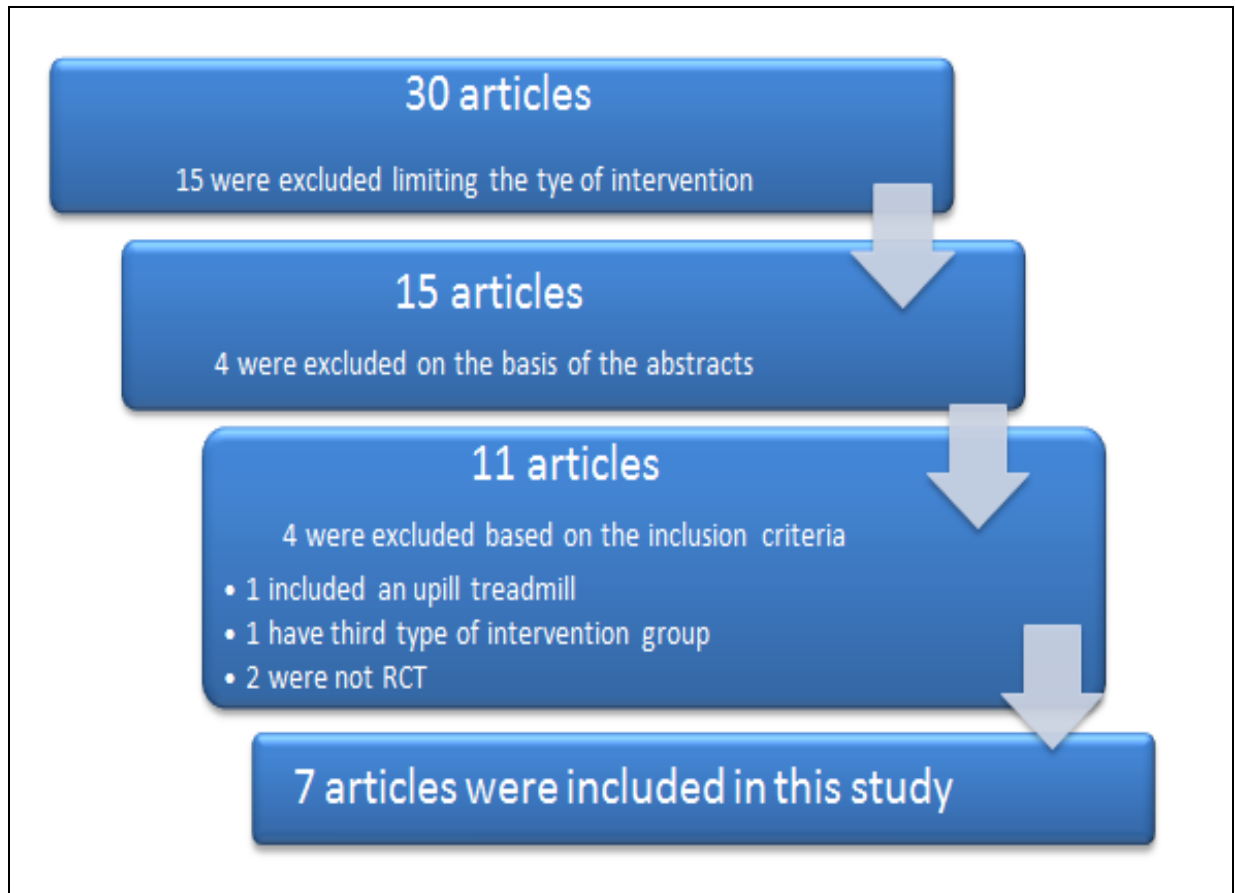
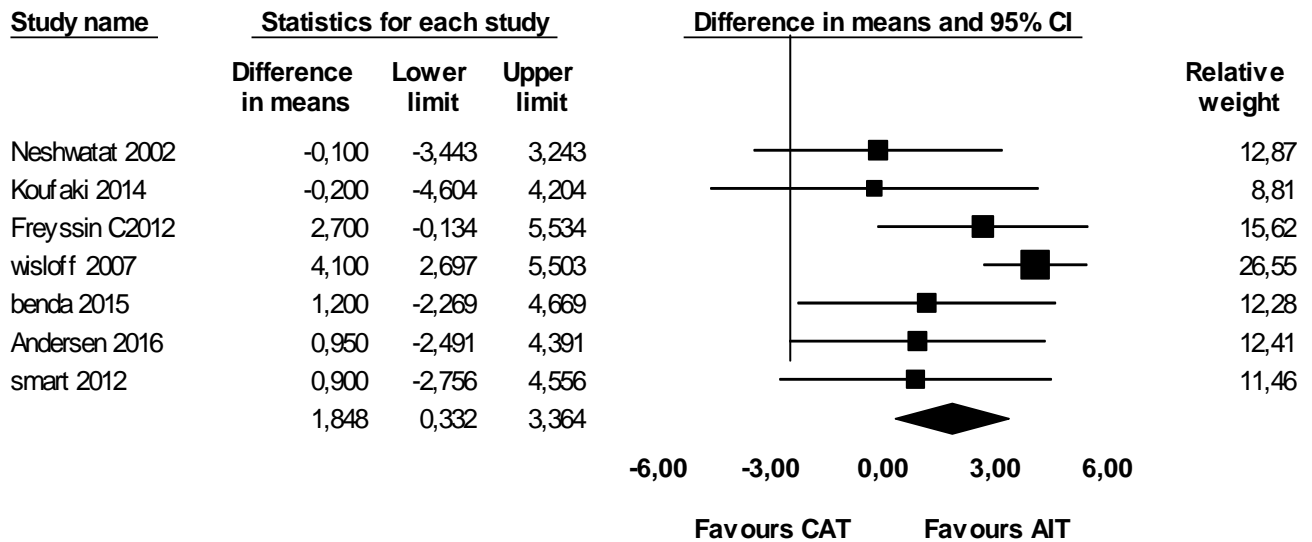


Figure 1- Flow chart for identifying eligible articles; RCT: randomized controlled trial.

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VO2peak	Mean	SD	Total	Mean	SD	Total
Neshwatat 2002	1,5	4,3	20	1,6	6,3	20
Koufaki 2014	2	5,1	16	2,2	7,5	17
Freyssin C2012	2,9	3,1	12	0,2	4,1	14
wisloff 2007	6	1,9	9	1,9	1,0	9
benda 2015	1,3	4,2	10	0,1	3,7	10
Andersen 2016	2,79	4,4	12	1,84	3,7	10
Smart 2012	2,5	5,6	10	1,6	3,3	13

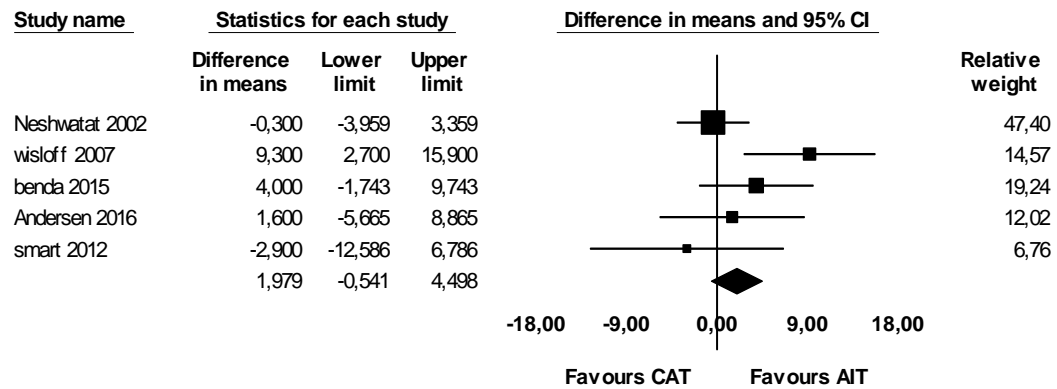


Heterogeneity: $\tau^2 = 1.741$, $\chi^2 = 10.796$, $df = 6$ ($P = 0.095$); $I^2 = 44.423\%$
 Test for overall effect: $Z = 2.389$ ($P = 0.017$)

Figure 2- Peak VO2 for treatment with continuous aerobic training (CAT) versus interval aerobic training (AIT); CI - confidence interval; SD - standard deviation.

State of Art

EF	AIT			CAT		
	Mean	SD	Total	Mean	SD	Total
Neshwata 2002	0,7	6,1	20	1	5,7	20
wisloff 2007	10	8,6	9	0,7	5,3	9
benda 2015	4	8,1	10	0	4,5	10
Andersen 2016	4,5	7,7	12	2,9	9,7	10
smart 2012	0,5	12,2	10	3,4	11,4	13

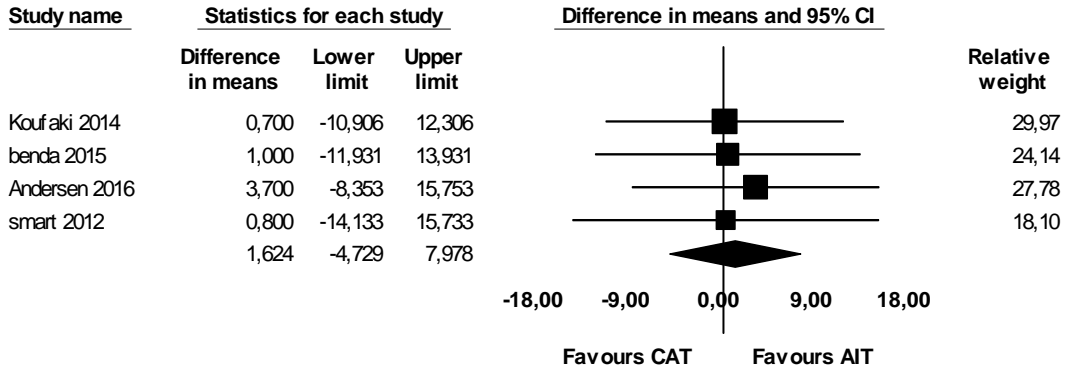


Heterogeneity: $\tau^2 = 8.705$, $\chi^2 = 7.678$, $df = 4$ ($P = 0.104$); $I^2 = 47.903\%$
 Test for overall effect: $Z = 1.273$ ($P = 0.203$)

Figure 3- EF-Ejection Fraction; CAT-Continuous Aerobic Training; AIT- Aerobic Interval training; CI - confidence interval; SD - standard deviation.

State of Art

QOL	AIT			CAT		
	Mean	SD	Total	Mean	SD	Total
Koufaki 2014	2,5	17,0	16	1,8	17,0	17
benda 2015	-1	14,5	10	-2	15,0	10
Andersen 2016	-14,6	16,1	12	-18,3	11,9	10
smart 2012	-11,8	19,5	10	-12,6	17,0	13



Heterogeneity: $\tau^2 = 0.000$, $\chi^2 = 0.159$, $df = 3$ ($P = 0.984$); $I^2 = 0.000\%$
 Test for overall effect: $Z = 0.501$ ($P = 0.616$)

Figure 4- QoL-Quality of Life; CAT-Continuous Aerobic Training; AIT-versus Aerobic Interval training; CI - confidence interval; SD - standard deviation.

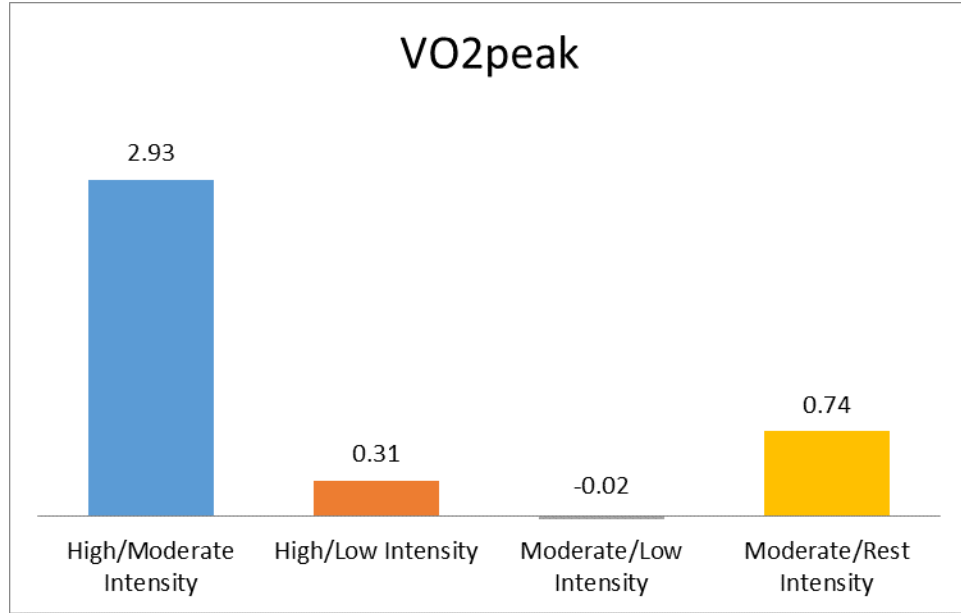


Figure 5- Significant improvement in the VO2 peak (ml/kg/min) for the high/moderate intensity program.

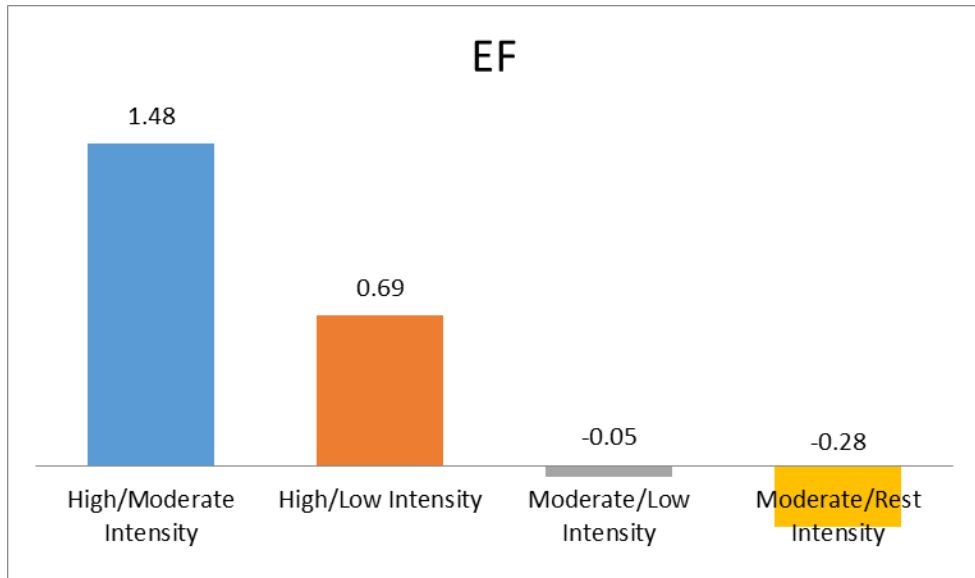


Figure 6- Significant improvement in EF for the high/moderate and the high/low intensity programs.

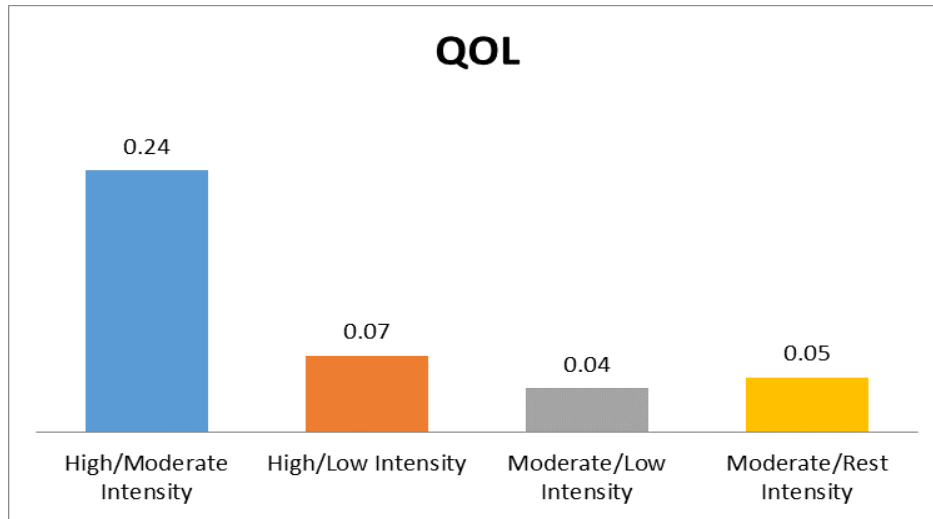


Figure 7-Additional benefits in QOL for the high/moderate intensity program.

Table 1 - Methodological classification of studies using the PEDro scale and clinical characteristics of patients randomized to interval training group (AIT) and continuous training group (CAT) in the different selected studies.

First author	Pedro scale	N:	Mean Age (Y)	EF (%)	NYHA
Neshwata et al. 2002	5	AIT:20	45.7	29.3	II-III
		CAT:20	47.7	27.3	II-III
		control:10	48.7	26.6	II-III
Wisslof et al. 2007	6	AIT: 9	76.5± 9	28.0 ±7.3	II-III
		CONT: 9	74.4±12	32.8 ±4.8	II-III
		Control: 9	75.5±13	26.2 ±8.0	II-III
Smart et al. 2012	5	AIT: 10	59.1±11	27±8	II -III
		CONT: 13	62.9±9.3	29.5±7.2	II -III
Freyssin et al. 2012	6	AIT:12	54± 9	27.8±4.7	II -III
		CONT:14	55±12	30.7±7.8	II -III
Koufaki et al. 2014	6	AIT:16	59.8 ±7.4	41.7 ±10.3	II-III
		CONT:17	59.7 ±10.8	35.2± 6.4	II-III
Benda et al. 2015	5	AIT: 10	63 ±8	37±6	8 in II and 2 in III
		CONT: 10	64± 8	38±6	8 in II and 2 in III
		Control: 9	67±7	40±11	8 in II and 1 in III
Andersen et al. 2016	8	AIT: 12	53.15 ± 7.0	35.40 ± 6.7	10 in II and 0 in III
		CONT: 10	54.02 ± 9.9	32.8 ± 7.7	11 in II and 1 in III

EF: ejection fraction; NYHA, New York Heart Association.

Table 2 - Study measurements and outcomes of different studies of aerobic training in chronic heart failure. Patients randomly assigned to interval aerobic training (AIT) and Continuous aerobic training (CAT) at baseline.

Category	Study	Duration	Frequency	Time of intervention	Intensity			
					AIT			CAT
					High Intensity	Moderate Intensity	Low Intensity	
High/Moderate Intensity 38 to 60mn	Wisslof et al. 2007	12 weeks	3 times/week	38mins – Category 1: 4mins-3mins	90-95	50-70		70-75
	Andersen et al. 2016	12 weeks	3 times/week	60mins - Category 1: 3mins-3mins	95	70		75
High/Low Intensity 60mn	Benda et al. 2015	12 weeks	2 times/week	60mins – Category 2:1min-2.5mins	90		30	60-75
Moderate/Low Intensity 15 to 30mn	Koufaki et al. 2014	24 weeks	2 times/week	30mins – Category 3:0.5min-1min		50	20-30	40-60
	Neshwata et al. 2002	3 weeks	6 times/week	15mins- Category 3: 60s-30s		35-50	35	75
Moderate/Rest Intensity 60 to 71mn	Freyssin et al. 2012	8 weeks	3 times/week	71mins – Category 4: 0.5min-1min		50-80	rest	50-80
	Smart et al. 2012	16 weeks	3 times/week	60mins – Category4: 1min-1min		70-80	rest	60-70

Category1: High/Moderate; Category 2: High/low; Category 3: Moderate/Low; Category 4: Moderate/Rest

AIM OF THE STUDY

After stating all the consequences of HF disease and following our reviews and meta-analysis to find the best recommendations for the non-pharmacological treatments, we explored 3 different hypothesis and objectives in 3 different studies:

First Aim

The first hypothesis attempted that the addition of IMT to AIT results in additional benefits on cardiopulmonary and skeletal muscle function, dyspnea and quality of life compared to IMT alone, aerobic alone or control.

Two recent studies have confirmed the additional effects of combining IMT to AIT in CHF patients compared to aerobic training alone (Winkelmann et al. 2009; Adamopoulos et al. 2014); But both studies didn't measure benefits earned at the level of skeletal muscle function, didn't compare their combined group patients to IMT group alone or to a control group and used the continuous mode of training instead of interval .

Therefore, the first aim of this study was to determine the effects of combined training on skeletal and respiratory muscle function, exercise capacity, left ventricular remodeling, dyspnea and QoL in CHF. The second aim was to find the best training exercise that could have additional benefits on measured parameters.

Second Aim

The second hypothesis attempted to assess the effects of RT and posits that the benefits observed in RT can be added to the effect of combined training: aerobic and inspiratory.

One study have confirmed important improvements in cardiopulmonary responses to exercise, as well as increases in skeletal muscle function and QoL (Laoutaris et al. 2013). However, AT+RT+IMT have not resulted in additional benefits in cardiac function over AT, except for left ventricular end-diastolic diameter (LVEDD) that was improved only after combined program. The use of continuous AT and not aerobic interval training (AIT) in the above study might be a reason for not finding a significant difference in favor of combined group. It has been shown previously that AIT is better than AT in reversing ventricular remodeling and improving endothelial function (Wisløff et al. 2007). Besides, these authors did

Aim of The Study

not compare the benefits of the combined training to RT alone and to a control group in a same patient population.

Therefore, the purpose of this study was to examine the additional effects of combined training: aerobics, respiratory, and resistance by comparing it to RT and control in patients with CHF.

Third Aim

The third hypothesis attempted to see if the improvement in skeletal muscle strength and endurance in different types of training reflects the neuromuscular function of the motor units and reduces the fatigue threshold in patients with HF.

To our knowledge, there are no studies that compare the different types of training using surface electromyography.

Therefore, the objective of this study is to study and compare the effects of different training programs on skeletal muscle function using surface electromyography in patients with CHF.

MATERIALS AND METHODS

MATERIALS AND METHODS

1. Ethics

The experimental protocols' approval was obtained from the Committee for Ethics in Research of Beirut Cardiac Institute (IRB, OTLY- P- 38F- 16) and was registered in ClinicalTrials.gov (Identifier or Trial Registration number: NCT03538249). Since human was included in this study, the National Institutes of Health (NIH) for protecting human research participants certificate was undertaken (annex). The patients were addressed with all needed information about the study and all signed an informed consent prior to initiation of their study period.

2. Study design and patients

A 3-month, randomized, single-blinded controlled study was conducted in patients with CHF and IMW for the evaluation of central and peripheral outcome measures, functional capacity and QoL. Randomization was conducted by using a research randomizer web site (Scott Plous and Jeff Breil, Lancaster, Pennsylvania), Subjects were block randomized with 1:1 to different groups. Patients who met the inclusion criteria and matched nothing of the exclusion criteria did undergo a medical examination, anthropometric measurements, and electrocardiographic measurements by a cardiologist. Then, they were allocated randomly either to an exercising group (each group includes a specific modality intervention) or to a non-exercising control group by the investigators who are not involved in the implementation of the execution of this project. 300 patients were assessed for eligibility and 240 were excluded due to some limitations (figure 4). Exercising groups included Aerobic Training, Inspiratory Muscle Training, Resistance training, Aerobic + Inspiratory Training and Aerobic + Inspiratory + Resistance training group. Patients in a specific group didn't have any idea about the other groups, and weren't told any potential effect of the intervention. A stable medication regimen was followed by all the subjects during the study period that included mainly ACE-I or ARBs (those who can't tolerate ACE-I), diuretics and beta-blockers. All patients were supervised by nutritionists and professionals in order to have a healthy and smoke-free lifestyle.

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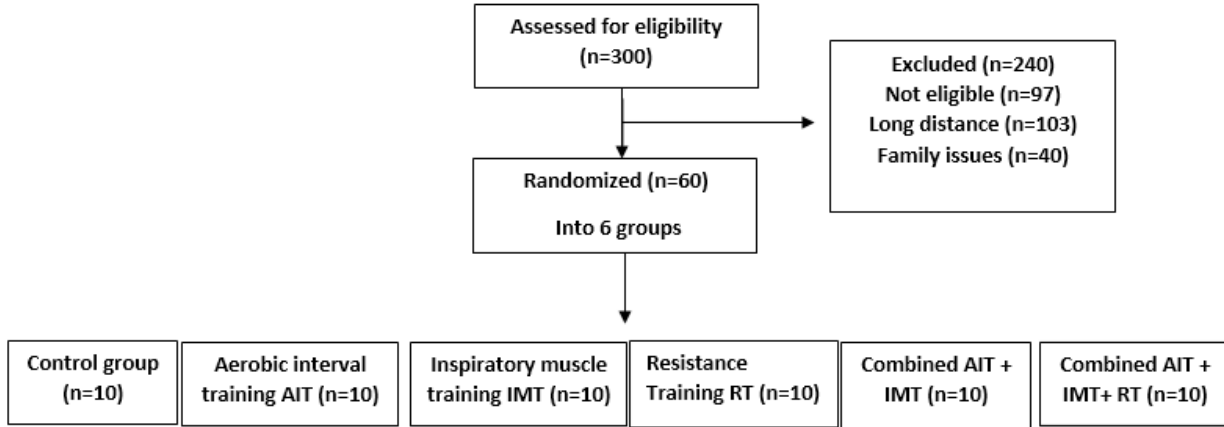


Figure 4- Flow Chart for Patients recruitments

3. Eligibility criteria

HF patients (male and female) who were included in our study must be ischemic or dilated cardiomyopathy, with an Ejection fraction (EF) $\leq 45\%$ and IMW [MIP $<70\%$ predicted], must be stable with NYHA class II or III and all must possess a sedentary life style (assessed using the IPAC physical activity questionnaire). Eligible subjects must be diagnosed with CHF for more than 6 months so long as there has been no admission to the hospital or any change in medications throughout the previous 3 months.

Subjects excluded were with pulmonary limitation [Forced expiratory volume (FEV1) and/or vital capacity $<60\%$ of predicted], orthopedic or neurologic disease, history of significant cardiac arrhythmia, history of myocardial infarction or cardiac surgery over the past 6 months, non-echogenic, unstable, poorly controlled BP and/or end-stage HF.

4. Outcome measures

Demographic, clinical characteristics of patients and their drug therapy lists were collected at the beginning and at the end of the study (Table 1).

Before and after the interventions, we evaluate pulmonary function tests using spirometry, respiratory muscle function using respiratory pressure meter, cardiac function and structure using echocardiography and stress test, skeletal muscle function using surface electromyography and Dynamometer measurements, functional capacity by the 6MWT, dyspnea

assessed with the Borg scale, and QoL using the MLWHFQ by a physiotherapist and/or cardiologist who does not know the distribution of the patients to the different interventions.

Table 1 - Demographic and clinical characteristics of patient population.

	Control	AIT	IMT	RT	AIT& IMT	AIT& IMT&RT
Ages (years)	52.6±11.2	51.6±13.8	52.5±13.7	55±6.7	51.8±8.3	57.6±11.6
Males/females	5/5	5/5	5/5	6/4	5/5	7/3
BMI	27.3±3.4	28.1±3.7	28.3±1.4	33.3±4.9	27.7±3.9	32.2±4.9
Medication (%)						
ACE-I	10	10	10	9	10	9
Beta Blockers	10	10	10	10	10	10
Anticoagulant	10	10	10	10	10	10
Diuretics	10	10	10	8	10	8

4.1- Cardiac function

4.1.1- Echocardiography test

Echocardiography is the test that enables an evaluation about the heart's function. It makes pictures of the heart and help in the analysis of different cardiac measures. Assessment of heart structure and function at rest was done using a Vivid S6 ultrasound probe (General electric healthcare GEMs supplies) whereby the patient was seated in the supine position. Two experienced cardiologists, blinded to subject's allocation and his/her study period, performed the test. Measurements of Ejection fraction, ventricular volumes and diameters were assessed using the biplane method of disks (Biplane Simpson's method) from an apical 4 chamber view. This method is highly recommended for measuring the LVEF. Parameters assessed during echocardiography were left ventricular ejection fraction (LVEF in %); left ventricular end systolic, diastolic diameter (LVESD and LVEDD in mm) and left ventricular end systolic, diastolic volume (LVESV and LVEDV in mm) (P. Ponikowski et al. 2016).

4.1.2- Stress test

Bruce treadmill protocol (figure 5) was used for the assessment of the cardiovascular status during a progressive incremental exercise (Bruce et al, 1973). During this test the patient will exercise on a treadmill throughout which the intensity and grade increases progressively

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according to Bruce protocol. The patient will also have an ECG leads placed on his chest and a sphygmomanometer cuff associated with him/her for BP monitoring. Exercise time in seconds, grade, METs (Metabolic Equivalent of a tasks), Maximal HR, Maximal Speed and BP/HR were recorded during and after the test.

The patient must stop eating 3 hours before performing the test and no major effort must be made 12 hours before the test, he must dress appropriately to the realization of a physical effort.

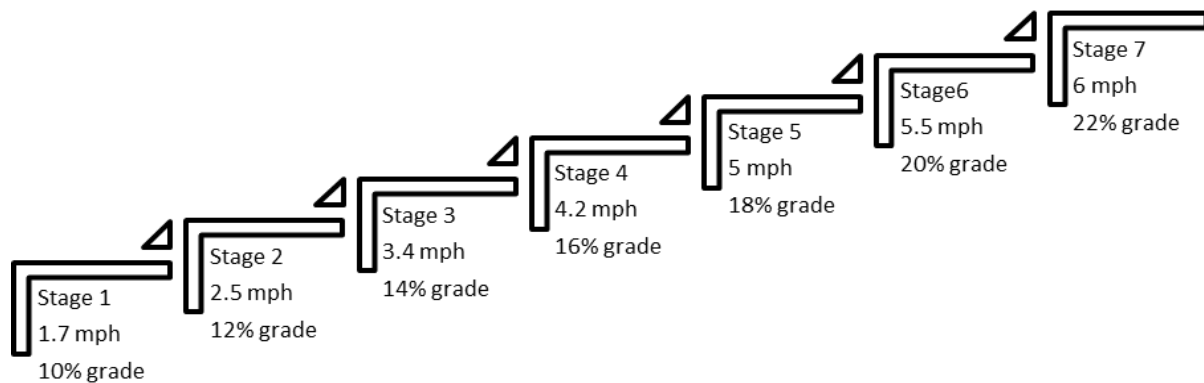


Figure 5 - Bruce incremental treadmill stress test. Mph, miles per hour.

4.2- Lung function

4.2.1- Pulmonary function test

Digital Spirometer was the test used to assess the pulmonary function; it is common, well known and not painful. It measures inhaled and exhaled air volumes as well as flow rate. During this test, subjects were seated and instructed to inhale deeply through a mouthpiece well fitted between the lips followed by a quick and forceful exhalation. Air leakage was prevented by using a nose clip during the maneuver; the latter had been repeated three times to guarantee maximal performance. Important parameters detected through this test were forced expiratory volume in 1 s (FEV1), Forced vital capacity (FVC) and FEV1 to FVC ratio. All data should be analyzed using a program developed by NHANES III, 1990, and we took the best results performed by the patients.

4.2.2- Respiratory muscle strength

The respiratory pressure meter (MicroRPM carefusion)—a portable hand-held device—was used to measure the maximal inspiratory pressure (MIP) and the maximal expiratory pressure (MEP). The results of the test appeared on a screen in cmH₂O. A PUMA PC Software that offers

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unique features can be associated with the hand-held MicroRPM in order to improve its functionality (P. Ponikowski et al. 2016).

During this test, the patient was instructed to tightly fit the mouthpiece associated with the instrument between both lips. Familiarization with the device and the ventilator operation was done before starting the test. To measure MIP, the subject must exhale to residual volume then perform a Mueller maneuver characterized by a forceful inhalation against the instrument as long as possible. To measure MEP, the subject must inhale to total lung capacity (TLC) and then exhale forcefully (Valsalva maneuver) over a 2 second minimum duration. Both maneuvers were repeated at least 3 times for obtaining the best values of MIP and MEP; note that values reported were the maximum pressures sustained over a one second period.

4.2.3- Respiratory muscle endurance

To measure the endurance of the inspiratory muscle (SMIP), patients were instructed to respire using the Power Breathe device set at 70% MIP. The maximum time (in seconds) tolerated was recorded and considered to evaluate the inspiratory muscle endurance, SMIP/time. This test was repeated 3 times, interspaced by 2 minutes rest (P. Ponikowski et al. 2016), and we took the best results performed by the patients.

4.3- Skeletal muscle function

4.3.1- Skeletal muscle strength test

A handheld dynamometer (Lafayette instrument) was used to assess the skeletal muscle strength by measuring the force generated by the quadriceps. This device is portable and light which facilitates the examination procedure. Before the test, subjects have been familiarized to the operative device and the intended protocol. Patients were seated in a sit up position at a knee and hip angulation of 60° and 120° respectively. Verbal encouragement was used during the test period. Maximum voluntary isometric force (MVIF) in kg was measured in 3 seconds; three sets of three repetitions were given to each patient to develop a maximum force. The rest period between the three sets was 2 minutes. MVIF was reported as the average of the nine values taken. Peak force, average force and peak time were recorded by the device and transformed to the computer software (Gayda et al. 2005).

4.3.2- Skeletal muscle endurance test

50% MVIF was used to assess the skeletal muscle endurance. The patient was instructed to maintain 50% of the MVIF for as long as possible till maximum tolerated and time elapsed was recorded. The procedure was repeated three times separated with 5 minutes rest periods. The maintain time (MT) was calculated as an average of the three sets. Verbal encouragement was given to the patient before and during the endurance test for achieving the best performance possible (Gayda et al. 2005).

4.3.3- Surface Electromyography

During strength and endurance test, surface electromyography (SEMG) activities were recorded from the vastus lateralis (VL), rectus femoris (RF), and vastus medialis (VM). Electrodes with a disc shape were located for VL on quarter distance proximal to the lateral tibial condyle on a line connecting this and the anterior-superior-iliac-spine (ASIS). For RF, electrodes were placed at mid distance along the line connecting the ASIS to the superior aspect of the patella. For VM, electrodes were placed at a position 20% of the distance along a line connecting the medial gap of the knee to the ASIS. Before electrodes application, the skin was cleaned. The signals of 3 muscles: VL, RF and VM were stored in LabView (32 bits). The root mean square (RMS) and median frequency (MF) were calculated by the matlab program. RMS and MF were averaged for each muscle (Gayda et al. 2005).

4.4- Physical activity

The entry criteria in this study postulated that patients must possess a sedentary lifestyle. The international physical activity questionnaire (IPAQ) (Craig et al. 2003) was used to assess the level of each patient's physical activity. The questionnaire was administered during first office meeting. It is comprised of 7 questions, patients were instructed to answer by the duration spent doing an activity. See figure 6 for the scoring technique.

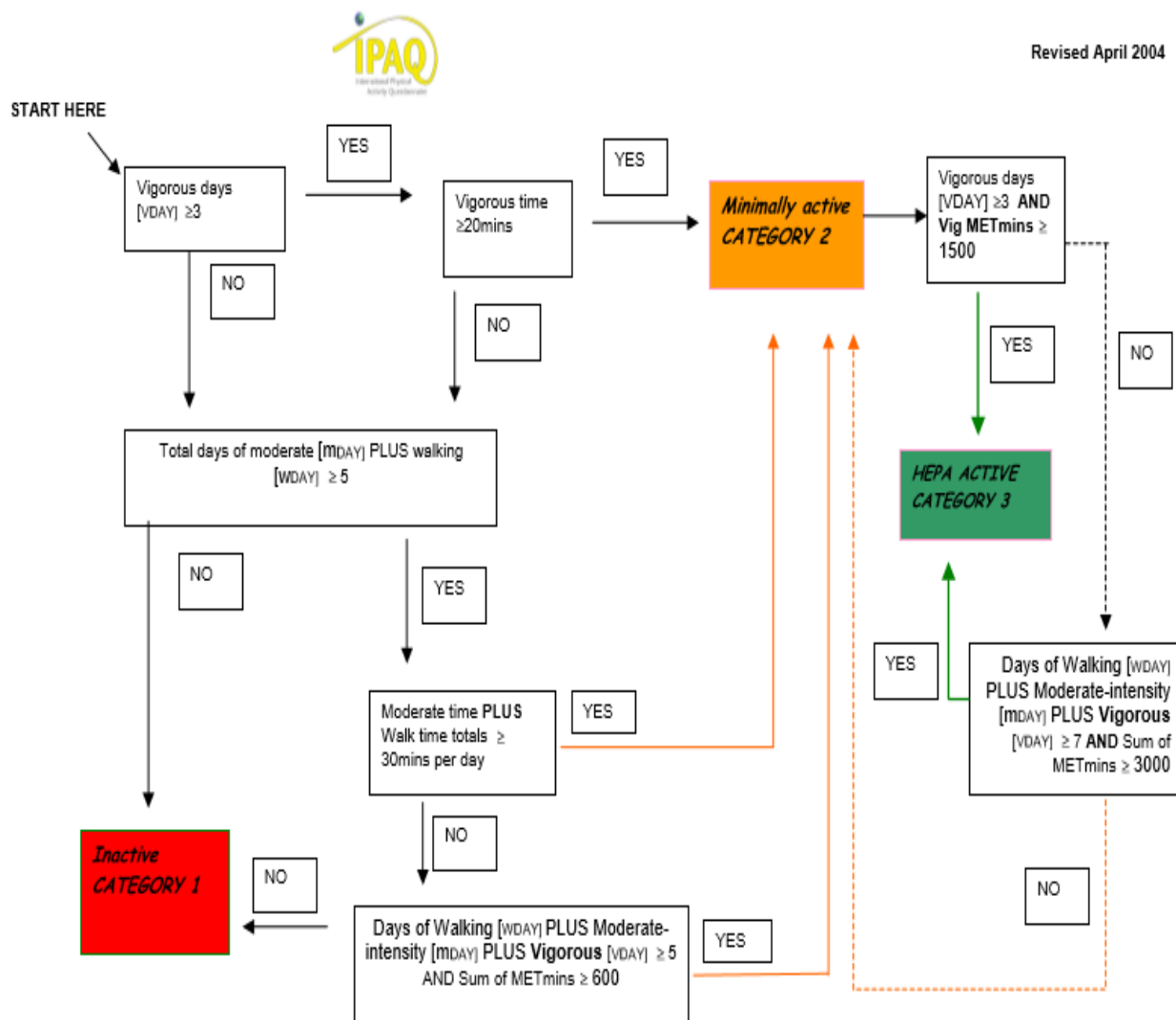


Figure 6 – International physical activity questionnaire scoring technique.

4.5- Six minute walk test

Functional capacity in CHF patients was predicted by using the 6MWT (Beatty, Schiller, and Whooley 2012). The latter is validated to be reliable and reproducible.

In the 1996, the 6MWT was first used by Guyatt et al. (Guyatt et al. 1985) in patients with heart disease. The 6MWT is adapted from a 12 minutes performance test described by Mcgavin et al. and modified by Butland et al. (Butland et al. 1982).

The test was performed in a 60 meters corridor under the supervision of a physical therapist. Initially, the patient had been familiarized to the corridor space and the time needed to complete the test. BP, HR, and arterial oxygen saturation were measured, before and after the

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test was performed. A stop watch was used to record the elapsed time as soon as the subject scurries from the starting slab. The physical therapist was encouraging the patient to walk as much as he/she can during the 6 minutes by telling “Go on, that is it” and “Great performance, just keep on track”. The patient was free to decrease his/her speed and stop if necessary. The test is repeated three times separated with 5 minutes rest and we took the best results performed by the patient.

4.6- Dyspnea

During each training session and during the stress test, the patient was asked to evaluate his/her exertion level according to Borg scale (Levinger et al. 2004).

Borg scale gives information about perceived exertion and not the extent of exercise difficulty. The scale is comprised of different intensity levels, where patients evaluated their exertion level according to a visual attached numerical scale from 6 to 20 with 6 corresponding to no fatigue or other symptoms and 20 to maximum exertion. Borg scale was affirmed for its sensitivity and reproducibility to be used as a subjective reference during submaximal workouts (Grant et al. 1999).

4.7- Quality of life

QoL was assessed using the MLWHFQ, which was validated for the use in clinical practice and research (Thomas S. Rector and Cohn 1992). MLWHFQ has been translated into and validated in Arabic and French. MLWHFQ assesses patients’ perceptions of the influence of HF on physical, socioeconomic, and psychologic aspects of life (Rector, Kubo, and Cohn 1987). This questionnaire is composed of 21 items using a 6 point response scale 0 (none) to 5 (very much). Low score indicates that the patient had mild problems associated with HF and a high score indicates high impact of HF on QoL. The total summary score can range from 0 to 105. The administration of the questionnaire was easy and questions were answered by the patients clearly. The question is “Did your HF prevent you from living as you wanted during the past month by...” 21 functions of daily living activity (Annex 3). Information revealed by the MLWHFQ has given an overview about physical, social and mental status of patients before and after the interventional process. Internal consistency reliability of the instrument has been high, with Cronbach’s alpha ranging from .73 to .93 in one study (Briançon et al. 1997). Test-retest reliability was high after a 7- to 21-day period (weighted kappa reliability coefficients .84)

(Rector et al., 1987) and even higher after a one-week interval ($r = .93$ total, $r = .89$ physical dimension, $r = .88$ emotional dimension) (Rector and Cohn 1992).

5. Interventions

At baseline there were no statistically significant differences between the six groups with respect to demographic characteristics, 60 Patients with ischemic or dilated HF (age 55 ± 8 : years, BMI: 27 ± 4 , EF: 36 ± 6 , Male/Female= 35/25) were randomly assigned to one of 6 groups. The training regimens were performed 3 times a week for 12 weeks.

Medicaments were followed properly by all patients according to their cardiac specialist instructions (ACE- or ARB, beta blockers, and diuretics). Pharmacological therapy has not been changed all over the 3-month training period.

Arterial blood oxygen saturation and HR were monitored using VIAMED pulse oximetry, and BP was measured using a sphygmomanometer prior to the initiation and subsequent to the termination of each exercise session.

5.1- Control

The control group included 10 patients, who undergone nothing of the training exercises and were instructed to continue their normal life activities during the three months trial.

5.2- Aerobic Training

All patients were enrolled under supervised exercise program performed 3 times a week on non-consecutive days, for 12 weeks. When a participant missed a training session, the session was rescheduled to ensure a total of 36 training sessions (i.e. 100% compliance). The exercise protocol training was adapted after making a systematic Review and Meta-analyses to analyze the evidence based practice of AT in HF patients by highlighting the different parameters from which practical recommendations are made (Chapter 6, Review 6.2). Thus interval training was used as training modality rather than using continuous training, due to its beneficial effects observed by *wisloff et al.* Training involved treadmill walking for 30 minutes at different intensities. Each session started with a warm up for 1 minute at low intensity and concluded with a cooling -down for 1 min at the same intensity, followed by a period exercising at the target HR that corresponded to the first ventilatory threshold on the stress test when the patient could not followed the effort. AIT consisted of four intervals of 4 minutes at 60% of maximal HR, and 5

intervals of 2 minutes at 50% from the maximum intensity of workload. Workload was increased by 5% every two weeks in order to reach 90% of the maximum workload at the end of the intervention. In order to control the intensity of the training, we have selected during the stress test, the speed that corresponds to 60% of MHR. In addition, all patients were monitored using an electrocardiography to continuously observe their heart rate. Borg scale, HR, and BP were determined before the warm-up and after the cooling down.

5.3- Inspiratory Muscle Training

Another systematic review and meta-analyses are driven to analyze the evidence based practice of IMT in HF patients by highlighting the different parameters from which practical recommendations are made (Chapter 6: Review 6.1). Patients received IMT for 20 min, 3 times per week, for 12 weeks using the PowerBreathe training device. This device uses a technique known as resistance training. This strengthens the breathing muscles by letting them work harder; in much the same way as you might use weights to increase the strength of your arm muscles.

When training with PowerBreathe, you will notice that you have to work harder to breathe in. This is the effect of resistance training acting on the muscles used to inhale-primarily the diaphragm and rib cage muscles. When breathing out, there is no resistance and you can breathe out normally, which allows the chest and breathing muscles to relax, naturally pushing the air from your lungs.

During training, patients were instructed to maintain diaphragmatic breathing, with a breathing rate at 15 to 20 breaths per minute. For the IMT group, inspiratory load was set at 60% of MIP since it has been shown by Laoutaris that the threshold pressure must be set at 60% of maximal inspiratory mouth pressure for individual subjects to achieve significant improvements in inspiratory muscle strength. Training loads were adjusted to maintain 60% of the MIP every two weeks (Laoutaris et al. 2013).

All subjects were observed during the initial IMT session for any adverse signs or symptoms and to verify proper IMT technique. To avoid impaired inspiration due to a full stomach, subjects were instructed to perform IMT prior to meals or 2 hours after eating and to wear a nose clip during IMT sessions to help the patient to breathe through his mouth rather than his nose.

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To start the session, we make sure that the patient is sitting upright and feel relaxed, and then he will hold the device by the handle cover; place the mouthpiece in his mouth so that the lips cover the outer shield to make a seal.

Then the patient is asked to take in as much air as he can, as quickly as he can, straightening his back and expanding his chest. In the second step, he should breathe out slowly and passively through the mouth until the lungs are empty, letting the muscles in the chest and shoulders relax.

The session is divided into one minute of warm up without resistance, 4 blocks of work for 3 minutes separated by 20 seconds of rest and one minute of cool down without resistance too. Patients' HR, BP and peripheral capillary oxygen saturation were monitorized before and after the IMT session. Measurements of MIP and MEP were repeated each two weeks so that the IMT prescription could be updated.

5.4- Resistance training

The training protocol was comprised of strength exercises that targeted the muscles of the quadriceps, the hamstrings and gluteus muscles of the lower extremities; Biceps, Triceps, Deltoid, and Pectoralis of the upper extremities. A total of seven strength exercises were used to train the upper body and six strength exercises to train the lower body limbs. Each workout was composed of 3 sets and each set of 10 repetitions, a minimum of 15 seconds rest period was allowed between sets. The patients started training at 60% of 1RM and each two weeks it was assessed and recalculated. The total training time was 30 minutes.

5.5- Combined Aerobic and Inspiratory Muscles Training

First, patients' measurements: HR, O₂ and BP were determined, and then subjects underwent AT as mentioned above.

At the end of AT, and at effort, the above measurements were retaken. Then, patients relax for 5mins in order to be ready for the IMT. Again, we measure BP, HR and O₂ and then start the session of IMT as mention above. Finally, as previously, we record the measurements to monitor patients at all stages.

5.6- Combined Aerobic, Resistance and Inspiratory Muscles Training

This training group included three exercise modalities, aerobic, inspiratory and resistance training. They underwent AIT followed by IMT and ended with RT, between each station the patients rest for approximately 5 minutes. RT protocol has followed the same form and rules associated with the above described RT group. HR, O₂ and BP were measured before and after each intervention.

5.7 STATISTICAL ANALYSIS

A-priori statistical power analysis revealed that $n = 10$ was the adequate sample size in order to evaluate standardized differences in the main parameters at 0.05 significance level of two-sided hypothesis, achieving power $> 95\%$. All continuous variables are expressed as mean \pm standard deviation of the mean ($m \pm SD$). Baseline comparisons between groups were performed using one way ANOVA-test for the normally distributed variables and Kruskal-Wallis test for the non-normally distributed variables and the chi-square test for the categorical variable (gender). The paired t-test and Wilcoxon signed-rank test were used to assess training induced changes (pre vs. post) within a particular group. The effect of intervention between groups, the effect of time and the effect of group-by-time interactions were evaluated using repeated measures analysis of variance (RMANOVA). Friedman test was used when data is not normally distributed. Normality was tested using Kolmogorov-Smirnov test. The inflation of type-I error due to multiple comparisons was controlled using the Bonferroni rule. Finally, in order to compare improvement between groups, effect size for some principal parameters was calculated. The effect size (d) of different parameters (pre- vs. post-) was calculated using the following equation: $d = \frac{\mu_1 - \mu_2}{S_p}$, where d is Cohen's effect size; μ_1, μ_2 are pre- and post intervention means, and S_p is the pooled estimate of variance calculated as follows: $S_p = \sqrt{\frac{(n_1-1)S_1^2 + (n_2-1)S_2^2}{n_1+n_2-2}}$, where n_1, n_2 are pre- and post intervention sample sizes and S_1, S_2 are pre- and post intervention standard deviations. Statistical analyses were performed in SPSS software (version 20, SPSS Inc., Chicago, Illinois, U.S.A).

RESULTS

RESULTS

In this section, we first summarize the main results obtained answering the aim stated above. Then, the detailed results are presented in the 3 articles that follow.

First aim

We have split our sample group of patients at random, as per the following: Aerobic (AIT), Inspiratory (IMT), Aerobic + Inspiratory (AIT+IMT) and control (n=10, for each group) to respond to the first aim. We have obtained the following results:

- Pulmonary Function: No significant results were detected for FVC, FEV1, and FEV1/FVC.
- Respiratory muscle: There are significant results in the 3 groups by comparing them to the control. But the results are most significant in the combined group (AIT+IMT).
 - PI_{max} (62%, p = 0.01)
 - PE_{max} (40%, p = 0.01)
 - SPI_{max} (71%, p = 0.017)
- Cardiac function: There is no improvement in the IMT. There is a significant improvement in AIT and combined respectively.
 - LVEF (14%, p=0.025 and 16.6%, p=0.042)
 - LVEDD (9.8%, P=0.015 and 7.3%, p=0.036)
 - LVESD (11.8%, p=0.012 and 9.34%, p=0.023)
- Stress test: There are significant results in the 3 groups by comparing them to the control. But the results are most significant in the combined group.
 - Grade (23.6%, p=0.004)
 - METS (34%, p=0.001)
 - Exercise time (62%, p=0.001)
- Functional Capacity: There are significant results in the 3 groups by comparing them to the control. But the results are most significant in the combined group.
 - Minnesota (56.4%, p=0.001)
 - NYHA (48%, p=0.008)

Results

6MWT (22.6%, p=0.017)

- Skeletal muscle function: There is no improvement in IMT. There is a significant improvement in AIT and combined. Strength (9.8%, p = 0.006 and 10.8%, p = 0.001), Endurance (31%, P = 0.008 and 31%, p = 0.009). RMS values were significantly increased in the response of the three muscles of the quadriceps in the aerobic and combined group, in both strength and endurance manipes. Regarding the muscle fatigue analysis, MF has shown that during endurance protocol, AIT, IMT, and combined trainings had significant positives effects on skeletal muscle fatigue.

Second aim

We recruited 20 patients divided into 2 groups (n=10 for each group): resistance group (RT) and combined group (AIT+IMT+RT) in order to respond to the second objective and the following results were obtained.

- Pulmonary Function: No significant results were detected for FVC, FEV1, and FEV1/FVC.
- Respiratory muscle: There are significant results in the 2 groups by comparing them to the control. But the results are most significant in the combined group.

MIP (60%, p=0.001)

MEP (44.6%, p=0.001)

SMIP (71%, p=0.007)

- Cardiac function: There is no improvement in the RT. There is a significant improvement in combined only.

LVEF (11.9%, p=0.021)

LVEDD (17.83%, P=0.044)

LVESD (20%, p=0.035)

- Stress test: There are significant results in the 2 groups by comparing it with the control. But the results are most significant in the combined group.

Stage (57%, p=0.016)

METS (37.23%, p=0.004)

Exercise time (68.6%, p=0.001)

Results

Dyspnea (26.3%, $p=0.0001$)

- Functional Capacity: There are significant results in the 2 groups by comparing them to the control. But the results are most significant in the combined group.

Minnesota (59.4%, $p=0.009$)

NYHA (45%, $p=0.006$)

6MWT (23.76%, $p=0.005$)

- Skeletal muscle function: There is a significant improvement in RT and combined group. Strength (17.8%, $p=0.04$ and 18%, $p=0.001$), Endurance (23.7%, $P=0.037$ and 41.5%, $p=0.041$). RMS values were significantly increased in the response of the three muscles in the resistance and combined group with additive benefits for the latest. Regarding muscle fatigue analysis, MF has shown that during endurance protocol, there was a little increase only for the resistance group. However, no improvements were shown in combined group.

Third aim

Finally, the third aim was to investigate the use of SEMG in clinical diagnosis, in HF patients, in order to monitor the progression of skeletal muscle activity and function. We firstly showed, in strength and endurance manipes, a significant increase in the RMS of the three muscles in the left and right legs in the double combined group (AIT+IMT) but only an increase in the left leg for the triple combined group (AIT+IMT+RT). Surprisingly, the higher benefit was shown for the double combined group and not the triple. In others words, the addition of RT on the double combined group doesn't show any additive effects.

Study 1: Inspiratory muscle training combined to aerobic interval training improves pulmonary responses, exercise capacity and quality of life in patients with chronic heart failure: Randomized controlled trial.

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Submitted to Respiratory Care Journal, September 2018, Impact Factor: 2.

ABSTRACT

Introduction: Chronic Heart failure (CHF) is a major public health problem in which supervised exercise programs are recommended as part of a non-pharmacological management. There are various reports of the success of aerobic interval training (AIT) and inspiratory muscle training (IMT) in the management of CHF patients. This study tested the hypothesis that the combination of AIT and IMT could result in additional benefits over the IMT and the AIT alone in terms of inspiratory muscle function, exercise capacity and quality of life (QoL) in patients with CHF and inspiratory muscle weakness. Unlike other studies, this is the first paper that studies the combination of an interval aerobic and inspiratory muscle training together and compares it to four different groups, in the same population and circumstances.

Methods: Forty patients with ejection fraction $\leq 45\%$ and IMW described by maximal inspiratory pressure $< 70\%$ predicted, underwent 3 exercise training sessions per week for 12 weeks. Patients were randomly allocated to one of four groups: the AIT group, the IMT group, the combined (AIT&IMT) group and the control group. Before and after completing their training period, all patients underwent different tests.

Results: No changes were detected in the control group. However, the combined group, when compared to AIT and IMT groups respectively, resulted in additional significant improvement in maximal inspiratory training (62%, 24%, 25%), exercise time (62%, 29%, 12%), the 6 minutes' Walk Test (23%, 15%, 18%) and the Minnesota Living with Heart Failure Questionnaire (56%, 47%, 36%).

Results

Conclusion: In patients with CHF and IMW, the combination of the AIT and the IMT resulted in additional benefits in respiratory muscle function, exercise performance and QoL compared to that of AIT or IMT alone.

Keywords: Chronic Heart Failure; Inspiratory Muscle Training; Interval Aerobic Training; Exercise Capacity; Quality of life.

Trial Registration number: NCT03538249

INTRODUCTION

Exercise intolerance is a common symptom faced by Chronic Heart Failure (CHF) patients (1,2), that usually hinders their daily routines and activities (3). It is now clear, that central hemodynamic issues are the main pathophysiology factors in the CHF outcomes. However, fatigue and dyspnea that are manifested consequently were correlated to peripheral skeletal muscle changes (1), such as altered metabolism, changes in fiber types, decreased capillary density and muscle bulk (4). These changes can directly influence the respiratory muscle pump performance, since the latter is composed of skeletal muscles. Respiratory muscles dysfunction affects ventilation process, gas exchange and oxygen delivery to the organs, leading to a loss in respiratory muscle strength and endurance that is common in HF patients (5). Thus, inspiratory muscle weakness (IMW) could be explained by poor perfusion of respiratory muscles, and is associated with sympathetically mediated chemoreflex and metaboreflex hyperactivity. It is arbitrarily defined as a maximum inspiratory pressure (MIP) less than 70% of predicted value (6).

Accordingly, non-pharmacological approaches might be beneficial in improving patient's quality of life (QoL) by improving both the skeletal and the respiratory muscles (1). Therefore, physical training administered through different types of exercises in CHF patients played an important role in complementary treatment protocols and was proved safe (2). For instance, the aerobic training has shown mild improvements in mortality rates associated with CHF (2), aerobic capacity, New York Heart Association (NYHA), functional class (7), and submaximal exercise endurance (8). Moreover, many authors (9–11) demonstrated that inspiratory muscle training (IMT) had positive outcomes on QoL, respiratory and peripheral muscle strength. Pedro Dall'Ago et al. (11) showed that CHF patients, with IMW, demonstrated an improvement in MIP upon receiving the IMT for 12 weeks. However, the combination of the aerobic interval training (AIT) and the IMT showed additional benefits in the inspiratory muscle endurance, the QoL and the dyspnea, as well as in the inflammatory and cardiac biomarkers (7).

To our knowledge, there are no studies that compared the following groups: the IMT, the AIT, their combination (IMT & AIT), and the control at the same time using the same given protocol.

Thus, the aim of our study was to examine the positive effects of the combined exercise group, including both the AIT and the IMT modalities, on lung and respiratory muscle function as well as exercise capacity and QoL over the IMT alone, the AIT alone and the control group.

METHODS

Study Design

A randomized, single-blinded, parallel controlled study was performed in patients who were diagnosed with stable CHF and IMW [MIP<70% predicted] and recruited from Beirut Cardiac Institute. Eligible subjects [Ejection fraction (EF) \leq 45%, NYHA class II or III, diagnosed with CHF for more than 6 months as long as there has been no admission to the hospital or any change in medications throughout the previous 3 months] were randomized to different exercising groups. Excluded subjects suffered from pulmonary limitation [Forced expiratory volume (FEV1) and/or vital capacity <60% of predicted], orthopedic or neurologic disease, had a history of significant cardiac arrhythmia, a history of myocardial infarction or a cardiac surgery over the past 6 months, non-echogenic, unstable, poorly controlled blood pressure and/or end-stage HF. A written informed consent form was signed and obtained from all the participating subjects and all of them were receiving the same type of medication that included mainly beta blockers, Angiotensin converting enzyme inhibitors (ACE-I) or Angiotensin II receptor blockers (ARB) and Diuretics. Furthermore, an approval for the experimental protocol was obtained from the Committee for Ethics in Research of Beirut Cardiac Institute.

Protocol

40 subjects were block randomized with 1:1 to different groups as shown in the consort diagram in Figure 1. Randomization was conducted by using a research randomiser web site (Scott Plous and Jeff Breil, Lancaster, Pennsylvania). All the training groups, despite the allocation, completed 3 supervised and non-consecutive exercise sessions per week that lasted for 12 weeks, performing a total of 36 sessions. The control group patients were allocated to a non-training time period, during which they were told to continue their life as before enrollment. Assessments of pulmonary function test, inspiratory muscle function tests, stress tests, 6-minute walk test (6MWT) and QoL were completed before and after the intervention. Note that the combined group participants underwent the same protocols of the inspiratory and the aerobic trainings stated below, with almost a 5 minutes rest in between. The adherence of patients was tracked using a daily diary where all the sessions were clearly recorded and noted. Oxygen saturation and heart rate (HR) were monitored using VIAMED pulse oximetry and blood pressure was measured using a sphygmomanometer prior and upon the termination of each exercise session. All evaluations were performed by investigators who were unaware of the allocation of patients to different interventions.

Aerobic Interval Training (AIT)

Results

Interval training was used as a training modality and not as a continuous training, due to its more pronounced effects as observed by Wisloff et al. (12). To be on the safe side and to not cause any harmful effect on patient's health condition, workload was set at a moderate intensity at first and is increased by 5% every two weeks in order to reach 90% of the maximum workload at the end of the intervention. AIT included walking on a treadmill for 30 minutes at different intensities: A 1-minute warm up initiates the workout at low intensity, then is followed by a period of exercising at 60% of maximal HR (MHR) which corresponds to the first ventilatory threshold on the stress test when the patient could not continue the effort, and is terminated with a cooling down for 1 min at a low intensity too (12). Training consisted of 4 intervals of 4 minutes at 60% of MHR, and 5 intervals of 2 minutes at 50% from the maximum intensity of workload. Borg scale, HR, and blood pressure were measured before the warm-up and after the cooling down.

Inspiratory Muscle Training (IMT)

Patients received IMT for 20 min, 3 times per week, for 12 weeks using the Power Breathe training device. This device uses a technique known as resistance training in order to strengthen the breathing muscles. During training, patients were instructed to maintain diaphragmatic breathing, with a breathing rate at 15 to 20 breaths per minute. A new study reviewed the literature and found that the threshold pressure should be set at 60% of maximal inspiratory mouth pressure to achieve significant improvements in inspiratory muscle strength (13). Based on these findings, patients in the IMT group were exercised at a training load of 60% of MIP (13). In addition, training loads were adjusted to maintain 60% of the MIP every two weeks (14).

The session is divided into one minute of warm up without resistance, 4 blocks of work for 3 minutes separated by 20 seconds of rest and one minute of cool down without resistance too (15). Patients' HR, blood pressure and peripheral capillary oxygen saturation were monitored before and after the IMT session.

Pulmonary Function Test

Digital Spirometer is the standard pulmonary function test used to assess the lung function of each patient. The analysis of data was performed using a program introduced previously by NHANES II in 1990. The maneuver was done 3 consecutive times and the largest recorded value was used in the analysis. Forced Vital Capacity (FVC) and forced expiratory muscle volume in one second (FEV1) were measured while the patient was in an upright sitting position.

Respiratory Muscle Test

To assess the respiratory muscle strength, MIP and the maximal expiratory pressure (MEP) were recorded using a hand-held mouth pressure meter [MicroRPM care fusion], connected to a PUMA PC Software that offers unique and advanced features. In addition, Sustained Maximal Inspiratory Pressure (SMIP) was used to assess the respiratory muscle endurance where the time was recorded in the period during which a patient is asked to maintain a diaphragmatic breathing at 70% MIP till exhaustion. This inspiratory effort was done 3 times, with 2 minutes of rest period.

Stress Test

To assess the exercise tolerance ability, Bruce treadmill exercise test (16) was performed. In fact, it is a maximal exercise test where the patient works to complete exhaustion as the treadmill speed and incline are increased every three minutes. The intensity of the exercise was represented by exercise time, and estimated Metabolic Equivalent of a Task (METs), which is equivalent to the energy needed by an individual sitting quietly, and represented in the literature by the oxygen consumption (VO₂) of approximately 3.5 ml/kg/min (17).

Functional Capacity

The estimated functional capacity was assessed using the maximum distance covered in the 6MWT (18). HR and blood pressure were monitored at effort, and patients were asked to self-grade their dyspnea at the end of the test using Borg scale (10,19).

Quality of Life

The QoL was assessed using the Minnesota Living with Heart Failure Questionnaire (MLWHF) (20). The MLWHFQ assesses a patient's perception of the impact of HF and HF treatment on physical, psychological, and social aspects of life. It comprises 21 items and two dimensions: physical and emotional. Patients were asked to answer, using a 6-point Likert scale (0–5), how much each of 21 facets prevented them from living as they desired. Items are totaled to give a health related QoL score.

Statistical analysis

A-priori statistical power analysis revealed that $n = 12$ was the adequate sample size in order to evaluate standardized differences in the main parameters at 0.05 significance level of two-sided hypothesis, achieving power > 95%. All continuous variables are expressed as mean \pm standard deviation of the mean ($m \pm SD$). Baseline comparisons between groups were performed using one way

ANOVA-test for the normally distributed variables and Kruskal-Wallis test for the non-normally distributed variables and the chi-square test for the categorical variables (gender and medication). The paired t-test and Wilcoxon signed-rank test were used to assess training induced changes (pre vs. post) within a particular group. The effect of intervention between groups, the effect of time and the effect of group-by-time interactions were evaluated using repeated measures analysis of variance (RMANOVA). Friedman test was used when data is not normally distributed. Normality was tested using Kolmogorov-Smirnov test. The inflation of type-I error due to multiple comparisons was controlled using the Bonferroni rule. Finally, in order to compare improvement between groups, effect size for some principal parameters was calculated. The effect size (d) of different parameters (pre- vs. post-) was calculated using the following equation: $d = \frac{\mu_1 - \mu_2}{S_p}$, where d is Cohen's effect size; μ_1, μ_2 are pre- and post-intervention means, and S_p is the pooled estimate of variance calculated as follows: $S_p = \sqrt{\frac{(n_1-1)S_1^2 + (n_2-1)S_2^2}{n_1+n_2-2}}$, where n_1, n_2 are pre- and post-intervention sample sizes and S_1, S_2 are pre- and post-intervention standard deviations. Statistical analyses were performed in SPSS software (version 20, SPSS Inc., Chicago, Illinois, U.S.A.).

RESULTS

Patient characteristics

A total of 40 patients were finally enrolled. Baseline characteristics were measured and are shown in Table 1. No important adverse events were observed in any of the patients. At baseline there were no statistically significant differences between the four groups with respect to demographic characteristics, Pulmonary Function Test, Respiratory Muscle Function, QoL, Functional Capacity, and Stress Test time (Table 1). Patients were on a stable pharmacological regimen, and all of them were taking ACE-I/ARB, beta-blocker and a diuretic.

Pulmonary Function Test

No significant difference between-group was observed after the intervention for FVC (L), FEV1 (L) and FEV1/FVC. No significant group-by-time interaction was observed. Within-group analysis was also performed, and a significant increase in FVC (L) was shown in the combined group (P=0.040). Data are not shown here.

Respiratory Muscle Function

Between-group analysis revealed that SMIP and MIP differed significantly after the intervention. In particular, participants in the combined and IMT groups were more benefited as compared to the control group. A significant group-by-time interaction was observed for MEP ($P = 0.013$), MIP ($P < 0.01$), and SMIP ($P < 0.01$). Thus, within-group analysis was also performed, and a significant increase in MEP, MIP, and SMIP was shown in the combined group and IMT group. Patients in the AIT group improved significantly MEP and MIP but not SMIP (Table 2). Post hoc analysis showed that there was a significant difference between “AIT & IMT” and control groups for MIP ($P = 0.011$) and SMIP ($P = 0.011$). To compare the degree of improvement between groups, the effect size was calculated (Figure 2), and the highest improvement was observed in the combined group.

Stress Test

Between-group analysis revealed that Mets and exercise time differed significantly after the intervention. In particular, participants in the combined, AIT and IMT groups were more benefited as compared with that of in the control group. A significant group-by-time interaction was observed for Mets ($P < 0.01$), and Exercise Time ($P < 0.01$). Thus, within-group analysis was also performed, and a significant increase in Mets, and Exercise Time was shown in the combined group, AIT and IMT groups (Table 3). Post hoc analysis showed that there was a significant difference between “AIT & IMT” and control groups for METs ($P = 0.011$) and Exercise Time ($P = 0.009$). To compare the degree of improvement between groups, the effect size was calculated (Figure 3), and the highest improvement was observed in the combined group.

Functional Capacity and Quality of Life

Between-group analysis revealed that 6MWT and Minnesota differed significantly after the intervention. In particular, participants in the combined, AIT and IMT groups were more benefited as compared with that of in the control group. A significant group-by-time interaction was observed for 6MWT ($P < 0.01$) and Minnesota ($P < 0.01$). Thus, within-group analysis was performed and a significant increase in 6MWT with significant decrease in Minnesota was shown in the combined, AIT and IMT groups (Table 4). Post hoc analysis showed that there was a significant difference between “AIT & IMT” and control groups for 6MWT ($P = 0.008$). For Minnesota, there was a significant difference between “AIT & IMT” and control groups ($P = 0.012$) and between AIT and control groups ($P = 0.012$). To compare the degree of improvement between groups, the effect size was calculated (Figure 4) and the highest improvement was observed in the combined group.

DISCUSSION

In our study, we showed that the AIT and the IMT and their combination were able to elucidate significant improvements over the control group, without causing any damage to the subjects in any of the modalities, but with additional benefits for the combined group.

Respiratory Muscle Function

Both, MIP and MEP were significantly improved in all the three groups, compared to the control group. However, SMIP is only increased in the IMT and AIT+IMT groups.

In our study, the combined exercise was the most beneficial among all groups regarding MIP, MEP and SMIP with an increase of 62%, 40% and 72% respectively.

The findings related to MIP confirm the claims made by Adamopoulos et al where MIP has improved in AIT and AIT+IMT groups. These results suggest that the aerobic training, although it doesn't train the respiratory muscles directly, is able to improve the inspiratory muscle performance, possibly by its "anti-inflammatory" effect. Concerning SMIP, the 72% improvement shown for the combined group might be more attributed to the IMT, since an incremental increase (51%) was shown for the IMT group versus no improvement shown for the AIT group. Note that the benefits credited to the IMT were approved in previous studies (9,11,22). Dall'Ago et al. (11) and Bosnak-Guclu et al. (9), reported a 115% and 50% increase in MIP respectively, which is greater than the increase reported in our IMT group (25%). Possible reasons include longer IMT duration, different training regimes, and different HF populations.

Previous HF studies have shown that improvements in respiratory muscle function may be attributed to a reduced activity of inspiratory chemoreflex and metaboreflex (22). In fact, chemoreflexes refers to the effects of the central and peripheral chemoreceptors on pulmonary ventilation. However, metaboreflex is triggered by skeletal muscle abnormalities, resulting in metaboreceptors activation. It is also mediated by stimulations that can discharge group III and IV muscle afferents (6). Alternatively, such improvements may be due to reduced activity of chemo and metaboreflexes, that may have been caused by decreased oscillatory ventilation, a desensitization of the type III/IV afferents secondary to a reduced metabolite accumulation, and an increased oxidative capacity of the respiratory muscles (23).

Stress Test

The analysis of the variables measured during the "Stress Test" gives an important evaluation of the cardiovascular fitness and functional capacity. Most important is the exercise time (24) since it was

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mostly improved in the combined groups where a synergetic effect between AIT and IMT was enough for exerting this amelioration in the exercise duration. In our study, this effect is reflected by a mean increment of 62% in the combined group, compared to 29% in the AIT and 10% in the IMT. In previous reports, Laoutaris et al (14) showed a 9% of increment in the exercise duration which is lower than the one recorded in this study. This is probably due to the fact that interval training is more effective in improving exercise time than continuous training.

However, Adamopoulos et al. (7) have shown that the combined group improved exercise time by 17%, which was not seen with the aerobic training group. They proposed that this improvement might be due to the amelioration in dyspnea and the IMT symptomatic relief.

Another finding is the additive effect between the AIT and the IMT concerning METs. Actually, the combined training resulted in a 34% of increment in METs. Such benefit could be related to the improved cardiorespiratory fitness of HF patients.

A possible explanation for the improvement in exercise performance might be because of the inhibition of the inspiratory metaboreflex hyperactivity that is usually shown in HF patients during physical exercise. This fact decreases sympathetic activity and peripheral vasoconstriction, leading to an increased blood flow to the active skeletal muscles, and an enhanced perfusion of the locomotor muscles (6,25).

Functional Capacity and Quality of Life

It have been shown that the IMT improves functional capacity in patients with CHF with IMW (11,26–28) whereas aerobic training partially improves functional capacity and QoL in these patients (2,29).

Patients in both IMT, and AIT groups increased their walking distance significantly (18.3% and 14.9% respectively). But a greater benefit was shown for the combined group (22.6%) and this can be explained by the significant amelioration in exercise performance.

In this study, we have shown that exercise training can improve the quality of CHF patients' life. Each exercise training program; IMT, AIT and combined protocols resulted respectively in a 36%, 46% and 56% decrease in the Minnesota score which reflects amelioration in the daily living limitations, mainly for the combined groups.

Consequently, an improvement was shown in both 6MWT and QOL for the IMT and the combined groups with a greater benefit for the latest, suggesting that the AIT may provide important symptomatic relief and improve daily life activities.

CONCLUSION

This randomized clinical trial verified that, in patients with CHF and IMW, the combination of the AIT and the IMT results in an additional improvement in the inspiratory muscle function, which could be mediated by a reduced activity of metaboreflex and chemoreflex. This effect may be related to the reduced functional capacity and the exercise intolerance observed in our study.

These findings may have important implications for exercise training in cardiac rehabilitation programs, but further investigation is needed, to highlight the effects of combined aerobic and inspiratory muscle training in CHF, in order to ensure the safety and effectiveness of such program.

LIMITATIONS AND PERSPECTIVES

The potential limitation of our method is the heterogeneity in training load, especially in the exercise duration. In fact, the aerobic and the inspiratory muscle trainings were performed three times a week for 30 minutes and 20 minutes respectively. However, the combined group included both training modalities and therefore underwent longer exercise duration that can reach 50 minutes per session. Therefore, this difference in the workload between the three groups might have influenced our results.

Thus, putting into perspective a comparison between different programs with an equivalent workload would be interesting in order to know if the effects are cumulative due to a large training volume or due to something else, more specifically to the specificity of each program.

Further studies though, might need to take into consideration this limitation in order to assess it and to look into the additional benefits of resistance training alone and combined to the AIT and the IMT group.

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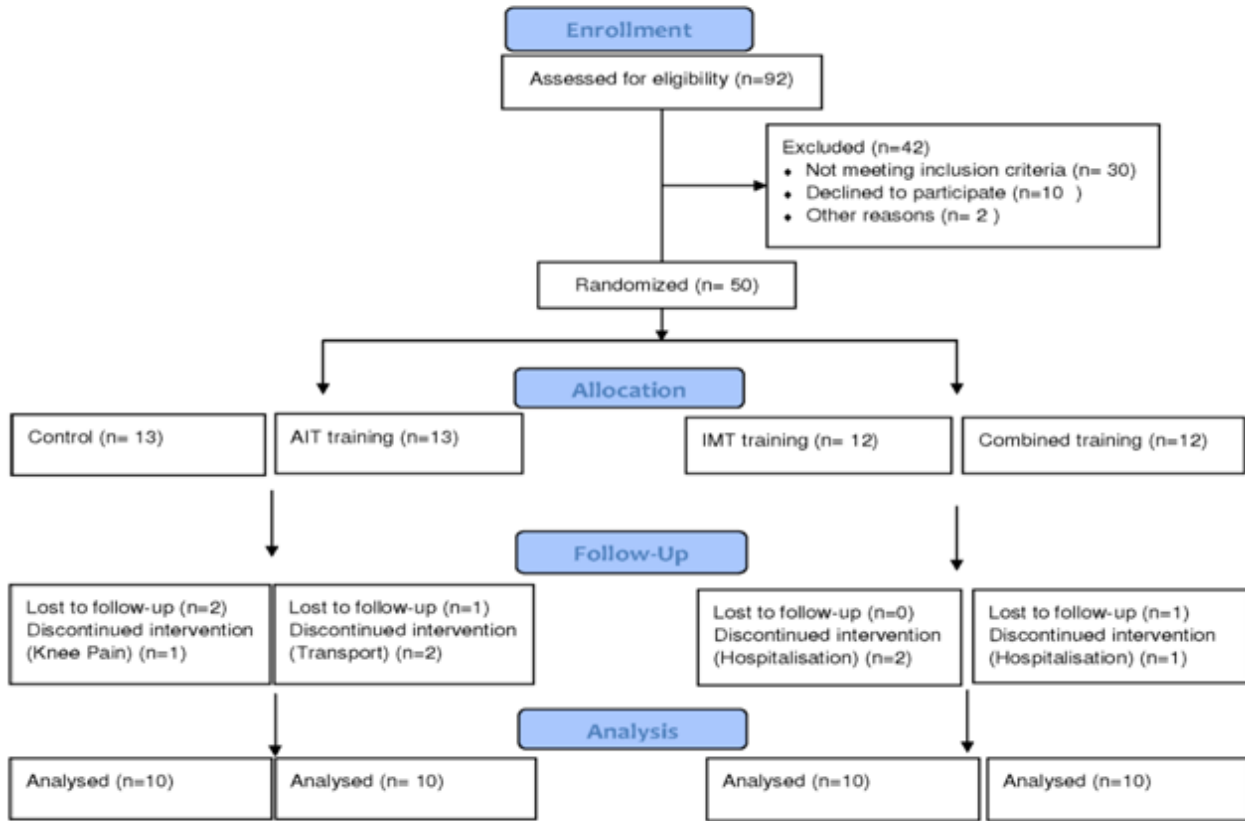


Figure 1 - Participant flow diagram - Consort (consolidated Standards of Reporting Trials) diagram of recruitment to the trial.

AIT: Aerobic Interval Training; IMT; Insoratory muscle training

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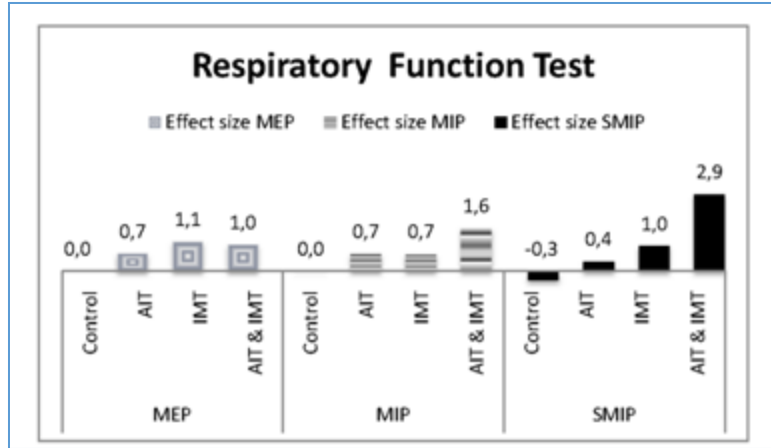


Figure 2 - Effect size on respiratory muscle function, MEP, maximal expiratory pressure; MIP, maximal inspiratory pressure; SMIP, sustained maximal inspiratory pressure.

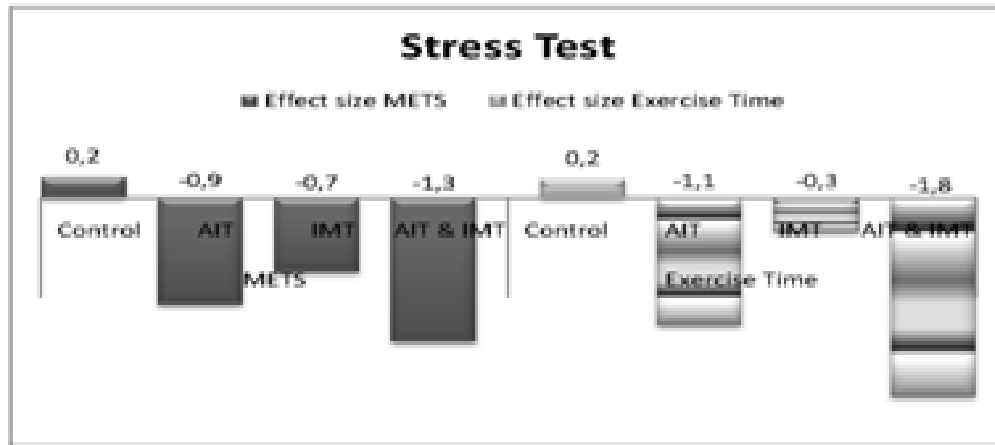


Figure 3 - Effect size on stress test; METS, metabolic equivalent of a task; Exercise Time.

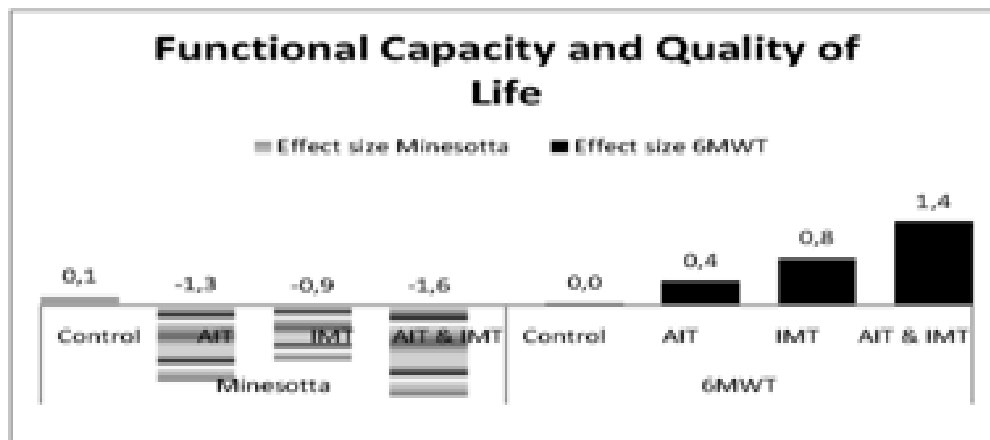


Figure 4 - Effect size on functional capacity and quality of life; 6MWT: six minutes' walk test.

Results

Table 1- Demographic and clinical characteristics of patient population.

	Control	AIT	IMT	AIT& IMT	P-value
Ages (years)	52.6±11.2	51.6±13.8	52.5±13.7	51.8±8.3	0.998
Males/females	5/5	5/5	5/5	5/5	0.943
BMI	27.3±3.4	28.1±3.7	28.3±1.4	27.7±3.9	0.918
FVC (L)	3.2±0.8	3.2±0.9	2.9±0.7	2.9±0.4	0.809
FEV1 (L)	2.4±0.9	2.7±0.8	2.4±0.6	2.3±0.5	0.748
FEV1/FVC	74.9±11.7	84.8±13.5	81.6±12.9	78.3±11.7	0.439
MIP (mmHg)	35.8±10.5	34.4±11.4	36.4±14.3	33.5±13.1	0.966
SMIP (s)	216.3±91	223.1±69.5	245±102.7	244.3±64.3	0.862
MEP (mmHg)	70.1±16.7	66.3±17.8	61.5±18.8	60.1±19.1	0.679
Minnesota score	29.9±10.6	24±6.5	28.1±11.7	24.8±11.3	0.626
6MWT (m)	455.3±113.1	427.6±153	449.6±96.4	462.8±73.1	0.933
Exercise time (s)	475.5±144.7	516.9±123.6	484.4±164	509.5±180.9	0.941

BMI, body mass index; **FVC**, forced vital capacity; **FEV1**, forced expiratory volume in 1 second; **MIP**, Maximal inspiratory pressure; **MEP**, maximal expiratory pressure; **SMIP**, sustained maximal inspiratory pressure; **6MWT**, six minute walk test.

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Table 2 - Respiratory Muscle Function.

	Control			AIT			IMT			AIT & IMT			P ^b
	Pre	Post	P ^a	Pre	Post	P ^a	Pre	Post	P ^a	Pre	Post	P ^a	
MEP (mmHg)	70.1±16.7	70.1±18.4	1	66.3±17.8	81.1±25.9	0.011	61.5±18.8	84.8±22.9	0.003	60.1±19.1	84.5±28.4	0.010	0.985
MIP (mmHg)	35.8±10.5	36±11.5	0.895	34.4±11.4	42.8±13.4	0.012*	36.4±14.3	45.5±13.5	0.001	33.5±13.1	54.4±12.5	0.012*	0.020*
SMIP (s)	216.9±90.9	184.9±92.3	0.624*	223.13±69.5	249.8±75.7	0.381	245±102.7	369±151.5	0.002	244.3±64.3	418.9±56.1	0.017*	0.016*

MEP, maximal expiratory pressure; MIP, maximal inspiratory pressure; SMIP, sustained maximal inspiratory pressure

^a P-Values derived using paired Student's t-test, after checking for the normality of the distributions.

^b P-Values between groups derived using repeated measures analysis of variance (RMANOVA).

*P^a derived using Wilcoxon signed-rank test.

*P^b-Values between groups derived using Friedman test.

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Table 3 - Stress Test

	Control			AIT			IMT			AIT & IMT			P ^b
	Pre	Post	P ^a	Pre	Post	P ^a	Pre	Post	P ^a	Pre	Post	P ^a	
METs	8.1±2.1	7.7±2.2	0.424	9.9±1.9	11.7±1.9	0.001	8±2.9	9.7±2.2	0.010	9.9±2.4	13.3±2.9	0.001	0.009
Exercise Time (s)	474.5±144.7	448.1±168.3	0.889*	516.9±123.6	669.1±144.9	0.001	484.4±164	542.5±157.3	0.047	500.9±180.9	812.8±172.9	0.000	0.048

METs, metabolic equivalent of a task

^a P-Values derived using paired Student's t-test, after checking for the normality of the distributions.

^b P-Values between groups derived using repeated measures analysis of variance (RMANOVA).

^{*}P^a derived using Wilcoxon signed-rank test.

^{*}P^b-Values between groups derived using Friedman test.

Table 4 - Functional Capacity and Quality of Life

	Control			AIT			IMT			AIT & IMT			P ^b
	Pre	Post	P ^a	Pre	Post	P ^a	Pre	Post	P ^a	Pre	Post	P ^a	
6MWT	455.3±113.1	457.2±104.9	0.905	427.6±153	491.5±170	0.000	449.6±96.4	532.1±113.9	0.022	462.8±73.1	567.5±75.9	0.017*	0.042*
Minnesota	29.9±10.6	31.6±13.8	0.348	24±6.5	12.8±10.4	0.002	28.1±11.7	18±9.7	0.012*	24.8±11.3	10.8±5.8	0.001	0.002*

6MWT, six minute walk test;

^a P-Values derived using paired Student's t-test after checking for the normality of the distributions.

^b P-Values between groups derived using repeated measures analysis of variance (RMANOVA).

^{*}P^a derived using Wilcoxon signed-rank test.

^{*}P^b-Values between groups derived using Friedman test.

Study 2: Combining Aerobic Interval Training and Inspiratory Muscle Training improves cardiac and skeletal Function in Chronic Heart Failure Patients with inspiratory muscle weakness.

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ABSTRACT

Objectives: The objective of this study was to evaluate the effects of aerobic interval training (AIT) combined with inspiratory muscle training (IMT) on cardiac and skeletal muscle function as well as on dyspnea and NYHA in patients with chronic heart failure (CHF) and inspiratory muscle weakness (IMW). Also, to investigate the use of EMG in clinical diagnosis, in order to monitor the progression of skeletal muscle activity and function.

Methods: 40 patients were randomly assigned to one of the following groups: AIT (n=10), IMT (n=10), combined [AIT & IMT] (n=10) and control group (n=10). The training regimens were performed 3 times a week for 12 weeks. Surface electromyography (SEMG) activities were recorded from the vastus lateralis (VL), rectus femoris (RF), and vastus medialis (VM) during strength and endurance manipes and the cardiac function was recorded during rest echocardiography.

Results: AIT&IMT group was superior to the three other groups in all parameters assessed: cardiac and skeletal muscle function, dyspnea (30%, $p<0.008$), NYHA (30%, $p<0.008$) and most importantly in root mean square (RMS) and median frequency (MF) in both strength and endurance manipes. Therefore, it has been shown that the combination of aerobic and inspiratory muscle training was the best in reversing the cardiac remodeling process especially for Left Ventricular Ejection Fraction (17%, $p<0.042$).

Conclusion: Combining AIT to IMT had optimized exercise training benefits. And the use of SEMG in the clinical laboratory was investigated, for the assessment and monitoring of skeletal muscle function.

Keys words: Chronic heart failure, Electromyography, Aerobic training, Inspiratory muscle training.

Trial Registration number: NCT0353824

INTRODUCTION

Heart Failure (HF) is a multi-systemic disease that is characterized by abnormalities in cardiac function, skeletal muscle, pulmonary function and many others (1). The main abnormality in HF is impaired left ventricular function, resulting in a decrease of cardiac output (CO). Accordingly, the heart will respond by allowing a greater amount of blood to fill the ventricle, and thus increasing its size and consequently its volume. This will end up with "ventricular remodeling" process that refers to an altered ventricular architecture, associated with an increased volume and an alteration of the configuration of the ventricular chamber (2).

Impaired exercise tolerance, breathlessness and dyspnea are considered the gold standard clinical manifestations of HF syndrome (3). These phenomena result in a poor quality of life (QoL) and a sedentary lifestyle. Diminished skeletal muscle mass and strength represent the origin of such limitations. In fact, many skeletal muscle changes occur such as muscle metabolism impairment, mitochondrial changes, altered fibers distribution, inflammation and muscle atrophy (4).

To assess skeletal muscle function, some features are extracted from the recorded electrical activity of the muscles known as Electromyography (EMG), such as amplitude or the root mean square value (RMS) and median frequency (MF) (5). These parameters aim towards detecting any abnormalities in the motor unit (MU), the smallest functional unit of the muscle. RMS is synonymous with MU recruitment. In other words, when RMS increases, additional motor units are recruited. This recruitment is dependent on the force level and increases with exercise intensity (6). However, MF corresponds more to the level of depolarization of MU during their contraction.

On the one hand, any metabolic, mechanical, and neuromuscular changes induced by endurance training will impact on RMS value towards an upward trend. On the other hand, inactivity, age and some diseases will drop the RMS but its representation will always be in the form of an increasing curve with a very low slope.

Recently, EMG activity was correlated with skeletal muscle fatigability in chronic HF patients (7), and it was associated with an increase in RMS and decrease of MF.

Cardiac rehabilitation, including exercise training -in its different types- is well spotlighted recently, mainly because of studies that show its benefits in various outcomes.

In fact, aerobic training (AT) and inspiratory muscle training (IMT) have been shown to be safe and with complementary benefits in chronic HF.

Many researches have suggested the importance of AT, IMT and their combination on different levels, i.e. cardiac function, peak VO₂, QoL, six minute walk test (6MWT) (8–10) and especially in reducing muscular dysfunction by enhancing muscular metabolism and functional capacity (3).

But the question is whether these different types of trainings reflect the neuromuscular function of motor units, reduce the fatigue threshold and reverse the remodeling process in HF patients. Therefore, the objective of this study is first to examine the efficiency of an Aerobic Interval Training (AIT) combined with IMT, thus, including both the AIT and the IMT modalities, on cardiac and skeletal muscle function as well as on dyspnea and NYHA over the IMT alone, the AIT alone and the control group. Also, to investigate the use of EMG in clinical diagnosis, in HF patients, in order to monitor the progression of skeletal muscle activity and function.

METHODS

Study Design

A randomized, single-blinded controlled study was performed in patients who were diagnosed with stable CHF and inspiratory muscle weakness (IMW) [MIP<70% predicted] and recruited from Beirut Cardiac Institute. Eligible subjects [Ejection fraction (EF) ≤ 45%, NYHA class II or III, diagnosed with CHF for more than 6 months as long as there has been no admission to the hospital or any changes in medication throughout the previous 3 months] were randomized to different exercising groups. Some subjects were excluded due to the following reasons: pulmonary limitation [Forced expiratory volume (FEV₁) and/or vital capacity <60% of predicted], orthopedic or neurologic disease, a history of significant cardiac arrhythmia, a history of myocardial infarction or a cardiac surgery over the past 6 months, non-echogenic, unstable, poorly controlled blood pressure and/or end-stage HF. All participants were receiving the same type of medication that included mainly beta blockers, Angiotensin converting enzyme inhibitors (ACE-I) (or Angiotensin II blockers) and Diuretics. Then, a written informed consent form was signed and obtained from all the participating subjects. Furthermore, an approval for the experimental protocol was obtained from the Committee for Ethics in Research of Beirut Cardiac Institute.

Protocol

Through this study, 40 subjects were randomly allocated to different groups having different exercise training modalities. Four groups were formed: the AIT group (n=10), the IMT group (n=10), the combined [AIT & IMT] group (n=10) and the control group (n=10). All the training groups, despite the

allocation (figure 1), completed 3 supervised and non-consecutive exercise sessions per week that lasted for 12 weeks, performing a total of 36 sessions. The control group patients were allocated to a non-training time period, during which they were told to continue their life as before enrollment. Assessments of pulmonary function test, inspiratory muscle function tests, echocardiography stress tests, skeletal muscle function tests, 6-minute walk test, dyspnea and QoL were completed before and after the allocation of subjects. Note that the AIT & IMT group participants underwent the same protocols of the inspiratory and the aerobic trainings stated above, with almost a 5 minutes rest in between. The adherence of patients was tracked using a daily diary where all the sessions were clearly recorded and noted. Oxygen saturation and heart rate were monitored using VIAMED pulse oximetry and blood pressure was measured using a sphygmomanometer prior and upon the termination of each exercise session.

Aerobic Interval Training (AIT)

The AIT included walking on a treadmill for 30 minutes. A 3-minute warm up initiated the workout, followed by 4 minutes at high intensity [60% of maximum heart rate (HRmax) increased later by 5%] interspaced by 2 minutes at low intensity (50% of the high intensity). The high intensity target was to reach 90% of the HRmax. However, this exercise was completed by a 3 minutes (cool down) progressive decrease of intensity at the end of the workout (11).

Inspiratory Muscle Training (IMT)

Patients were enrolled in the IMT group, where they trained using Power breathe IMT device at a load of 60% MIP (high intensity). Each session started with a 1 minute warm up at low intensity (30% MIP), followed by 4 consecutive sets of high intensity trainings partitioned by a 20 seconds rest period, and finalized with a 1-minute cooling down with low intensity inspiratory training (12).

Skeletal Muscle Function

The evaluation of the skeletal muscle strength_(M1): It was evaluated using a hand-held isokinetic apparatus (Manual Muscle Tester Lafayette 01165). Maximal Voluntary Isometric Force (MVIF) for the quadriceps was measured on the isokinetic apparatus; the patient was seated and positioned with a 60° knee and 120° hip angulation (13). Three sets with three repetitions each were performed in order to obtain maximum force. MVIF was an average to the best values obtained through the sets. The evaluation of the skeletal muscle endurance_(M2): Isometric endurance time (MT) was also measured when subjects maintained an isometric contraction at 50% of the reported MVIF. Verbal encouragement

helped the subjects to maintain the weight as long as they could (13). The maneuver was repeated three times to guarantee maximum performance.

Surface Electromyography

During strength and endurance manipes (M1 and M2 respectively), surface electromyography (SEMG) activities were recorded from the vastus lateralis (VL), rectus femoris (RF), and vastus medialis (VM). Electrodes with a disc shape were located for VL on quarter distance proximal to the lateral tibial condyle on a line connecting this and the anterior-superior-iliac-spine (ASIS). For RF, electrodes were place at mid distance along the line connecting the ASIS to the superior aspect of the patella. For VM, electrodes were placed at a position 20% of the distance along a line connecting the medial gap of the knee to the ASIS. Before electrodes application, the skin was cleaned. The signals of 3 VL, RF and VM were stored in LabView (32 bits). The root mean square (RMS) and median frequency (MF) were calculated by the matlab program. RMS and MF were averaged for each muscle (14).

Cardiac Function

The cardiac dysfunction at rest was confirmed by the echocardiographic method, with the help of two experienced cardiologists blinded to subject's allocation. Subjects were examined at rest in the left lateral supine position using a Vivid S6 ultrasound probe, General Electric Healthcare, GEMs supplies. Biplane Simpson's method (apical four-chamber view) was used for the estimation of echocardiographic measures. Parameters assessed during echocardiography were left ventricular ejection fraction (LVEF in %); left ventricular end systolic, diastolic diameter (LVESD and LVEDD in mm) and left ventricular end systolic, diastolic volume (LVESV and LVEDV in mm).

Dyspnea and Quality of life

During each training session, patients were asked to self-grade their dyspnea according to Borg scale (15). The scale is comprised of different intensity levels, where the patients evaluated their exertion level according to a visual attached numerical scale from 6 to 20 with 6 corresponding to no fatigue or other symptoms and 20 to maximum exertion. Borg scale was affirmed for its sensitivity and reproducibility to be used as a subjective reference during submaximal workouts (15). The QoL was assessed using the Minnesota Living with Heart Failure Questionnaire (MLWHF) (16). The MLWHFQ assesses a patient's perception of the impact of HF and HF treatment on physical, psychological, and social aspects of life. It comprises 21 items and two dimensions: physical and emotional. Patients were

asked to answer, using a 6-point Likert scale (0–5), how much each of 21 facets prevented them from living as they desired. Items are totaled to give a health related QoL score.

New York Heart Association functional classification

NYHA functional classification is also a determinant of HF patients' QoL, since it is concerned with symptoms and signs representing an obstacle that hinders the patients' life.

NYHA functional classification provides useful and complementary information about the presence and severity of HF. It classifies patients in one of four categories based on their limitations during physical activity. These classes are progressive and inviolate; once a patient moves to a higher class, regression to an earlier one is not observed.

Statistical analysis

A-priori statistical power analysis revealed that $n = 10$ was the adequate sample size in order to evaluate standardized differences in the main parameters at 0.05 significance level of two-sided hypothesis, achieving power $> 95\%$. All continuous variables are expressed as mean \pm standard deviation of the mean ($m \pm SD$). Baseline comparisons between groups were performed using one way ANOVA-test for the normally distributed variables and Kruskal-Wallis test for the non-normally distributed variables and the chi-square test for the categorical variable (gender). The paired t-test and Wilcoxon signed-rank test were used to assess training induced changes (pre vs. post) within a particular group. The effect of intervention between groups, the effect of time and the effect of group-by-time interactions were evaluated using repeated measures analysis of variance (RMANOVA). Friedman test was used when data is not normally distributed. Normality was tested using Kolmogorov-Smirnov test. The inflation of type-I error due to multiple comparisons was controlled using the Bonferroni rule. Finally, in order to compare improvement between groups, effect size for some principal parameters was calculated. The effect size (d) of different parameters (pre- vs. post-) was calculated using the following equation: $d = \frac{\mu_1 - \mu_2}{S_p}$, where d is Cohen's effect size; μ_1, μ_2 are pre- and post intervention means, and S_p

is the pooled estimate of variance calculated as follows: $S_p = \sqrt{\frac{(n_1 - 1)S_1^2 + (n_2 - 1)S_2^2}{n_1 + n_2 - 2}}$, where n_1, n_2 are pre- and post intervention sample sizes and S_1, S_2 are pre- and post intervention standard deviations. Statistical analyses were performed in SPSS software (version 20, SPSS Inc., Chicago, Illinois, U.S.A.

RESULTS

Patient Characteristics

A total of 40 patients were finally enrolled in the study. Baseline characteristics were measured and reported in Table 1. No important adverse effects were observed in any of the patients. At baseline there were no statistically significant differences among the four groups with respect to demographic characteristics, Functional Capacity, Cardiac Function and Structure, Endurance and Skeletal Muscle Function (Table 1). Patients were on a stable pharmacological regimen, and all of them were taking an ACE-I/ARB, a beta-blocker and a diuretic.

Skeletal Muscle Strength and Endurance

Participants in the AIT & IMT and the AIT groups derived more benefits than the control group. No significant group-by-time interaction was observed. Within-group analysis was performed and a significant increase in MVIF left and MVIF right in the AIT and the AIT & IMT group was recorded (Table 2). Participants in the AIT & IMT and the AIT groups derived more benefits than the control group. A significant group-by-time interaction was observed for MT Left ($P = 0.024$). Then, within-group analysis was performed and a significant increase in MT Right and MT Left was detected in the AIT group and the AIT & IMT group. Patients in both AIT and AIT & IMT groups improved MT Right and MT Left significantly (Table 2). In order to compare the improvement among the groups, the effect size was calculated. As shown in (Figure 2), the improvements were highly significant in the “AIT & IMT” group mainly for MVIF left and MT left.

Surface Electromyography

Parameter M1: Between-group analysis revealed that the response of Vastus lateralis, Rectus femoris and Vastus medialis differed significantly after the intervention for the Root mean square (Left Leg). In particular, participants in the Aerobic and Respiratory group were more benefited as compared to the control group. A significant group-by-time interaction was observed for Vastus lateralis ($P = 0.000$), Rectus femoris ($P = 0.000$), and Vastus medialis ($P = 0.000$). Thus, within-group analysis was also performed, and a significant increase in the response of the three muscles was shown in the Aerobic and Respiratory group. A significant increase in the response of Vastus lateralis and Rectus femoris was observed in the Aerobic group. For the Root mean square (Right Leg), no significant difference was observed between the groups for the three muscles. However, a significant increase in the response of the three muscles was observed for the Participants in the Aerobic and Respiratory group (Table 3).

Parameter M2: For the Root mean square (left and right leg), no significant difference was observed between the groups for the three muscles. However, a significant increase in the response of the three muscles was observed for the Participants in the Aerobic group and in the Aerobic and Respiratory group (Table 4). FM increase significantly after training in the Aerobic group ($P = 0.000$), Respiratory group ($P = 0.000$) and in the Aerobic and Respiratory group ($P = 0.000$) maintaining a linear regression as illustrated in Figures 4 to 6.

Cardiac Function and Structure

Participants in the AIT & IMT group were more benefited as compared with those in the control group. A significant group-by-time interaction was observed for LVEF ($P = 0.024$), LVEDV ($P = 0.000$) and LVESV ($P = 0.000$). Then, within-group analysis was performed, a significant increase in LVEF (0.042) and a significant decrease in LVEDD ($p = 0.036$), LVESD ($P = 0.023$), LVEDV ($P = 0.001$) and LVESV ($P = 0.001$) were recorded in the AIT & IMT group (Table 5). A significant improvement was also revealed for LVEF, LVEDD, LVESD, LVEDV and LVESV in the “AIT” group and mainly for LVEDV and LVESV in the “IMT” group.

In order to compare the improvement between groups, the effect size was calculated. As shown in (Figure 7), the improvements were highly significant in the “AIT & IMT” group mainly for LVEF and LVESD.

Functional capacity and Dyspnea

A significant difference between-group was observed after the intervention for the Dyspnea and NYHA only. In addition, a significant group-by-time interaction was detected for dyspnea ($p = 0.001$), 6MWT ($P = 0.042$) and NYHA ($P < 0.01$). Then, within-group analysis was performed a significant decrease in dyspnea and NYHA and a significant increase in 6MWT was observed in the AIT & IMT, the AIT and the IMT groups (Table 6).

DISCUSSION

Leg Skeletal Muscle Function

To our knowledge, this is the first study to assess the skeletal muscle function during an AIT & IMT exercise protocol in CHF patients. It is important since peripheral skeletal abnormalities contribute to exercise intolerance in HF subjects (17,18) and cardiac rehabilitation mainly tends toward improving cardiac patients' Qol and functional capacity (19). Fortunately, in our study, the AIT & IMT group

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showed significant improvements in skeletal muscle strength and endurance which is attributed to the aerobic treadmill training since IMT didn't show any significant improvement. Aerobic training was able to improve the MVIF exerted by the quadriceps in the lower left and right legs by around 10%, which is not different than the improvement (11%) in the MVIF reported in the patients of the AIT & IMT groups. Thus, IMT had no effect on the peripheral skeletal muscles and the attributed increment was due to the aerobic training.

The peripheral muscle endurance was also assessed. Results showed an improvement in the maintenance time of both left and right legs. The increase in both quadriceps generated strength and endurance reflected an improvement in the dyspnea sensation of the patients. In fact, this is related to the treadmill aerobic exercise since inspiratory exercise didn't show any improvement in the skeletal muscle function. Such improvements might be due to a decrease in peripheral muscle damage. As reported by Adamopoulos et al. in 1993 (20), the aerobic exercise training results in a reduction in the phosphocreatine depletion and the advanced phosphocreatine resynthesized recovery, which reflects an improvement in the oxidative capacity of the muscles.

Surface Electromyography

The additive aim of this study is to investigate the usefulness of EMG in HF patients, in order to monitor the progression of skeletal muscle activity and function. Skeletal muscle fatigue is linked to an increase in the SEMG signal amplitude (as the RMS) and EMG spectrum (as the MF) (21–24).

We firstly demonstrated a significant increase in the response of the three muscles in the combined group, in both strength and endurance manipes. RMS values were significantly increased in the aerobic and combined group. In fact, it is well known that the amplitude of the EMG signal is related to a certain extent to the strength that the muscle can produce. In other words, since the amplitude of the EMG signal is determined by the number of recruited motor units, the increase in RMS of the EMG signal after training was the result of an adaptation of the muscle fiber and a combination of recruitment of an increased number of motor units and an increased firing rate of each unit. This might suggest the existence of neural adaptations occurred with the training in order to compensate for muscle fatigue that is usually detected in HF patients (25).

In addition, we didn't find any increase in the response of the three muscles in the IMT group during strength protocol. However, RMS for the Rectus femoris muscle was improved in the IMT group during

endurance protocol. Thus, the improvement in the combined training was the result of the aerobic training and not the inspiratory training.

Concerning muscle fatigue analysis, MF extracted from the EMG signal is the optimal variable to assess muscle fatigue (26). Due to our huge data and since all patients were right-side dominant, we have shown only the results of EMG conducted on the right leg for the FM from manipe 2.

It has been shown that during endurance protocol, aerobic, inspiratory and combined trainings had positive effects on skeletal muscle fatigue indexes.

There is a possibility that this result is indirectly related to the higher recruitment of motor units and directly linked to an accumulation of anaerobic metabolism by-products such as lactate, protons, ammonium and an earlier recruitment of fast motor units (22–24). Another explanation could be due to the changes of motor unit's function that can occur and are still not totally clear.

Cardiac Function and Structure

The AIT resulted in significant improvements in the given central parameters: LVEF, LVEDD and LVESD, LVEDV and LVESV versus an improvement only in LVEDV and LVESD in the IMT group. However, higher improvements were obtained in the AIT & IMT group suggesting that the addition of IMT to AIT had more pronounced effect than pure inspiratory training. LVEF and LVESD were highly improved in the combined group and this confirm the safety and benefit of our program, which was also asserted in a previous study that utilized aerobic training in CHF patients (9). On the other hand, the decrease in LVESD and LVEDD reflects better left ventricular filling properties (27) that will improve LVEF. In addition, a meta-analysis done by Haykowsky et al. (28) showed that exercise training alleviated left ventricular remodeling in post-MI patients who were clinically stable (28) while our exercise training program relieved remodeling damage on the left ventricle and improved its function. LVESV and LVEDV decrease due to decreases in the afterload followed by increases in LVEF. This fact might be caused by an improved strength of contraction of the myocardium and a reduced cardiomegaly, or most probably by a reverse remodeling process that have occurred after exercise training.

Functional capacity and Dyspnea

Cardiac rehabilitation programs aim to improve the QoL of HF patients especially that this syndrome progresses to very severe symptoms and eventually can lead to severe exercise intolerance. In this study, we have shown that exercise training is able to improve the quality of CHF patients' life. In fact, there

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was a 36%, 46% and 56% decrease in the Minnesota total score in the IMT, AIT and AIT&IMT groups respectively. There is a possibility that this result is due to the improvement of skeletal muscle function and especially the diminution of skeletal muscle fatigue observed in our study. NYHA functional classification is also a determinant to heart failure patients' QoL, since it is concerned with symptoms and signs representing an obstacle that hinders the patients' life. As well, improvements were detected after exercise training in the IMT (30.4%), the AIT (39.1%) and the AIT & IMT (48%) groups. Noting that Adamopoulos et al. (29) and Laoutaris et al. (9) also reported NYHA functional class improvement in their patients after exercise training, but the improvement in our study was more important due to our subjects' greater improvement in functional capacity and skeletal muscle performance.

CONCLUSION AND LIMITATIONS

CHF patients often suffer from exercise intolerance and a poor QoL, mainly due to an impaired skeletal muscle function and a marked skeletal muscle fatigue. Cardiac rehabilitation programs recommend exercise training as a therapy that alleviates these symptoms. As expected, the addition of aerobic training to inspiratory muscle training had optimized exercise training benefits.

In this paper, the use of EMG in the clinical laboratory was investigated, for the assessment and monitoring of skeletal muscle function. It has been shown that the combination of aerobic and inspiratory muscle training was the best in reversing the cardiac remodeling process and improving skeletal muscle function, quality of life and dyspnea. As well, an increase in RMS value and in skeletal muscle fatigue index (MF) were noted. This is explained by an increased ability of a muscle to generate force, secondary to higher motor unit recruitment.

Although we conducted a large study, patient enrolment was slow and the patient number remains small and a higher number could have resulted in more significant improvement.

It is hoped that the above directions for future work will contribute towards more knowledge about skeletal muscle metabolism and neuromuscular modifications that occurs after any training program.

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Results

Table 1: Demographic and clinical characteristics of patient population.

	Control	AIT	IMT	AIT& IMT	P-value
Ages (years)	52.6±11.2	51.6±13.8	52.5±13.7	51.8±8.3	0.998
Males/females	5/5	5/5	5/5	5/5	0.943
BMI	27.3±3.4	28.1±3.7	28.3±1.4	27.7±3.9	0.918
MIP (mmHg)	35.8±10.5	34.4±11.4	36.4±14.3	33.5±13.1	0.966
6MWT (m)	455.3±113.1	427.6±153	449.6±96.4	462.8±73.1	0.933
Exercise time (s)	475.5±144.7	516.9±123.6	484.4±164	509.5±180.9	0.941
MT L (s)	123±48.3	98±35	99.4±47.7	105.8±39.6	0.767
LVEF rest (%)	35.1±7.4	37.6±5.7	35.4±6.5	38±5	0.828
LVESD rest (mm)	50±10.1	51.5±11.2	52.4±5	50.3±7.2	0.942
LVEDD rest (mm)	61.1±9.9	63±8.1	63±2.7	63±7.9	0.948

BMI, body mass index; FVC, forced vital capacity; FEV1, forced expiratory volume in 1 second; PImax, Maximal inspiratory pressure; PEmax, maximal expiratory pressure; SPImax, sustained maximal inspiratory pressure; METs, metabolic equivalent of a task; 6MWT, six minute walk test; MT L, maintenance left; MT R, maintenance right; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; LVEDD, left ventricular end-diastolic diameter.

Table 2- Skeletal Muscle strength and endurance.

	Control			AIT			IMT			AIT& IMT			P ^b
	Pre	Post	P ^a	Pre	Post	P ^a	Pre	Post	P ^a	Pre	Post	P ^a	
MVIF L (kg)	18.1±3.7	17.4±4.4	0.194	19.2±3	21.1±3.4	0.006	18.8±2.9	19.4±3.1	0.653	19.3±2.6	21.4±2.7	0.001	0.312
MVIF R (kg)	18±4.7	18.2±5.2	0.855	19.8±3.3	21.6±3.5	0.014	18.8±3.3	19.4±2.4	0.330	18.9±2.9	20.9±2.6	0.001	0.492
MT Right (s)	105±30.3	103.9±73.9	0.237	90.6±25.5	107.9±31.7	0.023	95.4±25.8	107.5±41.1	0.354	104.9±38.9	124.7±47.4	0.003	0.789
MT Left (s)	123±48.3	114.1±46.9	0.485	98±35	128.5±46.7	0.008	99.4±47.7	111.6±48.8	0.272	105.8±39.6	138.1±18.3	0.009	0.857

MVIF, maximal voluntary isometric force; L: Left; R: Right; MT, Maintain Time

^a P-Values derived using paired Student's t-test, after checking for the normality of the distributions.

^b P-Values between groups derived using repeated measures analysis of variance (RMANOVA).

*P^a-derived using Wilcoxon signed-rank test.

*P^b-Values between groups derived using Friedman test.

Results

Table 3- Evaluation of the skeletal muscle strength (M1).

Parameter M1	Control group (n = 10)		Aerobic group (n = 10)		Respiratory group (n = 10)		Aerobic & respiratory group (n = 10)		P-Values
	Pre (m ± SD)	Post (m ± SD)	Pre (m ± SD)	Post (m ± SD)	Pre (m ± SD)	Post (m ± SD)	Pre (m ± SD)	Post (m ± SD)	
Root mean square (Left Leg)									
Vastus lateralis	0.132±0.004	0.116±0.007	0.084±0.005	0.116±0.009	0.131±0.004	0.142±0.009	0.076±0.004	0.102±0.004	a: ns; b: 0.004; c: ns; d: 0.000; e: 0.000.
Rectus femoris	0.095±0.002	0.150±0.016	0.079±0.004	0.110±0.009	0.100±0.003	0.161±0.016	0.066±0.006	0.093±0.004	a: 0.006; b: 0.000; c: 0.000; d: 0.000; e: 0.000.
Vastus medialis	0.119±0.002	0.150±0.019	0.900±0.005	0.097±0.006	0.122±0.003	0.167±0.020	0.025±0.001	0.045±0.002	a: ns; b: ns; c: ns; d: 0.000; e: 0.000.
Root mean square (Right Leg)									
Vastus lateralis	0.120±0.004	0.100±0.009	0.159±0.027	0.189±0.025	0.131±0.005	0.111±0.010	0.103±0.005	0.186±0.027	a: ns; b: 0.001; c: ns; d: 0.006; e: ns.
Rectus femoris	0.088±0.002	0.108±0.008	0.087±0.003	0.100±0.005	0.096±0.002	0.119±0.009	.078±0.003	0.089±0.003	a: ns; b: ns; c: ns; d: 0.003; e: ns.
Vastus medialis	0.152±0.006	0.184±0.016	0.067±0.005	0.108±0.006	0.157±0.005	0.192±0.017	0.049±0.002	0.105±0.005	a: ns; b: 0.000; c: ns; d: 0.049; e: ns.

ns: not significant; a: Control group pre vs. Post; b: Aerobic group pre vs. Post; c: Respiratory group pre vs. Post; d: Aerobic & Respiratory group pre vs. Post; e: difference among groups

Results

Table 4 - Evaluation of the skeletal muscle endurance (M2).

Parameter M2	Control group (n = 10)		Aerobic group (n = 10)		Respiratory group (n = 10)		Aerobic & respiratory group (n = 10)		P-Values
	Pre (m ± SD)	Post (m ± SD)	Pre (m ± SD)	Post (m ± SD)	Pre (m ± SD)	Post (m ± SD)	Pre (m ± SD)	Post (m ± SD)	
<i>Root mean square (Left Leg)</i>									
Vastus lateralis	0.038±0.001	0.065±0.005	0.028±0.001	0.052±0.004	0.035±0.001	0.028±0.003	0.021±0.001	0.028±0.001	a: 0.000; b: 0.000; c: 0.042; d: 0.000; e: ns.
Rectus femoris	0.035±0.001	0.065±0.004	0.030±0.001	0.052±0.004	0.033±0.001	0.032±0.003	0.027±0.001	0.032±0.001	a: 0.000; b: 0.000; c: ns; d: 0.002; e: ns.
Vastus medialis	0.043±0.002	0.125±0.014	0.029±0.001	0.050±0.003	0.043±0.002	0.043±0.004	0.026±0.001	0.041±0.002	a: 0.000; b: 0.000; c: ns; d: 0.000; e: ns.
<i>Root mean square (Right Leg)</i>									
Vastus lateralis	0.030±0.001	0.082±0.007	0.032±0.001	0.051±0.005	0.030±0.001	0.055±0.013	0.022±0.001	0.042±0.002	a: 0.000; b: 0.001; c: ns; d: 0.000; e: ns.
Rectus femoris	0.026±0.001	0.069±0.006	0.028±0.001	0.045±0.004	0.022±0.001	0.043±0.004	0.018±0.001	0.037±0.002	a: 0.000; b: 0.000; c: 0.000; d: 0.003; e: ns.
Vastus medialis	0.032±0.001	0.104±0.007	0.028±0.001	0.050±0.008	0.032±0.001	0.042±0.007	0.022±0.001	0.215±0.021	a: 0.000; b: 0.007; c: ns; d: 0.000; e: ns.

Ns: not significant; a: Control group pre vs. Post; b: Aerobic group pre vs. Post; c: Respiratory group pre vs. Post; d: Aerobic & Respiratory group pre vs. Post; e: difference among groups.

Results

Table 5 - Cardiac Function and Structure.

	Control			AIT			IMT			AIT& IMT			P ^b
	Pre	Post	P ^a	Pre	Post	P ^a	Pre	Post	P ^a	Pre	Post	P ^a	
LVEF	35.1±7.4	33.8±9.5	0.413	37.6±5.7	42.9±8.1	0.025	35.4±6.5	33.6±7	0.389	38±5	44.3±8.8	0.042*	0.145*
LVEDD	61.1±9.9	61.1±10.2	1.000	63±8.1	56.8±8.4	0.015	63±2.7	61.8±2.5	0.225	63±7.9	58.4±7.9	0.036	0.990
LVESD	50±10.1	50.3±12.5	0.862	51.5±11.2	45.4±12.9	0.012	52.4±5	52.3±4.4	0.802	50.3±7.2	45.6±9.8	0.023	0.428*
LVEDV	227.3±19.4	227.5±20.5	1.000*	218.8±20.7	201.3±13.3	0.001	218.8±21.5	208.1±14.1	0.013	226±18.3	202±11.3	0.001	0.202
LVESV	158.1±11.3	156.9±14.9	0.608*	172.5±12.5	146.9±8.4	0.001	161.3±22.9	150±19.3	0.014*	172.5±12.5	145.6±9.4	0.001	0.936*

LVEF, left ventricular ejection fraction; LVEDD, left ventricular end diastolic diameter; LVESD, left ventricular end systolic diameter; LVEDV, left ventricular end diastolic volume; LVESV, left ventricular end systolic volume.

^a *P-Values derived using paired Student's t-test, after checking for the normality of the distributions.*

^b *P-Values between groups derived using repeated measures analysis of variance (RMANOVA).*

^{*} *P^a-derived using Wilcoxon signed-rank test.*

^{*} *P^b-Values between groups derived using Friedman test.*

Table 6 - Functional Capacity and Dyspnea.

	Control			AIT			IMT			AIT& IMT			P ^b
	Pre	Post	P ^a	Pre	Post	P ^a	Pre	Post	P ^a	Pre	Post	P ^a	
Dyspnea	12.8±2.3	12.5±2.3	0.685	12.3±1.0	9.5±1.4	0.008*	13.0±1.5	10.0±1.4	0.011*	13.3±1.9	9.3±1.9	0.008*	0.000*
6MWT	455.3±113.1	457.2±104.9	0.905	427.6±153	491.5±170	0.000	449.6±96.4	532.1±113.9	0.022	462.8±73.1	567.5±75.9	0.017*	0.042*
NYHA score	2.4±0.5	2.5±0.8	0.317*	2.3±0.5	1.4±0.5	0.008*	2.3±0.5	1.6±0.5	0.059*	2.5±0.5	1.3±0.5	0.008*	0.002*

6MWT, six minute walk test; NYHA, New york heart association.

^a *P-Values derived using paired Student's t-test, after checking for the normality of the distributions.*

^b *P-Values between groups derived using repeated measures analysis of variance (RMANOVA).*

^{*} *P^a-derived using Wilcoxon signed-rank test.*

^{*} *P^b-Values between groups derived using Friedman test.*

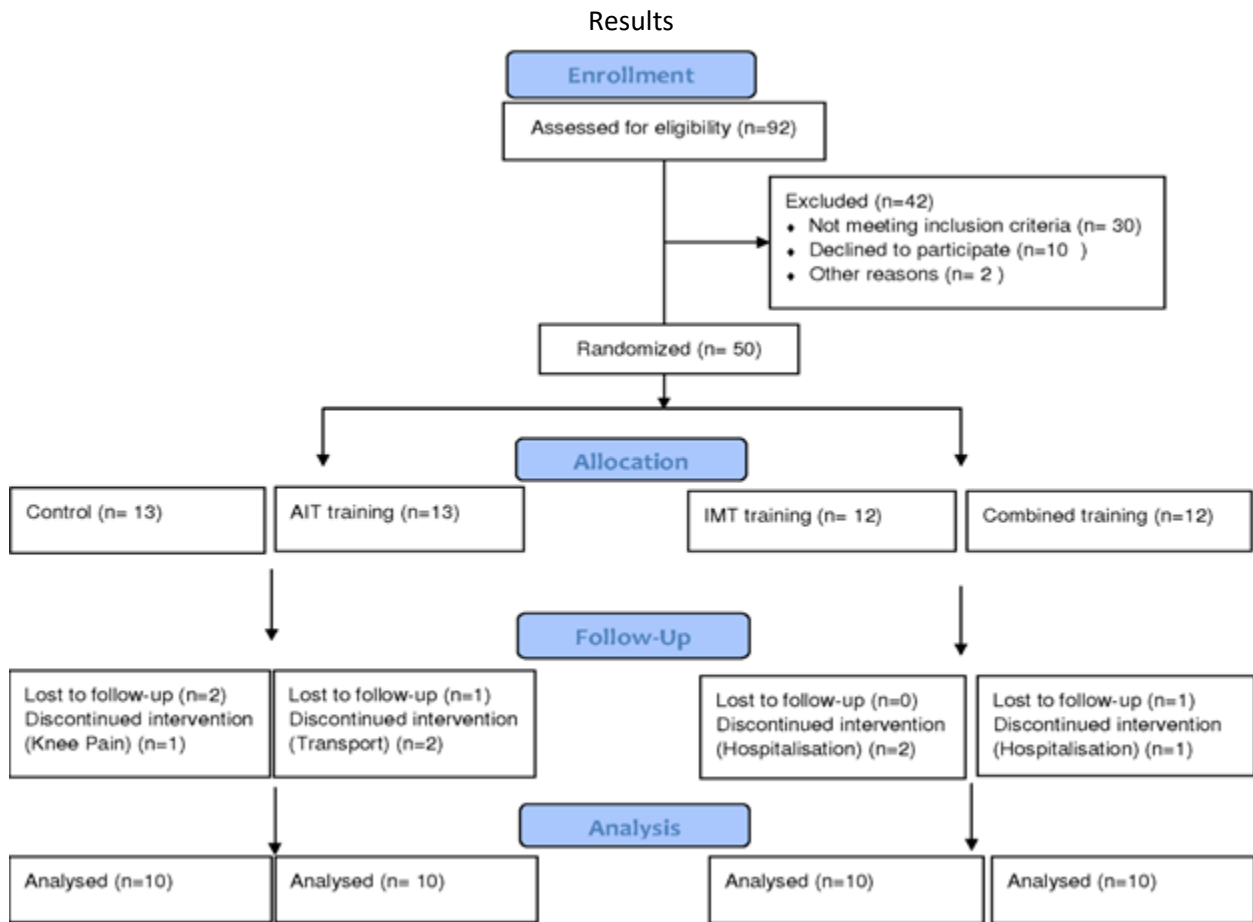


Figure 1 - Participant flow diagram - CONSORT (consolidated Standards of Reporting Trials) diagram of recruitment to the trial. AIT: Aerobic Interval Training; IMT: Inspiratory muscle training.

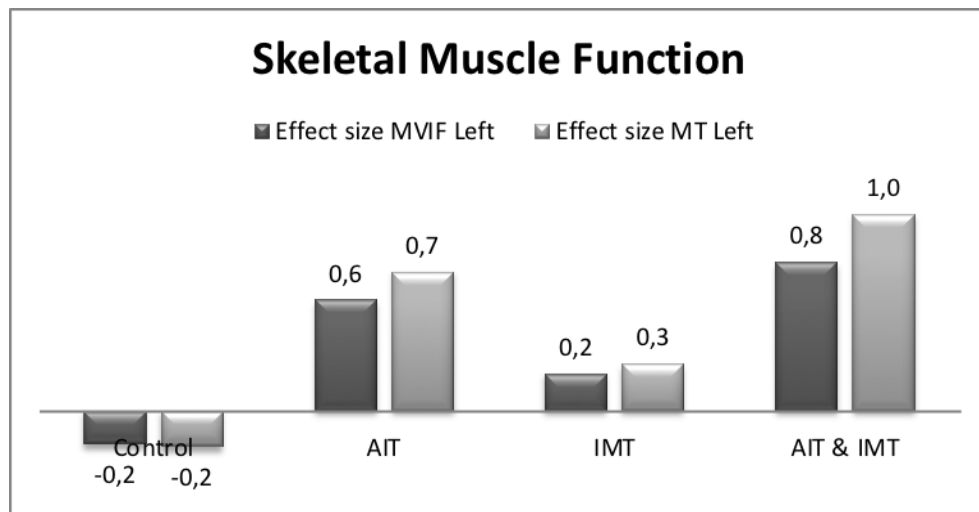


Figure 2 - Effect size on skeletal muscle function. MVIF, maximal voluntary isometric force; MT, Maintain Time.

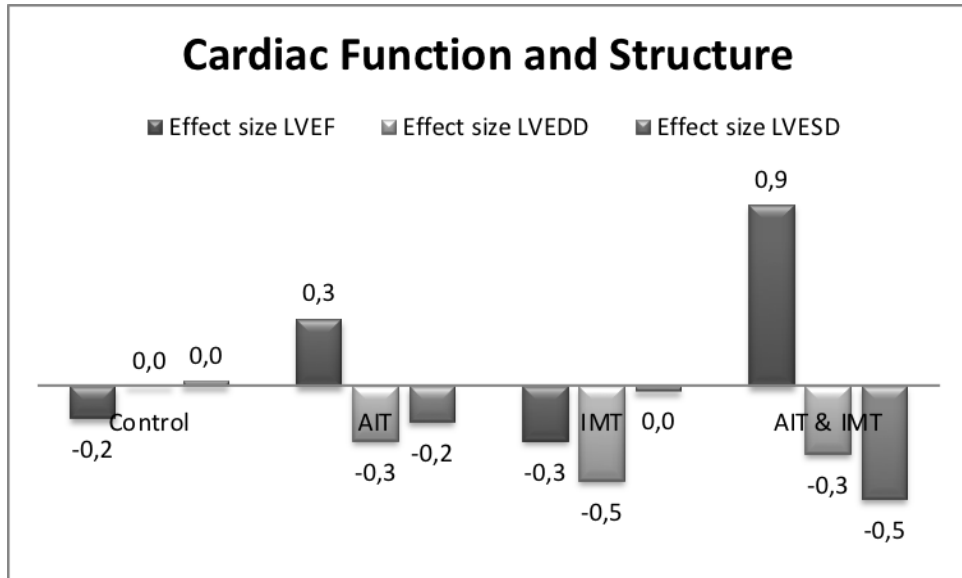
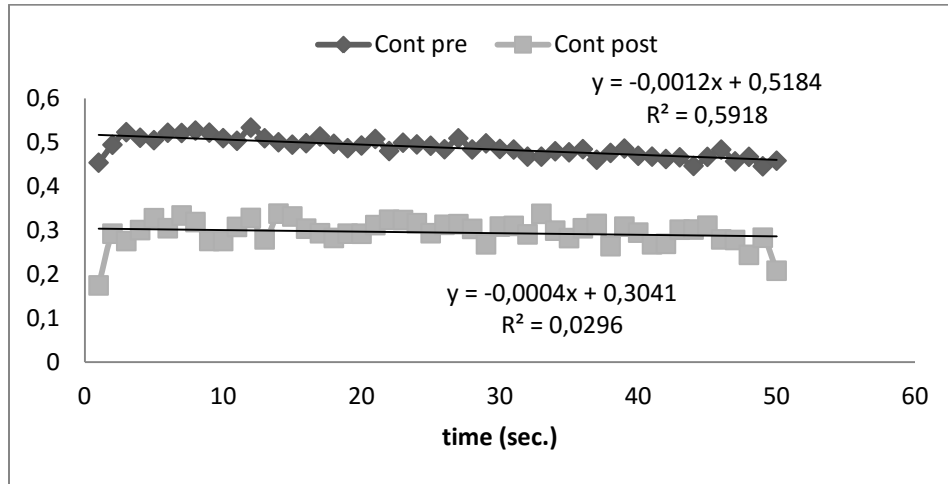


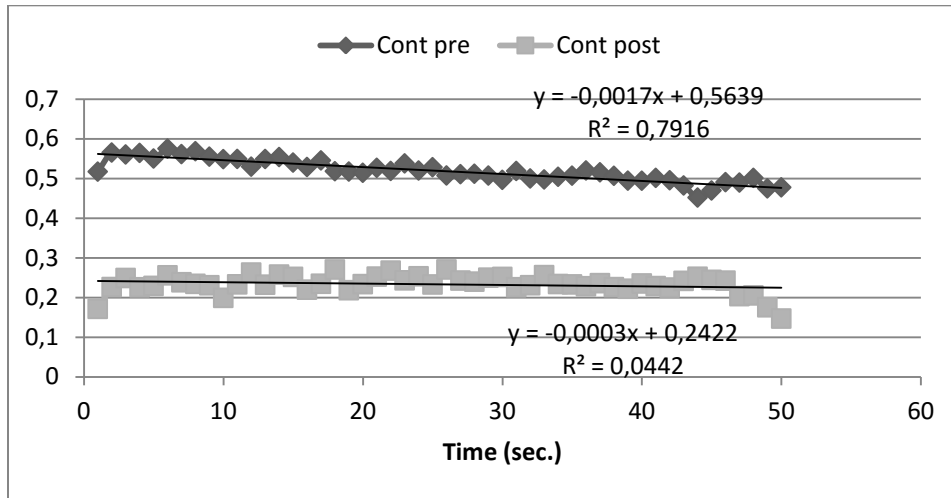
Figure 3- Effect size on cardiac function. LVEF, left ventricular ejection fraction; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter.

Results

FM for VL



FM for RF



FM for VM

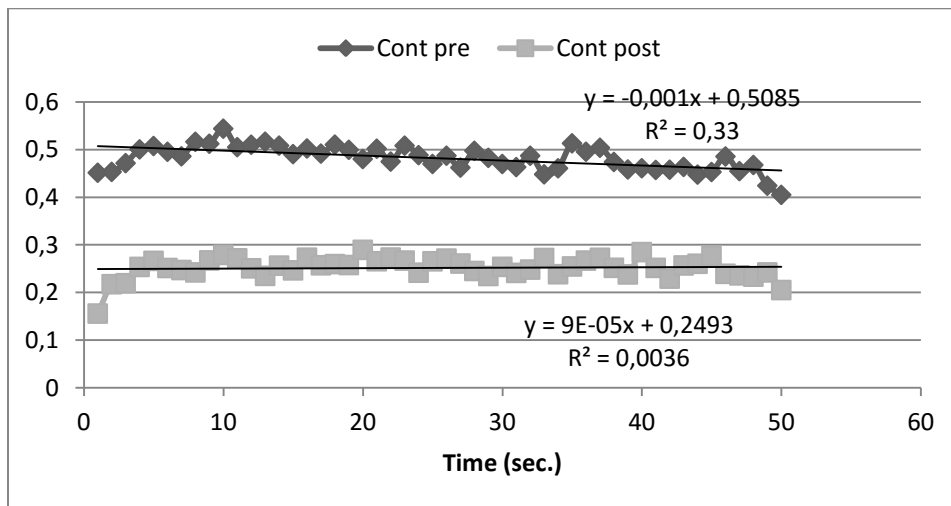
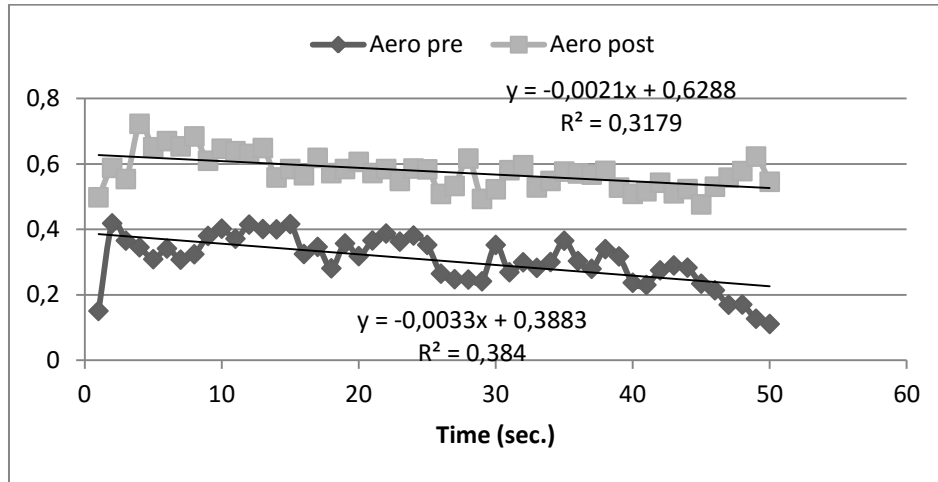


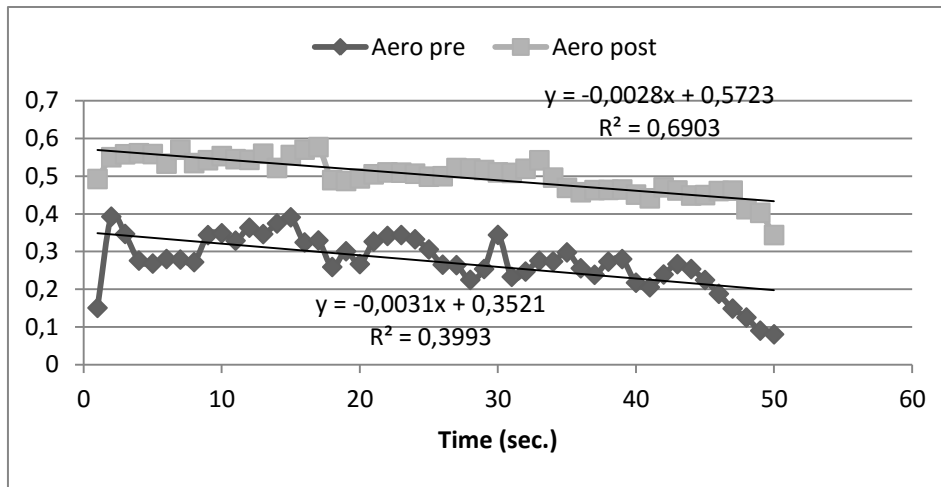
Figure 4 - Frequency Median (FM) modifications for the vastus lateralis (VL), rectus femoris (RF) and vastus medialis (VM) in the Control group after training (vs. pre values). Mean values fitted out with a linear regression.

Results

FM for VL



FM for RF



FM for VM

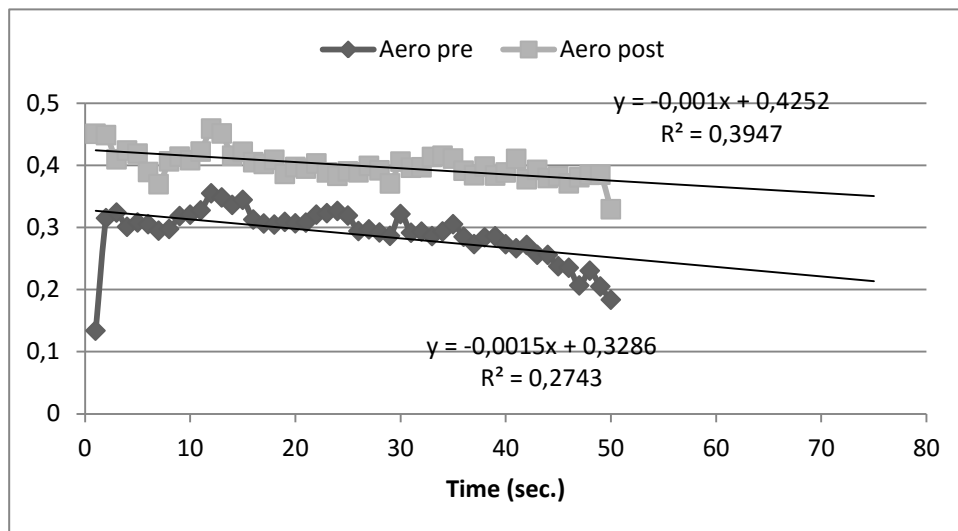
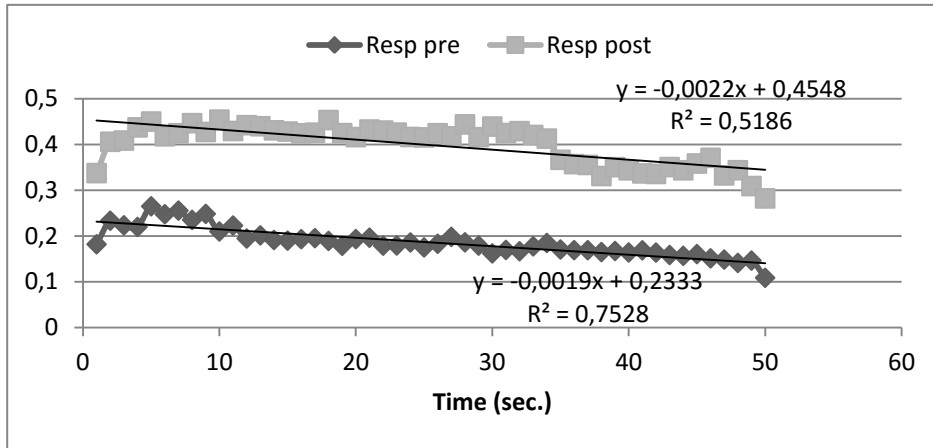


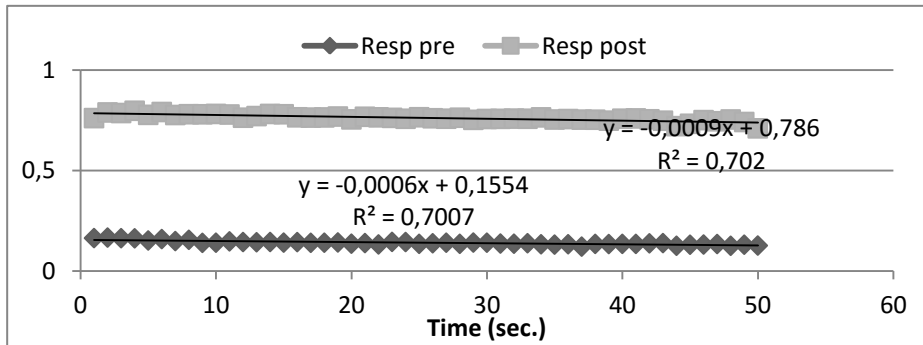
Figure 5 - Frequency Median (FM) modifications for the vastus lateralis (VL), rectus femoris (RF) and vastus medialis (VM) in the Aerobic group after training (vs. pre values). Mean values fitted out with a linear regression.

Results

FM for VL



FM for RF



FM for VM

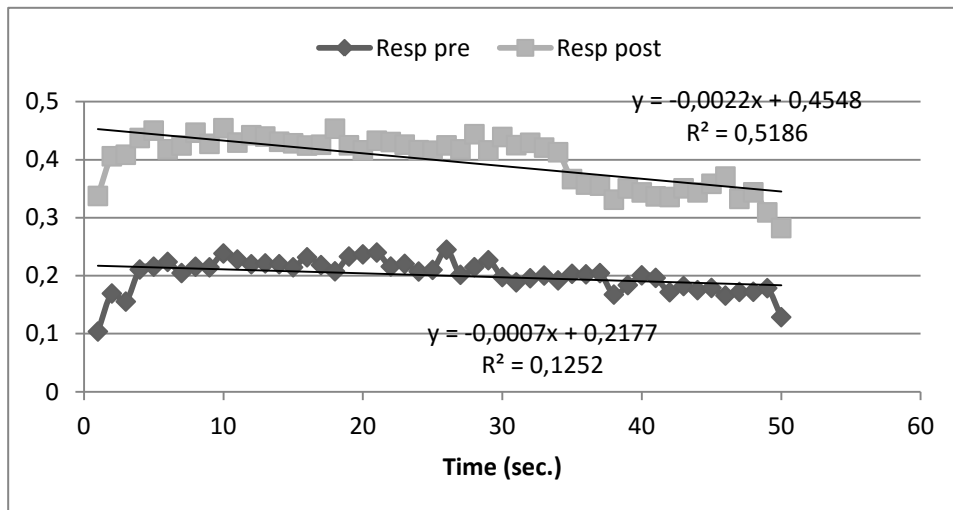
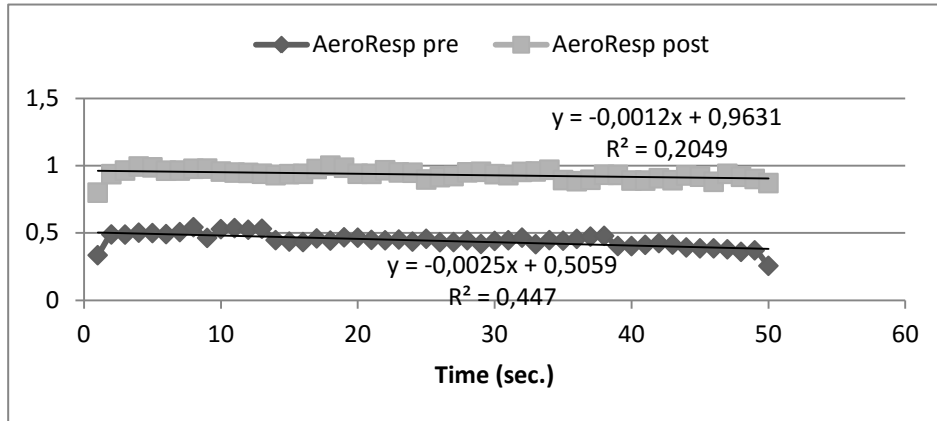


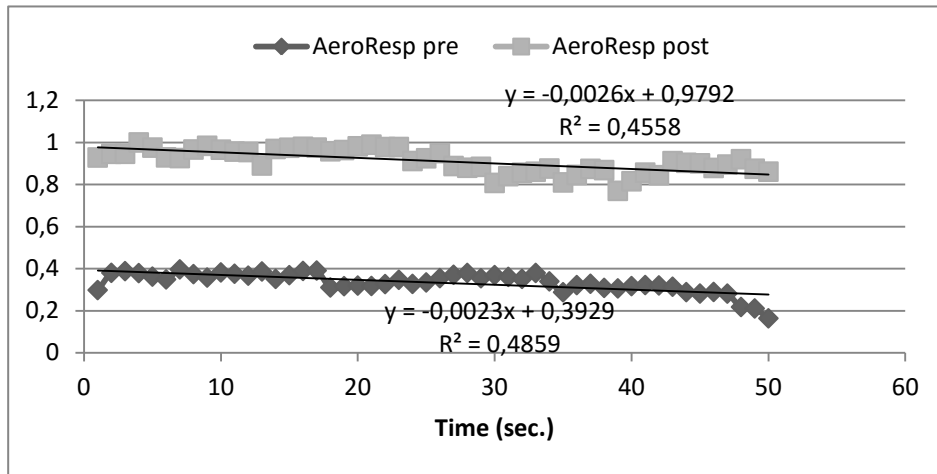
Figure 6 - Frequency Median (FM) modifications for the vastus lateralis (VL), rectus femoris (RF) and vastus medialis (VM) in the Respiratory group after training (vs. pre values). Mean values fitted out with a linear regression.

Results

FM for VL



FM for RF



FM for VM

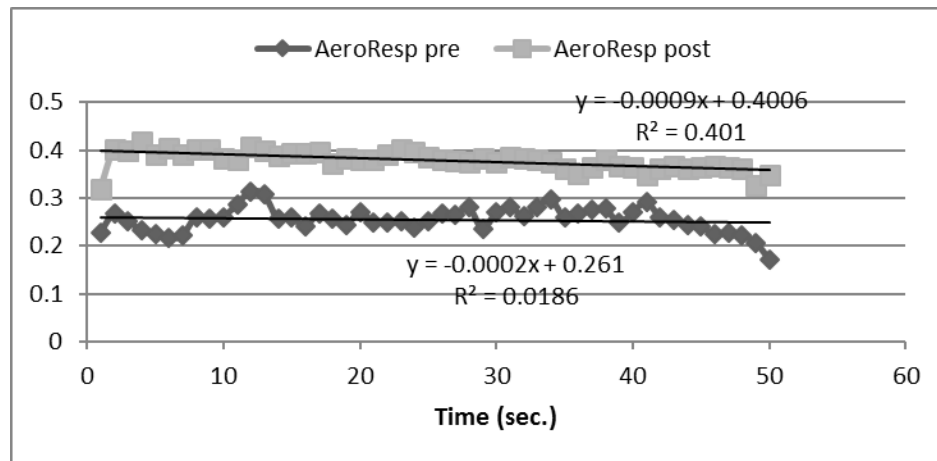


Figure 7-Frequency Median (FM) modifications for the vastus lateralis (VL), rectus femoris (RF) and vastus medialis (VM) in the Aerobic and respiratory group after training (vs. pre values). Mean values fitted out with a linear regression.

Study 3: Combined resistance, aerobic and inspiratory muscle training against resistance training in chronic heart failure-Additional benefits of resistance exercise: A randomized controlled trial.

Waiting for submission.

Abstract

Background: The hypothesis tested in chronic heart failure patients (CHF) with inspiratory muscle weakness (IMW) demonstrates that the addition of Resistance Training (RT) to Aerobic Interval Training (AIT) and Inspiratory Muscle Training (IMT) results in further improvements compared to RT in terms of dyspnea, cardiac, skeletal and inspiratory muscle function and quality of life.

Methods: thirty patients with ejection fraction (EF) $\leq 45\%$ and IMW described by maximal inspiratory pressure (MIP) $< 70\%$ predicted, had undergone 3 exercise training sessions per week for 12 weeks. Patients were randomly allocated to one of three groups: RT group, CT (AIT+RT+IMT) group or control group. RT performed at 60% of 1 repetition maximum (1RM). CT consisted of RT (same protocol as RT alone), AIT which was performed at 60% of maximum heart rate, and IMT which was performed at 60% MIP. Control group patients had no training at all. At the beginning and the end of the study, patients underwent pulmonary function test, respiratory muscle function test, echocardiography, exercise test, skeletal muscle function test, 6-minute walk test (6MWT) and were evaluated for their quality of life (QoL) using the Minnesota living with heart failure (MLWHF) questionnaire.

Results: Both RT and CT groups showed significant positive effects on EF%, exercise test variables, functional capacity, respiratory muscle function, skeletal muscle strength and endurance as well as dyspnea and QoL. CT was superior to RT in all parameters assessed, and most importantly in exercise time (68% versus 27%, $P=0.008$), respiratory muscle function (MIP, 60% versus 14%, $P=0.001$; SPI_{max} , 71% versus non-significant improvement in RT group, $P=0.022$) and skeletal muscle endurance. However, no improvements were detected in control group patients.

Results

Conclusion: For the first time, RT has been applied to improve respiratory muscle strength in CHF patients. In addition, the combination of AIT+RT+IMT was safe and resulted in additional benefits in cardiac, respiratory muscle and skeletal muscle function compared to the RT alone.

Keywords: Chronic heart failure; Aerobic interval training; Resistance training; Strength training; Inspiratory muscle training; Quality of life.

Trial Registration number: NCT03538249

INTRODUCTION

Patients with chronic heart failure (CHF) develop symptoms that limit their daily life activities; an important manifestation is the exercise intolerance (1) characterized by dyspnea and fatigue. A decrease in cardiac output (CO) has been describe as the main factor in HF pathogenesis (2). However, the improvement in central hemodynamic factors i.e. cardiac output, blood pressure, heart rate, was not able to reduce the level of exercise intolerance (3). Moreover, literature studies have demonstrated that CHF patients do develop skeletal muscle dysfunction (4) and inspiratory muscle weakness (IMW) (1). They found that these alterations contribute to fatigue and breathlessness in these subjects. Skeletal muscle abnormalities are mainly characterized by muscle fiber type switch, fiber atrophy and muscle wasting, as well as the reduction in mitochondrial volume density and mitochondrial aerobic capacity (4–6). Similar alterations have been detected in the respiratory muscle, with the exception of fiber type switch. In the peripheral skeletal muscles, the switch appeared to be in favor of type II b fast twitch fibers with low aerobic capacity that gets quickly fatigued (4) while respiratory muscles had a switch towards type I slow twitch fibers (4) (1).

It has been shown that exercise training reduces muscular dysfunction by enhancing muscular metabolism and functional capacity (7). In addition, improvements in inspiratory muscles and pulmonary function were also reported (8). The aim of exercise training was to improve the functional capacity and quality of life (QoL) in patients with CHF and reverse to an extent, muscular intrinsic alterations. Moreover, the results proved that aerobic training (AT), inspiratory muscle training (IMT) and resistance training (RT) are safe and have complementary benefits in CHF. AT has been the most commonly used exercise and is highly recommended by the European Society of Cardiology (9) and American College of Cardiology/American Heart Association guidelines (10). In fact, these types of exercise were proven safe and beneficial. It was able to increase the oxidative capacity of the muscles and had an effect on reversing the fiber type shift in the peripheral muscles as well as improving functional capacity and QoL (11). Nevertheless, other muscular dysfunctions encountered in CHF subjects were not directly improved by AT, such as respiratory muscle strength and skeletal muscle histological and metabolic features. Noting that the addition of IMT or RT to aerobic exercise has reversed partially the alterations in the respiratory and skeletal muscle capacity [9].

Results

Recently, Laoutaris et al. (12) investigated the effects of adding RT to both AT and IMT (ARIS) in CHF patients. Throughout their study, they proved the safety of this triple combination and reported important improvements in cardiopulmonary responses to exercise, as well as increased skeletal muscle function and QoL.

However, AT+RT+IMT (ARIS) have not resulted in additional benefits in cardiac function over AT, except for left ventricular end-diastolic diameter (LVEDD) that was improved only after ARIS. The use of continuous aerobic training (CAT) and not aerobic interval training (AIT) in their study might be a reason for not finding a significant difference in favor of combined group. It has been shown previously that AIT is better than AT in reversing ventricular remodeling and improving endothelial function (13). Besides, they did not compare the benefits of this combined training to RT alone in the same patient population.

Accordingly, we hypothesized that the addition of RT to AIT and IMT could result in additional benefits compared to the application of RT alone. Hence, the first aim of this study was to investigate the additional effects that AIT and IMT could add to RT at the pulmonary, respiratory, cardiac and skeletal muscle levels; whereas the second aim was to confirm the efficiency of exercise training in heart failure patients.

Method

Study Design

A 3-month randomized, single-blinded controlled study was conducted on patients with CHF and IMW for the evaluation of central and peripheral outcome measures, functional capacity and Quality of life. 53 patients were assessed for eligibility and 23 were excluded due to some limitations (figure 1). Exercising groups included a resistance training group and a combined training group: the former included training of upper and lower limbs using weights and dumbbells, and the latter included three types of training including aerobic interval training, inspiratory muscle training and resistance training. Patients within a specific group didn't have any idea about the other groups and weren't told about any potential effect of the intervention. A stable medication regimen was followed by all the subjects during the study period and included mainly ACE-I or ARBs (for those who couldn't tolerate ACE-I), diuretics and beta-blockers. The experimental protocols' approval was obtained from the Research Ethics Committee of Beirut Cardiac Institute. Since humans were included in this study, a certificate from the National

Results

Institutes of Health (NIH) for Protecting Human Research Participants (PHRP) was obtained. The patients received detailed information and gave written informed consent before their inclusion in the study.

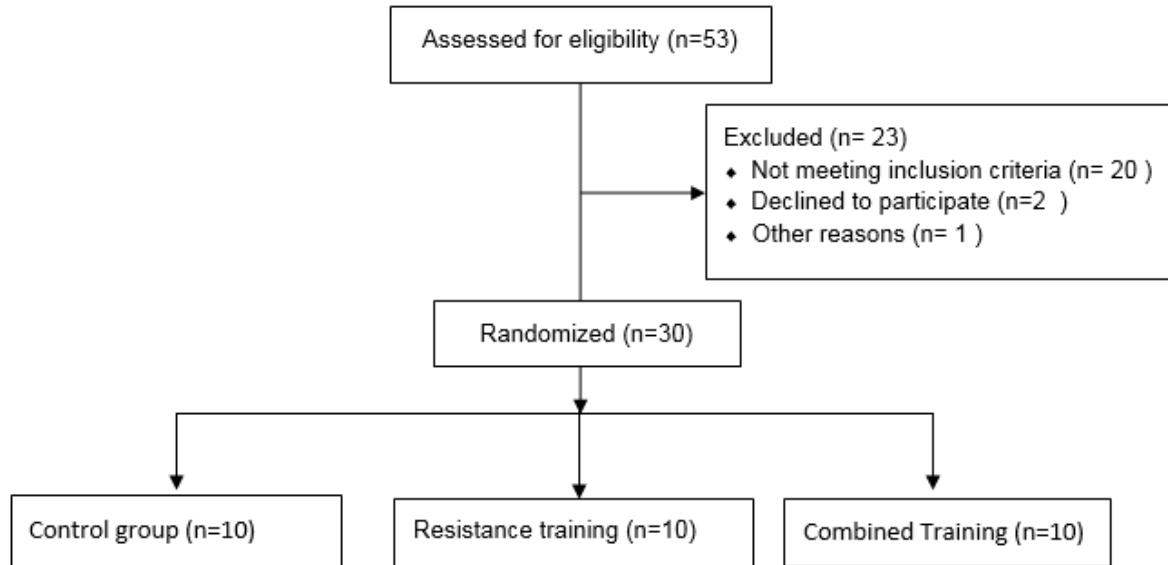


Figure 1- Flow chart of patient's recruitment.

Outcome Measures

Demographic, clinical characteristics and drug therapy lists for all patients were collected at the beginning and the end of the study. Arterial blood oxygen saturation and heart rate (HR) were monitored using VIAMED pulse oximetry, and blood pressure (BP) was measured using a sphygmomanometer prior to the initiation and after the termination of each exercise session.

Cardiac Function

Echocardiography test: it is a test that makes an evaluation of the heart function possible. It creates images of the heart and helps in the analysis of different cardiac measures. Assessment of heart structure and function at rest was done using a Vivid S6 ultrasound probe (General electric healthcare GEMs supplies) where the patient was seated in a supine position. Two experienced cardiologists, blinded to subject's allocation and his/her study period, performed the test. Measurements of ventricular volumes were assessed using the biplane method of disks (Biplane Simpson's method) from an apical 4 chamber view. Noting that this method is highly recommended for measuring the LVEF (9).

Exercise Test:

Bruce treadmill protocol was used for the assessment of cardiovascular status during a progressive incremental exercise. Patients exercises on a treadmill with intensity and grade increasing progressively throughout the test following Bruce protocol. They also had ECG leads placed on their chests and a sphygmomanometer cuff for BP monitoring. Exercise time, grade, METs and BP were recorded during and after the test.

Lung Function

Pulmonary function was assessed using Digital Spirometer device. During this test, subjects were seated and instructed to inhale deeply through a mouthpiece well fitted between the lips and to exhale quickly and forcefully straight after. Air leakage was prevented by using a nose clip during the maneuver that was repeated three times to guarantee maximal performance. The important parameters detected through this test were: forced expiratory volume in 1 s (FEV1), forced vital capacity (FVC) and FEV1 to FVC ratio.

Pulmonary Function test

Respiratory Muscle Strength: respiratory pressure meter (MicroRPM carefusion), a portable hand-held device, was used to measure maximal inspiratory pressure (MIP) and maximal expiratory pressure (MEP). The results of the test were displayed on a screen in cmH₂O. A PUMA PC Software that offers unique features could associated with the hand-held MicroRPM in order to improve its functionality. During this test, patients were instructed to tightly fit the mouthpiece attached to the instrument between both lips. Familiarization with the device and the ventilator operation was done before starting the test. To measure MIP, the subject had to exhale to residual volume then perform Mueller maneuver characterized by a forceful inhalation against the instrument as long as possible. To measure MEP, the subject must inhale to total lung capacity (TLC) and then exhale forcefully (Valsalva maneuver) over a minimum duration of 2 seconds. Both maneuvers were repeated at least 3 times in order to obtain the best values of MIP and MEP; noting that reported values were the maximum pressures sustained over a one second period.

Respiratory muscle endurance: To measure the endurance of the respiratory muscle, patients were instructed to breathe using Power Breathe set at 70% MIP/sustained maximal inspiratory

pressure (SPI_{max}). The maximum time (in seconds) tolerated was recorded and meant to evaluate inspiratory muscle endurance, $SPI_{max}/time$. This test was repeated 3 times, with 2 minute rest intervals.

Leg Skeletal muscle function

Skeletal Muscle Strength Test: A handheld dynamometer (Lafayette instrument) was used to assess the skeletal muscle strength by measuring the force generated by the quadriceps. Because this device is portable and light, the examination procedure is made easier. Before the test, the subjects had been familiarized with the operative device and the intended protocol. Patients were placed in an upright seated position at a knee and hip angulation of 60° and 120° respectively. Verbal encouragement was used during the test period. Maximum voluntary isometric force (MVIF) in kg was measured; three sets of three repetitions were given to each patient to develop maximum force with a 2 minutes rest period between each set. MVIF was reported as the average of the nine values taken. Peak force, average force and peak time were recorded by the device and transmitted to the computer software.

Skeletal Muscle Endurance Test: 50% MVIF was used to assess skeletal muscle endurance. Patients were told to maintain 50% of the MVIF as long as possible until maximum tolerable elapsed time is recorded. The procedure was repeated three times separated by 5 minutes of rest. Endurance time was calculated as the average of the three sets. Verbal encouragement was given to patients before and during the test to achieve the best possible performance.

Surface Electromyography

During strength and endurance manips (M1 and M2 respectively), surface electromyography (SEMG) activities were recorded from the vastus lateralis (VL), rectus femoris (RF), and vastus medialis (VM). Electrodes with a disc shape were located for VL on quarter distance proximal to the lateral tibial condyle on a line connecting this and the anterior-superior-iliac-spine (ASIS). For RF, electrodes were placed at mid distance along the line connecting the ASIS to the superior aspect of the patella. For VM, electrodes were placed at a position 20% of the distance along a line connecting the medial gap of the knee to the ASIS. Before electrodes application, the skin was cleaned. The signals of 3 VL, RF and VM were stored in LabView (32 bits). The root mean square (RMS) and median frequency (MF) were calculated by the matlab program. RMS and MF were averaged for each muscle (14).

Physical Activity

Inclusion criteria for this study required that patients had a sedentary lifestyle to avoid bias since some patients might be following a specific activity program. Thus, in order to make sure that all the patients met the criteria, the short international physical activity questionnaire (IPAQ) (14) was used to assess the level of each patient's physical activity. The questionnaire was administered over the phone or during the first office meeting. It is made up of 7 questions the patients were asked to answer telling the time they spend doing an activity. The activities include those done at work, at home, yard work, exercise and others.

Functional Capacity

Functional capacity in CHF patients was predicted by using the 6 minute walk test (6MWT) (15) which is evidenced to be reliable and reproducible.

The test was performed in a 60-meter corridor under the supervision of a physical therapist. Initially, patients had been familiarized with the corridor space and the time needed to complete the test. BP, HR, and arterial oxygen saturation were measured before and after the test. A stopwatch was used to record the elapsed time as soon as the subject's began the test. Patients were free to decrease their speed and stop if necessary. The test was repeated three times with 5 minutes of rest between sets.

Dyspnea

During each training session and during the exercise test, patients were asked to evaluate their exertion level using Borg scale (16). Borg scale provides information about perceived exertion but nothing on the level of difficulty of the exercise. The scale is a set of different intensity levels, where patients evaluate their exertion level using an attached visual numerical scale of 6 to 20 with 6 corresponding to no fatigue or other symptoms and 20 to maximum exertion. Borg scale is known for its sensitivity and reproducibility to be used as a subjective reference during submaximal workouts (17).

Quality of Life

QoL was assessed using Minnesota living with heart failure questionnaire (MLwHFQ), which was approved for the use in clinical practice and research (18). MLFQ has been translated into and approved in Arabic. This questionnaire is composed of 21 items used to qualify physical and

emotional aspects. A grading scale that evaluates the degree of HF impact on the QoL, with 0 (none) to 5 (very much), was used. Low scores indicate that patients had mild problems associated with HF and high scores indicate a high impact of HF on QoL. Introducing the questionnaire to the patients was easy and questions were answered clearly. The information collected thanks to MLHFQ provided an overview about the physical, social and mental status of patients before and after the interventional process.

Training programs

Patients were randomly assigned into three groups. The training regimens were performed 3 times a week for 12 weeks.

Control: The control group included 10 patients who did not exercise at all and were instructed to continue their normal life activities during the three months of trial.

Resistance Training: Ten patients were included in the RT group. The training protocol encompassed strength exercises that targeted the muscles of the quadriceps, the hamstrings and gluteus muscles of the lower extremities; Biceps, Triceps, Deltoid and Pectoralis of the upper extremities. A total of seven strength exercises were used to train the upper body and six strength exercises to train the lower body limbs. Each workout was composed of 3 sets and each set of 10 repetitions, with at least 15 seconds of rest between sets. The patients started training at 60% of 1RM that was assessed and recalculated every two weeks. All the patients started with 3 sets of 5 repetitions each but after the third session, all of them had completed the whole 3 sets with 10 repetitions each. The total training time was 30 minutes.

Combined Training (CT): This training group has included three exercise modalities: aerobic, inspiratory and resistance training. Ten patients were allocated to this combination group. They underwent AIT followed by IMT and ended with RT. Between each type of training, the patients rested for approximately 5 minutes. RT protocol has followed the same form and rules associated with the above described RT group. AIT included walking on a treadmill for 30 minutes. Interval training protocol was chosen due to its superiority to continuous aerobic training (13). A 3-minute warm up preceded the workout, followed by 4 bouts of 4 minutes each, at high intensity (60% of maximum HR which was increased by 5% every week taking into consideration the subject's endurance and perceived exertion) interspaced by 3 bouts of 2 minutes each at low intensity (50% of the high intensity). The high intensity target was to reach

90% of maximum heart rate. This exercise was ended with 3 minutes of progressive decrease in intensity.

IMT was performed using a portable Power Breathe training device. The training duration was 20 minutes organized as follows: 1 minute for warm-up, 4 sets of 3 minutes training at 60% MIP (19), and 1 minute for cooling down with a 20-second rest break between sets. MIP was assessed each week to guarantee an optimal 60% MIP intensity.

Statistical analysis

All continuous variables are expressed as mean \pm standard deviation of the mean (m \pm SD). Baseline comparisons among the groups were performed using one way ANOVA-test for the normally distributed variables and Kruskal-Wallis test for the non-normally distributed variables. The paired t-test and Wilcoxon signed-rank test were used to assess training induced changes (pre vs. post) within a particular group. The effect of intervention among the groups, the effect of time and the effect of group-by-time interactions were evaluated using repeated measures analysis of variance (RMANOVA). Friedman test was used when data was not normally distributed, knowing that normality was tested using Kolmogorov-Smirnov test. The inflation of type-I error due to multiple comparisons was controlled using Bonferroni rule. Statistical analyses were performed using SPSS software (version 20, SPSS Inc., Chicago, Illinois, U.S.A.).

RESULTS

A total of 53 patients were assessed for eligibility and 30 patients were recruited. No adverse effects have been recognized during the training period, and all patients in training groups seemed to be enthusiastic and interested. Compliance was monitored using a daily log booklet, and was excellent in the two training groups. Drugs were taken properly by all the patients according to their cardiac specialist instructions (ACE- or ARB, beta blockers, and diuretics). Pharmacological therapy has not been changed over the 3-month training period. At baseline, there were no statistically significant differences among the three groups (Control, RT, and CT) with respect to demographic characteristics, drugs, Cardiac Function, Exercise Test, Pulmonary Function Test, Functional capacity, quality of life, Respiratory muscle function and leg skeletal muscle function (Table 1).

Functional capacity and quality of life

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No significant difference among the groups was observed after the intervention. Participants in RT and CT groups had more benefits than the control group. A significant group-by-time interaction was observed for 6MWT ($P = 0.003$), MLwHFQ score ($P = 0.003$) and NYHA class ($P = 0.002$). Thus, within-group analysis was also performed and a significant increase in 6MWT distance (13% for RT and 24% for CT), a decrease in NYHA functional class (33% for RT and 45% for CT), and a decrease in MLwHFQ score (30% for RT and 59% for CT) were noticed. Patients in CT group improved significantly compared to patients in RT group (Table 2). In order to compare improvements among the groups, the effect size was calculated. As shown in (Figure 2) the improvements were significant in CT group mainly for 6MWT and MLWF score.

Cardiac Function

Between-group analysis revealed that LVEF (%) differed significantly after the intervention. In particular, participants in RT and CT groups had more benefits than the control group. A significant group-by-time interaction was observed for LVEF (%) ($P < 0.001$), LVEDD ($P = 0.020$), and LVESD ($P < 0.001$). Thus, within-group analysis was also performed and a significant increase in LVEF (%) was observed in RT (5%) and CT (12%) groups. Moreover, a significant decrease in LVEDD and LVESD was only observed in CT group. Patients in CT group improved much more than patients in RT group (Table 3). This shows that CT group reported the best improvements concerning cardiac function. In order to compare improvement among the groups, the effect size was calculated. As shown in (Figure 3) the improvements were significant in CT group mainly for EF (%).

Stress Test

Between-group analysis revealed that Exercise time, METs and Stage changed significantly after the intervention. In particular, participants in RT and CT groups had more benefits than those in the control group. A significant group-by-time interaction was observed for Exercise time ($P < 0.001$), METs ($P < 0.001$), and Stage ($P < 0.001$). Thus, within-group analysis was also performed and a significant increase in Exercise time (27% for RT and 68% for CT), METs (24% for RT and 37% for CT), Stage (31% for RT and 57% for CT) and an improvement in dyspnea sensation (15% for RT and 26% for CT) were observed. Patients in CT group improved much more than patients in RT group (Table 4). In order to compare improvements among the

groups, the effect size was calculated. As shown in (Figure 4) the improvements were highly significant in CT group mainly for Exercise Time, METs and Stage.

Respiratory muscle function

Between-group analysis revealed that MEP, MIP and SPI_{max} differed significantly after the intervention. In particular, participants in RT and CT groups benefited more than those in the control group. A significant group-by-time interaction was observed for MEP ($P = 0.004$), MIP ($P < 0.001$), and SPI_{max} ($P < 0.001$). Thus, within-group analysis was also performed and a significant increase in MEP (44%), MIP (60%) and SPI_{max} (71%) was observed in CT group. Patients in RT group improved significantly MEP (25%) and MIP (14%) but not SPI_{max} . Patients in CT group improved much more than patients in RT group (Table 5). In order to compare improvement among the groups, the effect size was calculated. As shown in (Figure 5) the improvements were highly significant in CT group mainly for MEP, MIP, and SPI_{max} .

Skeletal muscle function

Between-group analysis revealed that Maintenance right and MVIF left differed significantly after the intervention. In particular, participants in CT and RT groups had more benefits than the control group. A significant group-by-time interaction was observed for MVIF right ($P = 0.028$), MVIF left ($P = 0.013$), Maintenance left ($P = 0.022$), and Maintenance right ($P = 0.002$). Thus, within-group analysis was also performed and a significant increase in MVIF right (18%), Maintenance right (41%), MVIF left (12%) and Maintenance left (47%) was observed in CT group. Patients in RT group improved significantly MVIF right (18%), Maintenance right (24%), MVIF left (11%) but not Maintenance left. Patients in CT group improved much more than patients in RT group (Table 6). In order to compare improvement among the groups, the effect size was calculated. As shown in (Figure 6) the improvements were highly significant in CT group mainly for MVIF right and Maintenance right.

Electromyography

Parameter M1: Between-group analysis revealed that the response of Vastus lateralis, Rectus femoris and Vastus medialis differed significantly after the intervention for the Root mean square (Left Leg). In particular, participants in the combined group were more benefited as compared to the control group. A significant group-by-time interaction was observed for Vastus

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lateralis ($P = 0.000$), Rectus femoris ($P = 0.000$), and Vastus medialis ($P = 0.000$). Thus, within-group analysis was also performed, and a significant increase in the response of the three muscles for the left leg was shown in the combined group. For the Root mean square (Right Leg), no significant difference was observed between the groups for the three muscles. However, a significant increase in the response of Vastus lateralis and Rectus femoris was observed for the Participants in the Resistance group versus an increase in the response of vastus medialis for the combined group (Table 8).

Parameter M2: For the Root mean square (Left and Right Leg), no significant difference was observed between the groups for the three muscles. However, a significant increase in the response of the three muscles was observed for the Participants in the Resistance group and in combined group for Root mean square (Left Leg) (Table 9). FM decrease significantly after training for Vastus lateralis and Rectus femoris in the Resistance group. However no significant difference was observed after training in the combined group for the three muscles (Data not shown here).

Pulmonary Function Test

Between-group analysis revealed that FEV1/FVC differed significantly after the intervention. No significant group-by-time interaction was observed and no significant improvement was noticed for the three parameters FVC, FEV1 and FEV1/FVC (Table 7).

DISCUSSION

A wealth of evidence has proved leg skeletal muscle dysfunction in CHF patients (1,20,21). In this regard, targeting this skeletal muscle dysfunction by exercise training has been proved more beneficial than reversing the skeletal muscle deterioration. In fact, the most recent study is the triple training modality by Laoutaris and his colleagues (12) who demonstrated the importance of combining three types of exercise on muscle function and QoL. However, in their study, they used continuous aerobic training and not interval training. Thus, this study is the first randomized controlled study that combines RT, AIT and IMT in patients with CHF.

The major findings of this study:

- Both training regimens are able to bring out significant improvements in the cardiac function, NYHA functional class, functional capacity and respiratory muscle function

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(MIP and MEP in both training groups, but SPI_{max} only in the CT group). Combined training is superior to resistance training in improving all these parameters.

- Combined exercise training is better in improving skeletal muscle function than targeted skeletal muscle training.
- Resistance training improves respiratory muscle strength.

Since the control group had no significant improvements in any parameter assessed, we can confirm the effectiveness of this training program. Resistance training has also been demonstrated to be safe as no adverse effects were reported on the cardiac function in both training groups. The latter was also corroborated by several studies (22–24).

Cardiac Function

In our study, exercise improved left ventricular function significantly. Actually, we reported an improvement of 12% ($P=0.021$) in the left ventricle EF% after CT and a slight but significant improvement of 5% ($P=0.04$) after RT training. LVEDD and LVESD were significantly improved in CT patients only. PU et al. (23) didn't find any mild improvement in EF% after resistance training. This may be due to the different protocol used and/or due to the shorter interventional period (10 weeks vs. 12 weeks). In addition, Jankowska et al. (24) also didn't find significant improvements in either left ventricular EF% or left ventricular dimensions after resistance exercise. This difference observed between our study and Jankowska et al protocol can be related to the fact that these authors focused on training the lower limbs (i.e. quadriceps) and not the upper limbs. A difference due to baseline characteristics might contribute, but all the patients in our study were comparable to other studies characteristics especially concerning EF%. The CT group has shown 12% ($P=0.021$) of improvement in EF% which is higher than that reported by Laoutaris et al. (12) i.e. 9%. Furthermore, compared to their findings, a noticeable difference in left ventricular dimensions has been reported in favor of our triple training program; a decrease by 18% versus 2.7% in LVEDD and a decrease by 20% versus 0.7% in LVESD, respectively. This might be due to the intermittent intensity bouts used in our study. Non-significant decrease was found in LVESV and LVEDV, however this implies that exercise training hasn't caused any deterioration in ventricular volumes. The improvements in both EF% and left ventricular dimensions don't only imply safety, but also suggest an effect of

reverse remodeling and better filling properties (25). Therefore, both RT and CT groups were able to improve cardiac EF%, while CT group has shown higher and better improvements.

Exercise Test

Analysis of the parameters measured during stress test gives information about the cardiovascular fitness and functional capacity of patients. Highly important is exercise time (26), which is considered a strong prognostic variable in HF patients. In this study, exercise time has been improved significantly with 68.5% ($P=0.001$) of increment in the CT group and 27% ($P=0.01$) of increment in the RT group. The improvement in CT patients is higher than that reported by Laoutaris et al. (12) in their ARIS group. Otherwise lower resistance training intensity they used might be an important factor, but interval aerobic exercise in our study is suggested to be the main contributor to the difference observed. Furthermore, patients' stage on the treadmill was increased by 57% in CT group and 30% in RT group. Such improvement conveys an increase in endurance of both higher intensity and grade by the patients. During this stress test, patients were also assessed for dyspnea in both training groups and had significant decrease in dyspnea sensation. Since dyspnea was also improved in the RT group, strength training had an effect on the lung function of patients. The addition of RT to AIT and IMT resulted in a synergistic effect at the level of functional capacity and amelioration of CHF symptoms as well as IMT symptomatic relief effect (19). Thus, it is not surprising that exercise training has resulted in higher aerobic capacity in each patient, which was assessed by METs during the stress treadmill test. Note that METs has been proven to predict energy expenditure during exercise (27) and together with exercise time represent a tool for functional capacity assessment and evaluation of coronary artery disease severity if present (26). Upon these considerations, after exercise patients were said to have experienced improvements in breathing difficulties and a better functional capacity.

Respiratory Muscle Function

Exclusively, RT was able to significantly improve both MIP and MEP by 14% and 25% respectively. This finding shows that weight exercises improve functional capacity not only through improving skeletal muscle function but also through improving respiratory muscle function. Dyspnea improved profile discussed above due to RT might be correlated to the improvements in the inspiratory and expiratory muscle strength. As we know, this effect has not

been shown in CHF patients in previous studies, however, in healthy subjects it has been reported that strength training had beneficial effect on trans-diaphragmatic pressure. The increase in trans-diaphragmatic pressure constitutes a strengthening stimulus to the diaphragm, which might approve our findings somehow. Higher improvements in respiratory muscle function were reported in our study in the CT group compared to the findings by Laoutaris and his colleagues (12), MIP (59.8% versus 35%) and SPI_{max} (71% versus 33%). MEP that was not assessed by them has been improved significantly in our CT group only, which shows an improvement in both inspiratory and expiratory muscles. The higher improvement in our study might be due to different reasons. First, it could be related to interval training, where the intermittent bouts during each session induced a respiratory adaptation. This was also obvious through the higher dyspnea amelioration (26%) in our study compared to their study (2.8%). Second, the higher number of exercises in upper limbs in our study could also be the reason behind this better improvement. Previous studies approved the importance of IMT and its effects on respiratory muscle strength and endurance (28–30). Thus, it is essential to combine it with AT, which has been shown to improve inspiratory muscle strength (12), and RT would have extra benefits on respiratory muscle function.

Leg Skeletal Muscle Function

Assessment of the skeletal muscle function is important after exercise training. It has been proved that peripheral skeletal abnormalities contribute to exercise intolerance in HF subjects (4,31). Significant improvement in quadriceps muscle strength (assessed using the MVIF) and endurance (assessed using the MT) was observed in the RT and the CT groups as well, except for left leg endurance capacity in the RT group. Several studies have also reported a significant improvement in skeletal muscle function after RT or addition of RT to AT (24,32,33). This result proposes a reverse in some intrinsic muscular properties that were shown previously by exercise training (34,35), (36). Laoutaris et al. (12) were also able to prove significant improvements in both quadriceps muscle strength and endurance. However, they used different techniques from ours. In a previous study, PU et al. showed that strength training increases type I fiber and muscle oxidative capacity (23) significantly. These authors related the improvements in muscle strength and endurance, type I fiber area, and oxidative capacity to improved overall functional performance. The percentage of improvement in quadriceps strength was almost the same in both

groups. However, endurance time was substantially higher in the CT group, 41% and 47% for CT versus 24% and a non-significant improvement was noticed for RT concerning the right and left legs respectively. This might highlight the importance of aerobic interval training in improving submaximal activities, and resistance training in improving the force generated by the muscles. In fact, AIT has been shown to improve muscle mitochondrial function and calcium cycling (13), which might reflect its additive effects in our study.

Surface electromyography

RMS has increased in the resistance and combined groups with additive benefits for the latest. In normal subjects, muscle fatigue during strength exercise is associated with an increase in electrical activity generated per contraction due to the use of additional muscle fibers to compensate for fiber fatigue. Thus, the pronounced increase of EMG signal intensity in the combined group and its close correlation to muscular fatigability indicates an improvement in the impaired muscular excitation in CHF.

Concerning MF, there was a little increase only for two muscles for the resistance group. However, no improvement was shown for the combined group, although the addition of aerobic and inspiratory training on resistance training should result in additional benefits. This may be explained by the low number of patients enrolled in our study in each group.

Pulmonary Function

No significant changes have been detected in FVC, FEV1 or FEV1/FVC ratio in our study. The improvement in lung function is not essential since all included patients had normal lung function. What is really important is that the pulmonary status didn't change after the training period, thus meeting our selected exclusion criteria. FEV1/FVC was maintained between 75% and 80% in all patients (37). In addition, the flow-volume loops showed normal profiles. Therefore, we conclude that our patients didn't develop any adverse lung effect, which makes it easier for them to perform exercise training.

Functional Capacity and Quality of Life

Taking each training exercise separately, IMT has been shown to improve functional capacity in patients with CHF and IMW (28,38,39). AT and RT had also significant effects on improving functional and work capacity in CHF patients (23,32,40,41). In this study, we have proved that

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functional capacity assessed by the 6MWT has been significantly improved in both training groups but not in the control group. The improvement was higher in CT patients, and this is normally due to the additive effects of RT, AIT and IMT when combined together. Keeping in mind that the other functional capacity determinants that were discussed above, such as skeletal muscle function and dyspnea sensation, help in improving our patients' functional capacity as well. NYHA functional class assessment was another way to support improved functional status and QoL. There has been an improvement patients NYHA class in RT and CT groups, which was even better than that reported by Laoutaris et al. (12) (45% versus 24%). AIT is considered the main difference between our protocol and theirs, in addition to the different RT exercises and sets. Patients' QoL is an important measure when evaluating effects of chronic diseases and syndromes. In this regard, cardiac rehabilitation programs aim to improve QoL in HF, especially that this syndrome gets more acute and eventually to minimal exercise intolerance. In this study, QoL was evaluated using the MLwHFQ. Both training groups have had significant improvements (CT decreased by 59% whereas RT decreased by 30%). Improvements in both groups were higher than those detected by Laoutaris and his colleagues, which might be due to better improvements in functional capacity and amelioration in NYHA functional class.

LIMITATIONS

It was not possible to assess aerobic capacity through measuring peak oxygen consumption (VO₂max). However, we have used 6MWT and METs as prognostic outcomes. Both METs and 6MWT have been approved to be used instead of direct measurement of oxygen uptake (27), (42). In addition, there is heterogeneity in training load, especially in exercise duration. In fact, the CT group included three training modalities and therefore underwent longer exercise duration. So, this difference in workload between the two groups might have influenced our results.

Thus, comparing programs with an equivalent workload would be interesting in order to know if the effects are cumulative because of a large training volume or it is related to something else, more specifically to the specificity of each program.

CONCLUSION AND FUTURE WORK

The addition of RT to AIT and IMT was safe, efficient, and resulted in additional benefits over RT alone. CT improved skeletal muscle function, inspiratory muscle strength and endurance,

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cardiac function as well as functional capacity and QoL. Surprisingly, RT improved respiratory muscle function in addition to improving cardiac left ventricular EF%. Also, an additional improvement in the impaired muscular function is indicated by an improved electromyographic activity in patients with CHF.

Considering our findings, we highly recommend the use of combined training (AIT+RT+IMT) in CHF and IMW patients. We also support the conduction of further studies with larger number of patients and the addition of AIT+RT group to the three groups we have chosen. This study advocates for application of EMG in cardiac rehabilitation programs to evaluate muscle fatigue in CHF patients.

Cardiac biomarkers could also be assessed in order to confirm the safety and effectiveness of interventions. Furthermore, studies at the cellular level could be a plus if added to the non-invasive measurements we used. Finally, biopsies of skeletal muscle might give a clearer insight about potential skeletal muscle adaptations after exercise conditioning.

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Results

Table 1- Demographic and clinical characteristics of patient population.

	Control	RT	CT	P-value
Ages	52.6±11.2	55±6.7	57.6±11.6	0.440*
Females/Males	5/5	4/6	3/7	0.600*
BMI	31.3±3.4	33.3±4.9	32.2±4.9	0.514
Medication (%)				
ARB	10	50	40	0.254
B-blockers	33.3	33.3	33.3	0.994
Diuretics	38.1	28.6	33.3	0.773
ACE-I	36.4	31.8	31.8	0.899
EF (%)	36.1±8.2	36.6±2.6	38.4±5.6	0.729
LVEDD (mm)	58.3±6.6	64.6±5.2	58.3±6.1	0.069
LVEDS (mm)	46±5.9	52±8.1	50.8±10.4	0.454*
LVEDV (ml)	130±38.9	135.9±38.6	129.3±51.6	0.797*
LVESV (ml)	93.3±30.3	98.8±30.3	88.3±28.3	0.781
Exercise time	475.5±144.7	421.5±124.4	497±139.3	0.532
METs	8.1±2.1	8.3±1.9	9.4±2.0	0.337*
MLWHF_score	29.9±10.6	34.1±13.6	30.3±21.2	0.968*
FVC	3.2±0.8	2.9±0.8	3.2±0.9	0.873*
FEV1	2.4±0.9	2.5±0.7	2.6±0.7	0.912
FEV1/FVC	74.9±11.7	86.6±11.6	80.4±5.8	0.090
6MWT (meters)	455.3±113.1	425.7±62.9	477.6±94	0.539
MEP (mmHg)	70.1±16.7	89.6±29.5	91.3±10.1	0.094
MIP (mmHg)	35.8±10.5	44.3±7.5	42.6±8.3	0.151
SPI_{max} (seconds)	176±89.7	168.1±80.9	184.8±60.7	0.913
MVIF right (Kg)	18.0±4.7	19.7±4.1	19.9±2.9	0.578
Maintenance right (seconds)	105.0±30.3	90.6±24.9	94.9±22.3	0.536
Stage	2.8±0.9	2.6±0.9	2.8±0.9	0.921*
MVIF left (Kg)	18.1±3.7	21.2±2.6	21.7±4.9	0.152
Maintenance left (sec)	118±43.3	89.6±40.1	90.1±16.5	0.210
NYHA class	2±0.8	2.1±0.6	2±0.8	0.921*
Dyspnea	12.8±2.3	12.3±1.0	13.3±2	0.598*

BMI, body mass index; FEV1, forced expiratory volume in one second; FVC, forced vital capacity; LVEDD, left ventricular end-diastolic diameter; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; LVESV, left ventricular end-systolic volume. MEP, maximal expiratory pressure; METs, metabolic equivalent of task; MIP, maximal inspiratory pressure; MLWHFQ, Minnesota Living with Heart Failure Questionnaire; MVIF, maximal voluntary isometric force; NYHA, New York Heart Association; SPI_{max}, sustained maximal inspiratory pressure; 6MWT, six minute walk test.

* Baseline comparisons between groups were performed using Kruskal-Wallis test.

Results

Table 2- Functional capacity and quality of life.

	Control (n=8)			RT (n=8)			CT (n=8)			P ^b
	Pre	Post	P ^a	Pre	Post	P ^a	Pre	Post	P ^a	
6MWT (meters)	455.3±113.1	457.2±104.9	0.905	425.7±62.9	480.5±61.8	0.004	477.6±94	591.1±44.1	0.005	0.090
MLwHFQ score	29.9±10.6	31.6±13.8	0.348	34.1±13.6	23.8±7.9	0.017	30.3±21.2	12.3±8.8	0.009	0.286
NYHA class	2.0±0.8	2.3±1.0	0.317*	2.1±0.6	1.4±0.5	0.014*	2.0±0.8	1.1±0.4	0.006	0.225

MLwHFQ, Minnesota Living with Heart Failure Questionnaire; NYHA, New York Hear Association; 6MWT, six minute walk test.

^a P-Values derived using paired Student's t-test, after checking for the normality of the distributions.

^b P-Values between groups derived using repeated measures analysis of variance (RMANOVA).

*P^a derived using Wilcoxon signed-rank test.

Table 3- Cardiac function

	Control (n=8)			RT (n=8)			CT (n=8)			P ^b
	Pre	Post	P ^a	Pre	Post	P ^a	Pre	Post	P ^a	
LVEF (%)	36.1±8.2	35.1±8.8	0.412	36.6±2.6	38.5±3.1	0.040	38.4±5.6	43±5.2	0.021	0.005
LVEDD (mm)	58.3±6.6	58.3±12.8	1.000	64.6±5.2	63.8±4.9	0.291	58.3±6.1	47.9±4.4	0.044	0.136
LVESD (mm)	46±5.9	45.6±8.6	0.817	52±8.1	51±8.2	0.544	50.8±10.4	40.6±6.0	0.035	0.306
LVEDV (ml)	130±38.9	130.6±35.2	1.000*	135.9±38.6	131.6±52.0	0.584	129.3±51.6	121.3±44.4	0.674*	0.922
LVESV (ml)	93.3±30.3	94.8±22.8	0.735	98.8±30.3	92.6±35.1	0.141*	88.3±28.3	75.6±32.1	0.123*	0.598

LVEDD, left ventricular end-diastolic diameter; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; LVESV, left ventricular end-systolic volume.

^a P-Values derived using paired Student's t-test, after checking for the normality of the distributions.

^b P-Values between groups derived using repeated measures analysis of variance (RMANOVA).

*P^a derived using Wilcoxon signed-rank test.

Results

Table 4- Stress test.

	Control (n=8)			RT (n=8)			CT (n=8)			P ^b
	Pre	Post	P ^a	Pre	Post	P ^a	Pre	Post	P ^a	
Exercise time	475.5±144.7	448.1±168.3	0.889*	421.5±124.4	536±102.3	0.001	497±139.3	837.8±172.4	0.001	0.008
METs	8.1±2.1	7.7±2.2	0.424	8.3±1.9	10.3±1.7	0.008	9.4±2.0	12.9±1.4	0.004	0.003
Stage	2.8±0.9	2.6±0.7	0.564*	2.6±0.9	3.4±0.5	0.014*	2.8±0.9	4.4±0.9	0.016*	0.016*
Dyspnea	12.8±2.3	12.5±2.3	0.685	12.1±1.2	10.3±1.0	0.000	13.3±1.9	9.8±1.5	0.000	0.265

METs, metabolic equivalent of task.

^a P-Values derived using paired Student's t-test, after checking for the normality of the distributions.

^b P-Values between groups derived using repeated measures analysis of variance (RMANOVA).

*P^a derived using Wilcoxon signed-rank test.

*P^b-Values between groups derived using Friedman test

Table 5: Respiratory muscle function.

MEP, maximal expiratory pressure; MIP, maximal inspiratory pressure; SPI_{max}, sustained maximal inspiratory pressure.

	Control (n=8)			RT (n=8)			CT (n=8)			P ^b
	Pre	Post	P ^a	Pre	Post	P ^a	Pre	Post	P ^a	
MEP (mmHg)	70.1 ±16.7	70.1±18.4	1.000	89.6±29.5	112.1±32.7	0.042	91.3±10.1	132.0±27.9	0.001	0.003
MIP (mmHg)	35.8±10.5	36±11.5	0.895	44.3±7.5	50.5±8.8	0.004	42.6±8.3	68.1±8.4	0.000	0.001
SPI_{max} (seconds)	176±89.7	184.9±92.3	0.726*	168.1±80.9	195.6±87.1	0.072	184.8±60.7	316.1±41.1	0.001	0.022

^a P-Values derived using paired Student's t-test, after checking for the normality of the distributions.

^b P-Values between groups derived using repeated measures analysis of variance (RMANOVA).

*P^a derived using Wilcoxon signed-rank test.

*P^b-Values between groups derived using Friedman test.

Results

Table 6 - Skeletal muscle function.

	Control (n=8)			RT (n=8)			CT (n=8)			P ^b
	Pre	Post	P ^a	Pre	Post	P ^a	Pre	Post	P ^a	
MVIF right (Kg)	18.0±4.7	18.2±5.2	0.855	19.7±4.1	23.2±4.5	0.040	19.9±2.9	23.5±1.9	0.001	0.170
Maintenance right (seconds)	105±30.3	111.4±77.4	0.851	90.6±24.9	112.1±35.2	0.037	94.9±22.3	134.3±43.7	0.045	0.043*
MVIF left (Kg)	18.1±3.7	16.9±4.3	0.121	21.2±2.6	23.5±2.8	0.046	21.7±4.9	24.3±2.8	0.034	0.008
Maintenance left (seconds)	118±43.3	114.3±46.7	0.799	89.6±40.1	101.5±36.4	0.163	90.1±16.5	132.3±27.7	0.003	0.447

MVIF, maximal voluntary isometric force.

^a P-Values derived using paired Student's t-test, after checking for the normality of the distributions.

^b P-Values between groups derived using repeated measures analysis of variance (RMANOVA).

^a P^a derived using Wilcoxon signed-rank test.

^b P^b-Values between groups derived using Friedman test.

Table 7- Pulmonary function test.

	Control (n=8)			RT (n=8)			CT (n=8)			P ^b
	Pre	Post	P ^a	Pre	Post	P ^a	Pre	Post	P ^a	
FVC	3.2±0.8	3.1±0.9	0.160*	2.9±0.8	2.7±0.9	0.420	3.2±0.9	2.7±0.6	0.100	0.697
FEV1	2.4±0.9	2.3±0.9	0.378	2.5±0.7	2.3±0.6	0.181	2.6±0.7	2.4±0.7	0.413	0.915
FEV1/FVC	74.9±11.7	70.9±13.5	0.240	86.6±11.6	86.1±12.6	0.947	80.4±5.8	88.1±12.0	0.161	0.011

FEV1, forced expiratory volume in one second; FVC, forced vital capacity.

^a P-Values derived using paired Student's t-test, after checking for the normality of the distributions.

^b P-Values between groups derived using repeated measures analysis of variance (RMANOVA).

^a P^a derived using Wilcoxon signed-rank test.

Results

Table 8 - Pulmonary function test.

Parameter M1	Control group (n = 4)		Resistance group (n = 5)		Combined Group (n = 6)		p-Values
	Pre (m ± SE)	Post (m ± SE)	Pre (m ± SE)	Post (m ± SE)	Pre (m ± SE)	Post (m ± SE)	
Root mean square (Left Leg)							
Vastus lateralis	0.132±0.004	0.116±0.007	0.118±0.005	0.123±0.004	0.090±0.004	0.116±0.006	a: ns; b: ns; c: 0.000; d: 0.000;
Rectus femoris	0.095±0.002	0.150±0.016	0.096±0.003	0.123±0.002	0.085±0.001	0.097±0.002	a: 0.006; b: ns; c: 0.000; d: 0.000;
Vastus medialis	0.119±0.002	0.150±0.019	0.112±0.003	0.117±0.004	0.082±0.003	0.114±0.007	a: ns; b: ns; c: 0.004; d: 0.000;
Root mean square (Right Leg)							
Vastus lateralis	0.120±0.004	0.100±0.009	0.113±0.005	0.128±0.004	0.103±0.006	0.110±0.005	a: ns; b: 0.000; c: ns; d: ns;
Rectus femoris	0.088±0.002	0.108±0.008	0.088±0.005	0.106±0.002	0.088±0.002	0.094±0.003	a: ns; b: 0.002; c: ns; d: ns;
Vastus medialis	0.152±0.006	0.184±0.016	0.139±0.010	0.143±0.005	0.097±0.007	0.113±0.006	a: ns; b: ns; c: 0.000; d: ns;

Ns: not significant; a: Control group pre vs. Post; b: Resistance group pre vs. Post; c: Combined group pre vs. Post; d: difference among groups

Results

Table 9- Pulmonary function test.

Parameter M2	Control group (n = 4)		Resistance group (n = 5)		Combined Group (n = 6)		p-Values
	Pre (m ± SE)	Post (m ± SE)	Pre (m ± SE)	Post (m ± SE)	Pre (m ± SE)	Post (m ± SE)	
Root mean square (Left Leg)							
Vastus lateralis	0.038±0.001	0.065±0.005	0.025±0.001	0.035±0.001	0.038±0.001	0.042±0.002	a: 0.000; b: 0.000; c: 0.049; d: ns;
Rectus femoris	0.035±0.001	0.065±0.004	0.026±0.001	0.035±0.001	0.035±0.001	0.045±0.002	a: 0.000; b: 0.000; c: 0.000; d: ns;
Vastus medialis	0.043±0.002	0.125±0.014	0.025±0.001	0.040±0.002	0.036±0.001	0.042±0.003	a: 0.000; b: 0.000; c: 0.019; d: ns;
Root mean square (Right Leg)							
Vastus lateralis	0.030±0.001	0.082±0.007	0.027±0.001	0.029±0.001	0.035±0.001	0.037±0.002	a: 0.000; b: ns; c: ns; d: ns;
Rectus femoris	0.026±0.001	0.069±0.006	0.023±0.001	0.027±0.000	0.034±0.001	0.036±0.001	a: 0.000; b: 0.000; c: ns; d: ns;
Vastus medialis	0.032±0.001	0.104±0.007	0.023±0.001	0.029±0.001	0.036±0.001	0.034±0.001	a: 0.000; b: 0.000; c: ns; d: ns;

ns: not significant; a: Control group pre vs. Post; b: Resistance group pre vs. Post; c: Combined group pre vs. Post; d: difference among groups

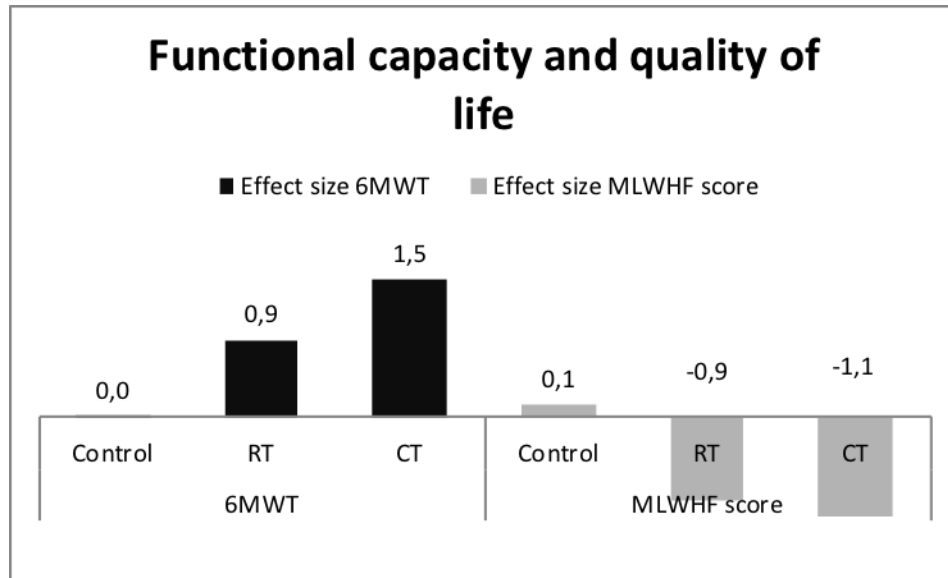


Figure 2- Effect size on functional capacity. 6MWT, six minute walk test MLWHF: Minnesota Living with Heart Failure Questionnaire.

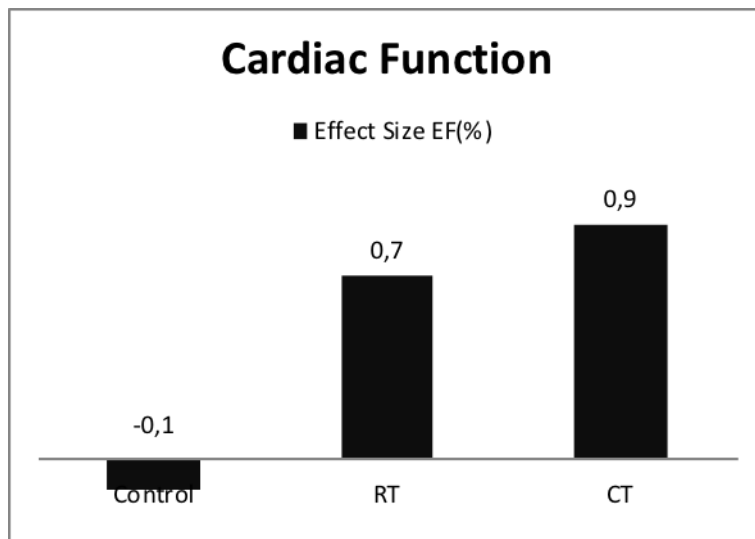


Figure 3- Effect size on cardiac function. EF, left ventricular ejection fraction.

Results

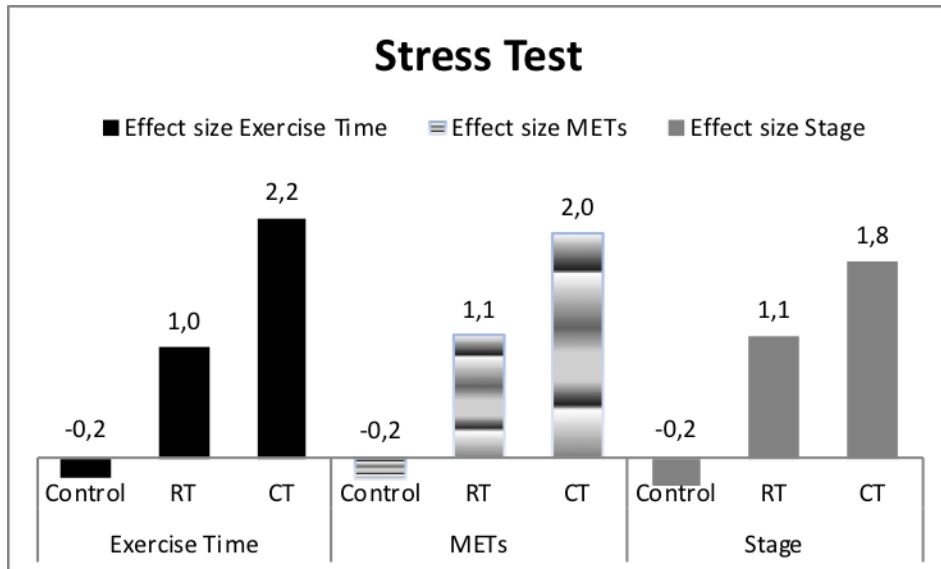


Figure 4 - Effect size on stress test. Mets: Metabolic Equivalent of Tasks.

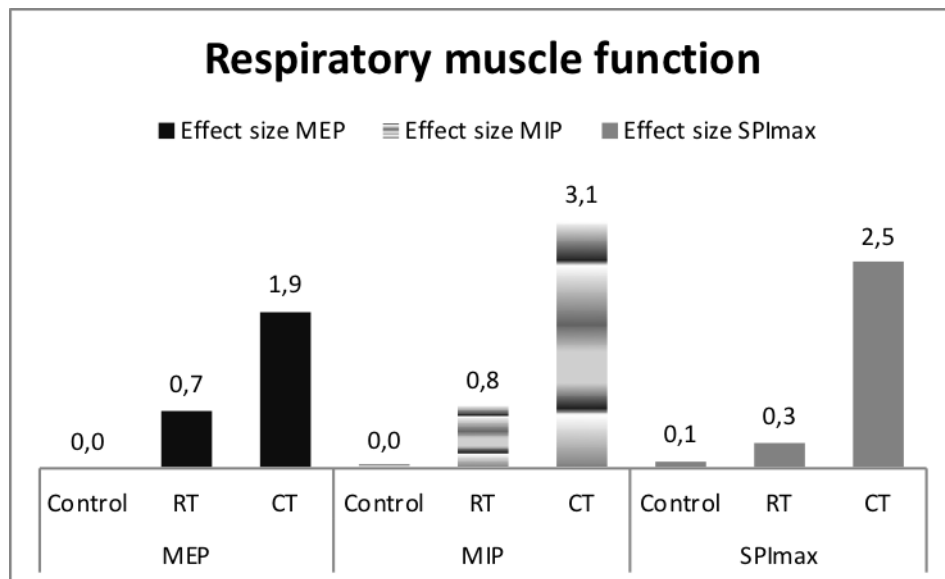


Figure 5 -Effect size on respiratory muscle function. MEP, maximal expiratory pressure; MIP, maximal inspiratory pressure; SMIP, sustained maximal inspiratory pressure.

Results

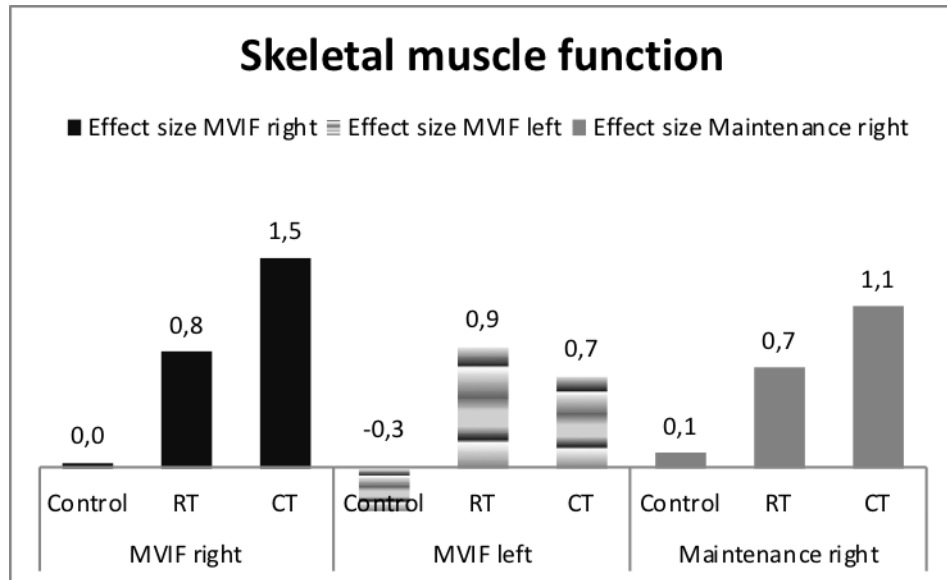


Figure 6 - Effect size on skeletal muscle function. MVIF, maximal voluntary isometric force; MT, Maintain Time.

DISCUSSION

DISCUSSION

Because exercise training tackles both central and peripheral disorders, it is considered an attractive therapy from a pathophysiological point of view, and according to Dafoe and Huston, the exercise remains the pioneer of cardiac rehabilitation programs (Dafoe and Huston 1997). Indeed, 25 years of research have demonstrated the numerous benefits of exercise training that are clinically translated into anti-remodeling effects, a better functional capacity and QoL, and a reduced dyspnea sensation and mortality rates.

Accordingly, the 2016 European Society of Cardiology heart failure guidelines (P. Ponikowski et al. 2016) firmly recommend regular exercise training for HF patients but experts agree that more research is required to determine the optimal exercise type and protocol for these patients.

Therefore, the overall purpose of this thesis was to examine the effects of a structured program of exercise training in CHF patients. Accordingly, data from two research was examined in order to establish the influence of the intervention on cardiopulmonary responses, skeletal muscle function and quality of life in Patients with CHF with inspiratory muscle weakness. Secondly, a combination of resistance, aerobic and inspiratory muscle training was examined in order to characterize the additional benefits of resistance training in CHF patients.

This thesis had two key aims: firstly, to examine the benefits of each of the five exercise modalities: aerobic, inspiratory, resistance, aerobic + inspiratory and aerobic + inspiratory + resistance, and secondly to determine the best exercise modality to follow in order to recommend it in guidelines as a useful intervention for HF patients.

The most important finding to appear from the data collected is the additive and incremental benefits that result from combining two or more exercise modality together. Indeed, the improvement in inspiratory muscle function, functional capacity, dyspnea and quality of life with the combined groups was higher than the improvement gained from each modality alone. In addition, combined groups appear to be not only easy to use for clinical practice and well-tolerated but also ensure safety.

Pulmonary Function

No significant changes have been detected in FVC, FEV1 or FEV1/FVC ratio in all groups, except for IMT+AIT group where there is 10.3% improvement in FVC. These results reaffirm the findings of a study conducted by Adamopoulos (Adamopoulos et al. 2014) which found no significant changes in pulmonary function parameters. A possible explanation for this result might be because all included patients had normal lung function. In addition, the non-significant changes detected for these parameters were in accordance to the variability in weight in some of patients. In fact, height, sex and weight were used in the reference equations for lung function parameters and particularly, weight gain that is present in some patients in our study is significantly related to lung dysfunction, thus affecting the respiratory parameters.

Inspiratory Muscle Function

The combination of AIT and IMT was safe and resulted in incremental benefits over AIT and IMT alone in patients with CHF.

The AIT + IMT resulted in a mean 62.4% and 40.6% increment in MIP and MEP respectively while IMT increased these parameters by a mean of 25% and 37.9%.

For IMT, these findings are consistent with those of Alba Ramirez (Ramírez et al. 2002) who showed that external intercostal muscles have the ability to express a structural reorganization after specific inspiratory training, which could be translated to better ventilation and larger increase in inspiratory strength.

On the other hand, the additive benefits of AIT to IMT are consistent with Adamopoulos study (Adamopoulos et al. 2014) which reported an increase of MIP in AT/SHAM group and with Winkelmann study (Winkelmann et al. 2009) which shows that AT increased MIP by a mean of 72%. These improvements may be partially attributed to the aerobic training and can be explained by the fact that all patients selected in our study had IMW, thus any exercise training, being AIT, IMT or RT may be beneficial in improving respiratory muscle strength. From the research conducted by Smart and al. in 2011 (Smart and Steele 2011) and Nunes and al. in 2013 (Nunes et al. 2013), it shows that, by decreasing the amount of cytokines, particularly TNF- α , AIT is able to enhance the strength of inspiratory muscles, since high-dose TNF- α has been shown to stimulate the loss of skeletal muscle myosin and promote muscle atrophy, contributing thus to respiratory muscle dysfunction (Wong, Selig, and Hare 2011).

Discussion

Besides, RT was able to significantly improve both MIP and MEP by 14% and 25% respectively. This finding shows that weight exercises improve functional capacity not only through improving skeletal muscle function but also through improving respiratory muscle function.

In which concerns the triple combined group, higher improvements in respiratory muscle function were reported in our study when compared to those found by Laoutaris and his colleagues (Ioannis D. Laoutaris et al. 2013), MIP (59.8% versus 35%) and SMIP (71% versus 33%). A possible explanation for this result might be due to the fact that interval training, used in our study, is proved to be more effective in improving respiratory outcomes than Laoutaris continuous training (Ioannis D. Laoutaris et al. 2013).

For SMIP, larger improvement was shown for the double and triple combined groups compared to IMT group, versus non-significant improvement for AT and RT groups, and this is owing to the fact the AT and RT alone didn't improve the sustained pressure effectively. This result may have been also affected by the intensity of IMT applied. In fact, previous studies have shown that selective IMT at 30% MIP resulted in an improvement in MIP but not in SMIP (Johnson, Cowley, and Kinnear 1998). In that respect, the 60% MIP intensity applied in our study allows the improvement of SMIP and therefore improves respiratory muscle work capacity and endurance as well as dyspnea.

Possible mechanisms for improved respiratory endurance could include the increased level of aerobic oxidative metabolism in respiratory muscles which lead to the increased resistance to fatigue (Mancini et al. 1994). In addition, it is possible that the increase in SMIP is reached through the improvement in strength training. In fact, stronger muscles perform any given task at a lower percentage of their maximum capacity than weak muscles do; strong muscles are therefore able to sustain a given activity for longer periods (McConnell et al. 2003) .

Skeletal Muscle Function

Decreased muscle strength and perceived fatigue are frequently associated with exercise intolerance and may be responsible for several limitations in HF. Thus, assessing skeletal muscle strength and endurance is very important after exercise training.

Discussion

Fortunately, in our study, all group showed significant improvements in skeletal muscle strength except for IMT group, and the larger benefits were for the triple combined group.

The improvement shown in the double and triple combined groups were attributed to the aerobic treadmill training and the resistance training since IMT alone didn't show any significant improvement. In fact, aerobic training was able to improve the MVIF exerted by the quadriceps in the lower left and right legs by around 10%, which is not different than the 11% improvement in the MVIF reported in the patients of the AIT & IMT group. Thus, IMT had no effect on the peripheral skeletal muscles and the attributed increment was due to the aerobic training.

Concerning resistance training, it offers greater development of muscular strength since the improvement of MVIF in the left and right legs was respectively 11% and 18%.

A unifying explanation for these positive results could be that both aerobic and strength training partially reverse skeletal muscle abnormalities by reducing the pro-oxidant state, improving calcium homeostasis and mitochondrial function and increasing the ratio of type 1 and type 2 muscle fibers, which therefore, reduces skeletal muscle fatigability and improve skeletal muscle metabolism (Brum et al. 2011).

However, for endurance time, all groups showed significant improvement except for IMT group and the RT group (for the left leg endurance capacity). MT in the triple combined group was substantially higher than the RT group (41% and 47% versus 24% and a non-significant improvement concerning the right and left legs respectively). This might highlight the importance of aerobic interval training in improving submaximal activities, and the capability of resistance training in improving the force generated by the muscles.

Surface electromyography

There is growing evidence that skeletal muscle is adversely affected in CHF patients and is a potent contributor of the reduced exercise capacity characteristic of this condition. Skeletal muscle fatigability, in particular, has been largely correlated with exercise capacity and disease progression in CHF patients, yet little data exists on the electrical activity of the muscles before and after exercise. For that, this study investigated the use of EMG in clinical diagnosis, in HF patients, in order to monitor the progression of skeletal muscle activity and function.

Discussion

We assessed EMG activities from three muscles: vastus lateralis (VL), rectus femoris (RF), and vastus medialis (VM) and compared the different results between six groups: control group, AIT, IMT, RT, AIT&IMT and AIT&IMT&RT.

We firstly demonstrated, in both strength and endurance manipes a significant increase in the RMS of the three muscles in the left and right legs in the double combined group but only an increase in the left leg for the triple combined group. Surprisingly, the higher benefit was shown for the double combined group and not the triple. In others words, the addition of RT on the double combined group doesn't show any additive effects. There is a possibility that this result is due to the low number of patients in our study, to the difference age, body mass index and male/female distribution between double and triple combined groups and can also be affected by the total training duration that could be higher.

The increase in RMS of the EMG signal after training was the result of an adaptation of the muscle fiber and a combination of recruitment of an increased number of motor units and an increased firing rate of each unit.

In addition, we didn't find any increase in the response of the three muscles in the IMT group nor during strength or endurance protocols (except for one muscle in the endurance protocol). Thus, the improvement in the combined training was the result of the aerobic training and not the inspiratory training.

Concerning MF which is an optimal way to assess muscle fatigue, we have taken the results of the endurance manipe and not the strength one, because in strength manipe, the force lasts for only 3 seconds which prevent us to detect the muscle fatigue in an objective way. It has been shown that during endurance protocol, aerobic, inspiratory, resistance and double combined trainings had positive effects on skeletal muscle fatigue indexes.

This result may be affected by the higher recruitment of motor units and the accumulation of anaerobic metabolism by-products such as lactate, protons, ammonium (Gayda et al. 2005).

Cardiac Function

It is widely recognized that AT improves cardiac pump performance. However, the effects of AT on cardiac function in HF are still controversial (Brum et al. 2011). Although some studies and Meta-analyses have not shown improvement in heart function in HF individuals (van Tol et al. 2013), other studies have confirmed a significant increase in contractility and cardiac

Discussion

function (M. Haykowsky et al. 2011). It is also important to emphasize that, despite these contradictory data, AT actually improves myocardial blood flow reserve independently of ventricular function improvement.

Our main findings were that AT, the double and triple combined groups, increased LVEF by 14.1%, 16.6% and 12% respectively, versus a slight improvement of 5% after RT training. The latest result did not support the findings of PU et al. (Pu et al. 2001) who didn't find any mild improvement in EF after resistance training. This may be due to the different protocol used and/or due to the shorter interventional period (10 weeks vs. 12 weeks). In addition, Jankowska et al. (Jankowska et al. 2008) also didn't find significant improvements in either left ventricular EF or left ventricular dimensions after resistance exercise. This difference observed between our study and Jankowska et al protocol can be related to the fact that these authors focused on training the lower limbs (i.e. quadriceps) and not only the upper limbs. These data indicate that aerobic training, and resistance training, alone or combined with IMT, are effective in improving the ejection fraction in patients with CHF.

Besides, these findings did not seem to be consistent with other research regarding the contradictory results of the effect of AT on cardiac function in patients with HF, some variables such as the intensity of the training and the methods used to assess the cardiac function in human studies, may have influenced the observed results. Interestingly *Haykowsky et al* (M. J. Haykowsky et al. 2007) conducted a meta-analysis of 14 studies and found that the intensity of exercise adopted during training sessions play an important role in the extent of cardiovascular adaptation in HF patients. They found that AT sessions performed at intensities above 60% HR peak are more suitable, leading to improved cardiac function in HF patients. In fact, *Wisloff et al* (Wisloff et al. 2007) suggested that a threshold intensity (during which a workout should be executed) may exist to benefit the heart. They have also shown that AIT (70-95% of HR peak) improved EF more than moderate continuous training (70% of HR peak) and led to reverse remodeling of the left ventricle.

The AIT resulted in significant improvements in the given central parameters: LVEDD and LVESD. However, higher improvements were obtained in the AIT & IMT and the AIT&IMT&RT groups suggesting that the addition of AIT to IMT and RT had more pronounced effect than pure aerobic training. Furthermore, compared to Laoutaris findings (Ioannis D. Laoutaris et al. 2013), a noticeable difference in left ventricular dimensions has been reported in

favor of our triple training program; a decrease by 18% versus 2.7% in LVEDD and a decrease by 20% versus 0.7% in LVESD, respectively. This might be due to the intermittent intensity bouts used in our study.

The decrease in LVESD and LVEDD reflects better left ventricular filling properties that have consequently improved LVEF. These improvements don't only imply safety, but also suggest an effect of reverse remodeling. While aerobic training group and double and triple combined groups have shown higher and better improvements on cardiac function, RT was able to improve only the ejection fraction.

Stress Test

As mentioned above, the analysis of the variables measured during the "Stress Test" gives an important evaluation of the cardiovascular fitness and functional capacity of CHF patients.

In our study, exercise time, METS improved after the intervention in all groups, with additional benefits for the triple combined group.

In fact, exercise time improved for 68.6% for triple combined group versus 62.3% for double combined group. These results seemed to reaffirm the findings of Laoutaris (Ioannis D. Laoutaris et al. 2013) study which shows an improvement in exercise time, but by only 16%, and this may have been affected by the continuous aerobic training conducted in Laoutaris study, versus an interval aerobic training in ours.

The additive benefit of the interval training is due to its characteristic alteration between work and recovery phases and with high and moderate intensity training. During the rest periods, the body works to restore itself to a neutral state, replenishing everything he has utilized (K. Meyer et al. 1990). This makes it possible for patients with HF to complete short periods of work at a higher intensity and to use the muscles more intensively which challenge the heart pumping ability more than it would be possible during continuous exercise, thereby improving the resistance to fatigue and increasing exercise time (Piepoli et al. 2011).

As well, conditioning of inspiratory muscles in IMT group, could attenuate the inspiratory metaboreflex which could then improve blood flow redistribution to skeletal muscles in the body. This fact improves exercise performance due to decreased sympathetic activity and peripheral vasoconstriction, leading to an enhanced perfusion of the locomotor muscles, thereby

delaying the time to fatigue and improving exercise tolerance (Ribeiro, Chiappa, and Callegaro 2012).

Same results were found for METS and Grade which confirm the added benefit of each training modality in improving the overall exercise performance, and also shows the superiority of the triple combined group.

Functional Capacity, Quality of Life and Dyspnea

It has been shown that all training modalities improve functional capacity, whether for 6MWT, NYHA, MLWHFQ or dyspnea parameters. All these were mostly improved in the triple combined group, and this is normally due to the additive effects of RT, AIT and IMT when combined together, except for dyspnea scale where the high improvement was shown in the double combined group, and this may be explained by looking at the difference of age and BMI between the double and triple combined groups that could affect the results (Age: 52 versus 58, BMI: 28 versus 32 for the double and triple combined groups respectively).

This study confirms the claims made in previous researches where Laoutaris shows that AIT can partially reverse all skeletal muscle abnormalities improving the functional status, the QoL and possibly the survival prospects (Laoutaris et al. 2013). On the other hand, IMT is proven to be effective in improving exercise capacity which is probably related to the reduction of dyspnea, therefore less dyspnea perception during functions can help patients be more independent in activities of daily living, thus, improving their QoL (Bosnak-Guclu et al. 2011).

NYHA functional classification is also a determinant of HF patients' QoL, since it is concerned with symptoms and signs representing an obstacle that hinders the patients' life. As well, improvements were detected after exercise training in all groups with always the additional benefits for the triple combined group. Noting that Adamopoulos et al. (Adamopoulos et al. 2014) and Laoutaris et al. (Laoutaris et al. 2013) also reported NYHA functional class improvement in their patients after exercise training, but the improvement in our study was more important due to our subjects' greater improvement in functional capacity and skeletal muscle performance.

Discussion

Finally, almost all groups have improved cardiopulmonary responses; skeletal muscle function and quality of life in patients with CHF with inspiratory muscle weakness, but the combined group modalities had a more pronounced effect on all these parameters.

Thus, our results have shown the superiority of the combined group modalities, which is proven to have an effect on all parameters discussed, thereby leading to reverse remodeling of the deteriorated heart in HF.

CONCLUSION AND PERSPECTIVES

This study shows that any exercise training, being AT, IMT or RT, improves inspiratory muscle function, QOL, exercise performance and dyspnea in patients with CHF in addition to a greater sense of wellbeing and a better functional capacity.

On the other hand, the combination of the AIT and the IMT results in an additional improvement in the inspiratory muscle function, skeletal muscle performance, exercise time and METs, functional capacity, QoL and dyspnea in patients with CHF with IMW. In contrast to the IMT, the AIT alone can improve skeletal muscle strength and endurance as well as cardiac structure and function determined by LVEF, LVESD and LVEDD.

However, the addition of RT to AIT and IMT was the most powerful regarding functional capacity and quality of life parameters and resulted in additional benefits over the double combined group and all training modalities in the above parameters. In fact, this additive benefit results from the effect of RT in improving respiratory muscle function and cardiac left ventricular EF%.

Our findings indicate that assessing electrical activity of skeletal muscles is a must during further studies, since an increase in the response and fatigability of such muscles was shown in our study, particularly in the double combined group.

Considering our findings, we highly recommend the use of triple combined training (AIT+RT+IMT) in CHF and IMW patients. In fact, it is an effective, safe and inexpensive adjuvant treatment, improving the efficiency of cardiac rehabilitation programs within the public health system. It can be also incorporated into the overall drug and non-drug management of CHF patients with low ejection fraction. Its effects on outcome are probably very dependent on the long-term compliance to an exercise-based way of life after a hospital-based rehabilitation program and are probably not negligible, even on top of optimal therapy.

We also support the conduction of further studies with higher number of patients and the addition of AIT+RT group to the three groups we have taken. Cardiac biomarkers and studies at the cellular level could also be assessed in order to confirm the safety and effectiveness of interventions. Furthermore, biopsies of skeletal muscle might give a clearer insight about potential skeletal muscle adaptations after exercise conditioning.

LIMITATIONS

Although we conducted a large study, patient enrolment was slow and the patient number remains small and a higher number could have resulted in more significant improvement.

In addition, it was not feasible to assess aerobic capacity through measuring peak oxygen consumption (VO₂max). However, we have used 6MWT and METs as prognostic outcomes. Both METs and 6MWT have been approved to be used instead of direct measurement of oxygen uptake (Guyatt et al. 1985).

Furthermore the training period was maintained for only 12 weeks, which does not allow us to conclude that the effect on functional capacity and quality of life is long-term. However, one-year follow-up showed that the effects on quality of life are partially maintained (Ulbrich et al. 2016). In addition, there is heterogeneity in training load, especially in exercise duration might have influenced our results.

Finally, all patients selected have IMW, for that, new studies should be conducted, to compare the outcomes in HF patients with/without IMW for better understanding the effects of such exercise training in its different combinations.

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ANNEX

1. Certificate of Completion (NIH): Protecting human Research Participants



2. Minnesota Living With Heart Failure

MINNESOTA LIVING WITH HEART FAILURE® QUESTIONNAIRE

The following questions ask how much your heart failure (heart condition) affected your life during the past month (4 weeks). After each question, circle the 0, 1, 2, 3, 4 or 5 to show how much your life was affected. If a question does not apply to you, circle the 0 after that question.

Did your heart failure prevent you from living as you wanted during the past month (4 weeks) by -	No	Very Little				Very Much
1. causing swelling in your ankles or legs?	0	1	2	3	4	5
2. making you sit or lie down to rest during the day?	0	1	2	3	4	5
3. making your walking about or climbing stairs difficult?	0	1	2	3	4	5
4. making your working around the house or yard difficult?	0	1	2	3	4	5
5. making your going places away from home difficult?	0	1	2	3	4	5
6. making your sleeping well at night difficult?	0	1	2	3	4	5
7. making your relating to or doing things with your friends or family difficult?	0	1	2	3	4	5
8. making your working to earn a living difficult?	0	1	2	3	4	5
9. making your recreational pastimes, sports or hobbies difficult?	0	1	2	3	4	5
10. making your sexual activities difficult?	0	1	2	3	4	5
11. making you eat less of the foods you like?	0	1	2	3	4	5
12. making you short of breath?	0	1	2	3	4	5
13. making you tired, fatigued, or low on energy?	0	1	2	3	4	5
14. making you stay in a hospital?	0	1	2	3	4	5
15. costing you money for medical care?	0	1	2	3	4	5
16. giving you side effects from treatments?	0	1	2	3	4	5
17. making you feel you are a burden to your family or friends?	0	1	2	3	4	5
18. making you feel a loss of self-control in your life?	0	1	2	3	4	5
19. making you worry?	0	1	2	3	4	5
20. making it difficult for you to concentrate or remember things?	0	1	2	3	4	5
21. making you feel depressed?	0	1	2	3	4	5

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3. Consent Form

Researcher Name:

Zahra Sadek: Physiotherapist, first year student doctorate at the Lebanese University and Picardie de Jules Vernes University.

Dr. Wiam Ramadan: Assistant Professor at the Lebanese International University (LIU)

Research Title: Respiratory muscles: Functional characterization and effects of different types of training on patients with stable chronic heart failure.

Place of research: Beirut Cardiac Institute, Beirut, Lebanon.

We have the honor to invite you to participate in a scientific research to be conducted at Beirut cardiac institute in Beirut. Please read the following information carefully before making a decision to share or not. You can request clarification or additional information about anything mentioned in this form or this study in general from your doctor.

A. Description of scientific research and its purpose and interpretation of its course

The objective of this research is to identify the physiological functions that arise in the exercise of the inability to exert effort and shortness of breath, especially the functions of the muscles (respiratory and skeletal) and the functions of the heart and respiratory system in patients with chronic heart failure; And the effects of various rehabilitation programs on the function of the heart, arteries, respiratory and skeletal muscle functions.

In this study, we examined the efficacy hypothesis of a program consisting of three training modalities: aerobic training, resistance training, and selective inspiratory muscle training on the heart and lung function, skeletal and respiratory muscles function, exercise capacity, and quality of life by comparing them with other methods on patients with chronic heart failure.

The duration of the treatment is twelve weeks, at the rate of three sessions per week, for one hour. Any session that has not been completed will be added to the end of the program, where each participant can have 36 sessions of physiotherapy. All sessions must be supervised by a specialist doctor (Dr. Rigab Hamdan, Malik Hamada, Malik Moussa, Hassan Mansour) in Cardiology and Physical therapist specialist (Zahra Zadek).

Before the start and after the sessions, we will do some necessary tests: ECG, echocardiography, spirometry, Respiratory muscle testing, skeletal muscle test, stress test. The patient will not pay any additional costs to the hospital when conducting these tests.

B. Benefits that may result from this research and adverse effects or reaction

There are no adverse effects or reactions that can be caused by participation in this research, all training programs are approved by independent professional ethics committees. On the contrary, this program has many benefits including:

- Relieve symptoms caused by heart failure
- Improve the ability to exercise and endure the effort
- Improve quality of life
- Reduce the rate of hospitalization
- Improve the daily effort endurance

If you agree to participate in this study, your name will remain confidential. No one shall have the access to your medical file, unless provided by law, except for the doctor responsible for the study, his assistants, and the independent professional ethics committees. If any negative medical condition happened through participation in this study, there shall be no financial, moral or medical compensation by the Lebanese International University or Beirut cardiac institute or the Lebanese University to cover costs if they are not covered by medical or hospital insurance companies or any government programs.

Author's approval:

I have explained in detail to the participant in this medical research of _____ , its nature, its process and its negative effects. I have answered all his questions clearly. I will inform the participant of any changes in the course of this research or its negative effects or benefits that can be obtained during the research.

Name of researcher

Researcher's approval:

Date

Name of participant _____ Telephone number _____

I have read this acceptance form and understood its content. All my questions were answered. Therefore, I am free to choose, I have the right to conduct this research and I agree to participate in it. I know that the researcher Dr. _____ and his colleagues, and his assistants will be ready to answer my questions and that I can contact them by phone. I also know that I am free to withdraw from this research whenever I wish even after signing the consent without affecting the medical care provided to me.

Participant Name:

Participant's signature:

Date: