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TÍTULO:

EFFECTOS DE UN PROGRAMA DE EJERCICIO AERÓBICO CONTÍNUO DE MODERADA INTENSIDAD VS. INTERVÁLICO DE ALTA INTENSIDAD SOBRE FACTORES PREDICTIVOS DE SUPERVIVENCIA EN PACIENTES CON CARDIOPATÍA ISQUÉMICA: UN ENSAYO CONTROLADO ALEATORIZADO

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AUTORIZAN:

La presentación de la Tesis Doctoral titulada "EFECTOS DE UN PROGRAMA DE EJERCICIO AERÓBICO CONTÍNUO DE MODERADA INTENSIDAD VS. INTERVÁLICO DE ALTA INTENSIDAD SOBRE FACTORES PREDICTIVOS DE SUPERVIVENCIA EN PACIENTES CON CARDIOPATÍA ISQUÉMICA: UN ENSAYO CONTROLADO ALEATORIZADO", realizada por D. Koldobika Villelabeitia Jaureguizar, bajo nuestra inmediata dirección y supervisión, y que presenta para la obtención del grado de Doctor por la Universidad Francisco de Vitoria en Madrid.

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La presente tesis doctoral, de acuerdo con el informe correspondiente autorizado por los directores de tesis, y en cumplimiento con la normativa aprobada por el Órgano Responsable del Programa de Doctorado, se presenta como un compendio de tres publicaciones. Las referencias completas de los artículos que constituyen el cuerpo de la tesis son los siguientes:

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“ Cuando creíamos que teníamos todas las respuestas, de pronto, cambiaron todas las preguntas”.

Mario Benedetti

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1. ABREVIATURAS

1 ABREVIATURAS

ACC: American College of Cardiology.

AHA: American Heart Association.

CI: Cardiopatía Isquémica.

CVRS: Calidad de Vida Relacionada con la Salud.

ECMI: Entrenamiento Continuo de Moderada Intensidad.

ECV: Enfermedades Cardiovasculares.

EM: Eficiencia Mecánica muscular.

ESC: European Society of Cardiology.

FEVI: Fracción de Eyección del Ventrículo Izquierdo.

FC: Frecuencia Cardíaca.

HIIT: High Intensity Interval Training o Entrenamiento interválico de alta intensidad.

MET: Metabolic Equivalent Task.

OMS: Organización Mundial de la Salud.

PRCV: Programas de Rehabilitación Cardiovascular.

RFC: Recuperación de la Frecuencia Cardíaca.

RFC-1: Recuperación de la Frecuencia Cardíaca en el primer minuto.

RFC-2: Recuperación de la Frecuencia Cardíaca en el segundo minuto.

SNA: Sistema Nervioso Autónomo.

SRT: Steep Ramp Test.

VT₁: Primer umbral ventilatorio.

VT₂: Segundo umbral ventilatorio.

VO₂ max: Consumo de O₂ máximo.

VO₂ pico: Consumo de O₂ pico.

6MWD: Six Minutes Walk Distance o prueba de los seis minutos andando.

2. RESUMEN

2 RESUMEN

2.1 Resumen

Título:

Efectos de un programa de ejercicio aeróbico continuo de moderada intensidad vs. Interválico de alta intensidad sobre factores predictivos de supervivencia en pacientes con cardiopatía isquémica: Un ensayo controlado aleatorizado.

Introducción:

La prescripción de ejercicio físico mejora la capacidad funcional y la morbimortalidad de los pacientes con enfermedades cardiovasculares. La mayoría de las investigaciones han estudiado los efectos del ejercicio físico aeróbico continuo de moderada intensidad (ECMI) en pacientes con enfermedad cardiovascular, sin embargo, el entrenamiento aeróbico interválico de alta intensidad (HIIT) comienza a despertar un gran interés por los resultados obtenidos sobre determinados parámetros pronóstico de morbi-mortalidad.

Objetivos:

Los objetivos principales de este estudio fueron comparar el efecto de dos modalidades de entrenamiento aeróbico (ECMI vs HIIT) sobre la capacidad funcional, la recuperación de la frecuencia cardíaca en el primer y segundo minuto (RFC-1 vs RFC-2) tras una prueba de esfuerzo hasta el agotamiento, y sobre los valores de eficiencia mecánica (EM), en pacientes con cardiopatía isquémica. Los objetivos secundarios fueron verificar la seguridad a la hora de aplicar entrenamiento físico de alta intensidad y conocer el impacto de ambos entrenamientos (ECMI vs HIIT) sobre la calidad de vida relacionada con la salud en pacientes con cardiopatía isquémica.

Métodos:

Ensayo clínico prospectivo y aleatorizado (NCT02168712) con pacientes diagnosticados de enfermedad coronaria estable de clase funcional I y/o II. Tras firmar un consentimiento informado fueron aleatorizados en relación 1-1 en dos grupos: ECMI o HIIT. En ambos grupos, los entrenamientos se realizaron en cicloergómetro con sesiones de 40 minutos, 3 días/semana. Se analizaron parámetros ergoespirométricos durante la prueba de esfuerzo y posterior recuperación, aspectos relacionados con la calidad de vida pre y post-programa, así como un registro de incidencias durante el programa.

Resultados:

Ambos grupos de entrenamiento aumentaron el VO_2 ($\text{ml kg}^{-1} \text{min}^{-1}$) y la carga (vatios) asociados tanto al nivel de esfuerzo máximo (VO_2 pico) como al submáximo (VT_1 y VT_2), con mayores incrementos a favor del HIIT ($p < 0,05$). Sólo se observó un aumento significativo de la RFC-1 y RFC-2 en el grupo HIIT ($p < 0,001$). Se obtuvo una correlación significativa entre los valores de VO_2 pico con RFC-1 ($p < 0,001$) y RFC-2 ($p < 0,001$). La EM en el VT_1 aumentó significativamente en ambos grupos de entrenamiento aeróbico, con un mayor aumento en el grupo HIIT ($p < 0,01$). La EM en VO_2 pico y en VT_2 solo aumentó significativamente en el grupo HIIT ($p < 0,001$). Ambos entrenamientos mejoraron los resultados de los test de la calidad de vida con mejores resultados en el grupo interválico. No se registró ningún tipo de eventos en ninguna de las modalidades.

Conclusiones:

La aplicación de un programa de entrenamiento tipo HIIT en pacientes con enfermedad coronaria consigue mayores mejoras en el VO_2 pico, en la carga asociada a los umbrales ventilatorios, en los índices de RFC post-ejercicio y en la eficiencia mecánica muscular frente al ECMI. Todo ello sin un riesgo cardiovascular añadido y con un mayor impacto en los test de calidad de vida.

Palabras clave:

Cardiopatía isquémica; Entrenamiento continuo; Entrenamiento interválico; Recuperación de la frecuencia cardiaca; Eficiencia mecánica muscular.

2.2 Abstract

Title:

Effect of moderate continuous vs high-intensity interval training on predictive factors of survival with coronary artery disease: A randomized controlled trial.

Introduction:

The prescription of physical exercise improves functional capacity and decreases morbidity and mortality of patients with cardiovascular diseases. Most studies have focused on moderate continuous training (MCT) in patients with cardiovascular diseases; however, a body of evidence has begun to emerge demonstrating that high-intensity interval training (HIIT) has significantly better results in terms of morbidity and mortality.

Objective:

The principal objective of this study was to compare the effect of two exercise training protocols (MCT vs HIIT) on functional capacity, heart rate recovery at the first and second minute (HRR-1 vs. HRR-2) after an exercise test to the point of exhaustion, and on the values of mechanical efficiency (ME) in patients with ischemic heart disease. The secondary outcome was to determine the impact of the type of exercise on quality of life and to verify the safety of following these two exercise programs

Methods:

A prospective, randomized clinical trial (NCT02168712) was conducted with patients with stable functional class I or II coronary artery disease. After signing a consent form, patients were randomized on a one-to-one basis to either the MCT or the HIIT group. The mode of exercise training was a cycle ergometer with 40 minutes per sessions, 3 days per week (total of 24 sessions over 2 months). Ergospirometric parameters were analyzed during the stress test and subsequent recovery, aspects related to pre- and post-program quality of life, as well as a record of incidents during the program.

Results:

Both exercise programs increase VO_2 ($ml\ kg^{-1}\ min^{-1}$) and load (watts) associated to maximum effort level (VO_2 peak) and the submaximum level (VT_1 and VT_2) with a higher increase in the HIIT group ($p < 0.05$). Increase in RFC-1 and RFC-2 was only observed in the HIIT group ($p < 0.001$). We found a significant correlation between the VO_2 peak values with HRR-1 ($p < 0.001$) and HRR-2 ($p < 0.001$). The ME at VT_1

significantly increased in both groups, with a greater increase in the HIIT group ($p < 0.01$). The ME at VO_2 peak and VT_2 only significantly increased in the HIIT group). Both training protocols improved quality of life with better results in HIIT. No adverse events were reported in either of the groups.

Conclusions:

The application of HIIT program in patients with coronary disease achieves greater improvements in VO_2 peak, in load associated with ventilatory thresholds, in post-exercise HHR index and in mechanical muscle efficiency compared to MCT. All of this without any increase in cardiovascular risk and greater improvement in quality of life tests.

Keywords:

Coronary heart disease; Continuous exercise training; Interval exercise training; heart rate recovery; Mechanical efficiency.

3. INTRODUCCION

3 INTRODUCCIÓN

3.1 Poder terapéutico del ejercicio físico en las enfermedades cardiovasculares.

Las enfermedades cardiovasculares (ECV) son la principal causa de mortalidad en los países desarrollados, siendo la cardiopatía isquémica la que ocasiona mayor número de fallecimientos (31%). Las ECV son la causa de, aproximadamente, un tercio de la mortalidad en personas mayores de 35 años, provocando en Europa 1,9 millones de muertes cada año (Sionis et al., 2015).

Según el estudio epidemiológico de Framingham, los factores de riesgo que pueden contribuir al desarrollo de las ECV son varios, incluyendo: el consumo de tabaco, la dislipemia, la hipertensión arterial, la diabetes, la obesidad, la inactividad física y la baja condición física (O'Donnell and Elosua, 2008).

De acuerdo a lo anterior, el sedentarismo y los bajos niveles de actividad física de la población en general, suponen un problema de salud pública que se reconoce como un factor independiente de riesgo cardiovascular, y que incrementa 1,9 veces (IC 95% 1,6-2,2) el riesgo de padecer una enfermedad coronaria (Cornelissen and Fagard, 2005). Esta inactividad física puede contribuir al inicio precoz y/o a la progresión de las ECV, particularmente en el caso de la cardiopatía isquémica (CI) (Berlin and Colditz, 1990). Por el contrario, este riesgo disminuye a medida que aumentan los niveles de actividad física realizada y/o el nivel de condición física (Myers et al., 2004).

En las últimas décadas, numerosas publicaciones han mostrado el poder terapéutico del ejercicio físico en las ECV, observando una relación inversa entre el ejercicio físico regular y el riesgo de enfermedad coronaria, eventos cardiacos y/o mortalidad (Paffenbarger et al., 1993). Un meta-análisis realizado por Nocon y colaboradores (Nocon et al., 2008), que incluyó 33 estudios con 883.372 participantes, mostró que los individuos con altos niveles de actividad física, presentaban una disminución del riesgo de muerte por ECV del 35% y una disminución del riesgo de muerte por cualquier causa del 33%, en comparación con los individuos con un bajo nivel de actividad física.

Los programas de rehabilitación cardíaca (PRCV), se convierten en una de las mejores estrategias para reducir la mortalidad y mejorar la calidad de vida en pacientes con ECV (Anderson et al., 2016). Dentro de estos programas, la prescripción

del ejercicio físico es un componente clave y decisivo, siendo reconocida como una intervención no farmacológica dentro de la prevención secundaria de las ECV. La Organización Mundial de la Salud (OMS) define a la rehabilitación cardiaca como "la suma de las actividades necesarias para asegurar a los pacientes cardiológicos unas condiciones físicas, mentales y sociales óptimas que les permitan ocupar, por sus propios medios, un lugar tan normal como les sea posible en la sociedad" (WHO 1964, n.d.). Por tanto, los PRCV deben ofrecer un enfoque multidisciplinario con un abordaje integral, incluyendo actuaciones físicas, psicológicas, dietéticas y educativas, todas ellas orientadas hacia un incremento de la capacidad física, la modificación de los factores de riesgo cardiovascular, la creación de hábitos cardiosaludables y la mejora en la calidad de vida de los pacientes con ECV.

Los efectos beneficiosos del ejercicio físico son múltiples y diversos. Diferentes estudios han puesto de manifiesto su efecto favorable sobre los factores de riesgo clásicos de la ECV (Boraita Pérez, 2008). Así, el ejercicio físico mejora el perfil lipídico, disminuye la tensión arterial, previene la aparición de diabetes no insulino-dependiente, facilita la supresión del tabaco, previene la depresión y reduce el sobrepeso y/u obesidad. También son conocidos sus efectos positivos sobre la hemostasia (Boraita Pérez, 2008), la función endotelial (Hambrecht et al., 2000), la contractilidad miocárdica, la función autonómica (Borresen and Lambert, 2008), la capacidad aeróbica (Myers et al., 2002) y la calidad de vida. Se ha comprobado que los sujetos sometidos a entrenamiento aeróbico experimentan una mejoría en los patrones de función diastólica y efectos positivos sobre la función sistólica (Ueshima et al., 2005; Yu et al., 2004). Todos estos efectos beneficiosos, constituyen una importante mejora en el factor pronóstico de los pacientes con ECV, considerándose el ejercicio como la piedra angular en la que deben basarse los PRCV.

Un meta-análisis realizado con 63 estudios, donde se evaluaron los efectos de la rehabilitación cardiaca en pacientes con enfermedad coronaria, concluyó que la rehabilitación cardiaca basada en el ejercicio físico, redujo la mortalidad cardiovascular y los ingresos hospitalarios, asociándose además a una mejoría en la calidad de vida (Anderson et al., 2016). En este sentido, las principales guías de actuación, tanto de la Sociedad Europea de Cardiología (ESC) (Piepoli et al., 2016), como de las Sociedades americanas, American College of Cardiology (ACC) y/o American Heart Association (AHA) (Smith et al., 2011), otorgan a los PRCV una indicación Clase IA tras un síndrome coronario agudo o tras un procedimiento de revascularización coronaria.

Uno de los efectos principales del ejercicio físico es la mejora de la capacidad aeróbica o funcional. La variable fisiológica que mejor representa la capacidad funcional es el consumo máximo de O_2 (VO_2 max.), y se define como la cantidad máxima de O_2 que el organismo es capaz de absorber, transportar y consumir por unidad de tiempo. El VO_2 se puede medir en valores absolutos ($L \cdot \text{min}^{-1}$), o ajustado al peso de cada sujeto ($\text{ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$). En reposo se consumen $3,5 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ de O_2 para cubrir las necesidades basales (equivalente a 1 MET o "Metabolic Equivalent Task"). A medida que se realizan actividades de mayor intensidad, el VO_2 del organismo aumenta, hasta alcanzar un punto en el que, a pesar de incrementar la intensidad, el organismo ya no es capaz de aumentar el VO_2 , llegando así al concepto de VO_2 max. Existe una gran variabilidad en los valores del VO_2 max. entre los diferentes sujetos dependiendo de factores como la herencia genética, edad, género, composición corporal, nivel de salud y/o nivel de entrenamiento físico (López Chicharro J and Fernández Vaquero A, 2006). Su determinación a través de una ergoespirometría, exige el cumplimiento de determinados criterios durante la realización del ejercicio incremental hasta el máximo esfuerzo (criterios de maximalidad). Los criterios utilizados para determinar que un test de esfuerzo cumple con los requisitos de maximalidad son: la aparición de una meseta en la cinética del VO_2 , alcanzar un Cociente Respiratorio $\geq 1,10$, superar una frecuencia cardíaca $\geq 85\%$ de la máxima teórica y superar unos niveles de lactato en sangre $\geq 8 \text{ mmol/L}$. Estos criterios difícilmente se alcanzan en pacientes con ECV, siendo más correcto utilizar el concepto de VO_2 pico, haciendo referencia al máximo valor de VO_2 que se ha alcanzado en una prueba de esfuerzo incremental hasta el agotamiento.

Son muchos los autores (Kavanagh et al., 2002; Kodama et al., 2009; Myers et al., 2002) que consideran el VO_2 pico como el mejor factor predictivo de supervivencia tanto en hombres como en mujeres con o sin ECV. De hecho, se ha demostrado que un bajo nivel de condición física constituye el factor de riesgo cardiovascular más importante, por encima de los factores de riesgo clásicos.

En el año 1999, Dorn y colaboradores (Dorn et al., 1999), tras un seguimiento durante 19 años a 651 pacientes de entre 30 y 64 años de edad diagnosticados de infarto de miocardio, objetivaron que un aumento de $3,5 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ se asociaba con una reducción del 8% al 14% en la mortalidad, independientemente de su capacidad funcional inicial. En el año 2002, Myers y colaboradores (Myers et al., 2002), realizaron un seguimiento durante $6,2 \pm 3,7$ años a 6.213 sujetos sometidos a una prueba de esfuerzo en tapiz rodante, encontraron que los METs alcanzados (en $\text{ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$), eran el mayor factor predictor de mortalidad tanto en sujetos sanos como en sujetos

con enfermedad coronaria. Documentaron que el riesgo de mortalidad era el doble en pacientes con capacidad de esfuerzo < 5 METs que en aquellos que lograban sobrepasar los 8 METs. También mostraron que un incremento de 3,5 ml·kg⁻¹·min⁻¹ (1 MET) en la capacidad de esfuerzo, se traducía en un incremento de la supervivencia de un 12%. De forma similar, Gullati y colaboradores (Gulati et al., 2003), confirmaron en su estudio con 5.721 mujeres asintomáticas, que por cada incremento de 3,5 ml·kg⁻¹·min⁻¹ en la capacidad de ejercicio, el riesgo de muerte se reducía un 17%.

El meta-análisis realizado por Kodama y colaboradores (Kodama et al., 2009), de 33 estudios con 84.323 individuos, concluyó que un aumento de 3,5 ml·kg⁻¹·min⁻¹ en el VO₂ se asociaba a una reducción del riesgo de mortalidad por cualquier causa de un 13%, y a una reducción de eventos cardiovasculares de un 15%.

3.2 Entrenamiento aeróbico continuo vs interválico.

Las guías de actuación no se encuentran muy estandarizadas respecto al ejercicio físico para grupos concretos de pacientes con ECV (cardiopatía isquémica, insuficiencia cardíaca, arteriopatía periférica etc.). No existen protocolos específicos y la prescripción del ejercicio sigue siendo una cuestión de juicio clínico basada en los objetivos, estado de salud, nivel de aptitud física, edad y/o preferencias del paciente.

Según el principio de sobrecarga, un programa de entrenamiento físico deberá representar un estímulo de intensidad suficiente (superior a la intensidad del estímulo que representan las actividades regulares de la vida diaria), para producir las adaptaciones cardiovasculares deseadas. Este principio, también llamado "principio del estímulo eficaz de carga", se fundamenta en la necesidad de utilizar cargas de entrenamiento que estén acordes con las características individuales del sujeto y su condición física (López Chicharro J and Fernández Vaquero A, 2006). Si el estímulo es de una intensidad que no sobrepasa dicho umbral, el esfuerzo realizado no provocará mejoras ni adaptaciones beneficiosas. Este principio, está relacionado con la cantidad o dosis de esfuerzo físico, y dependerá directamente de la intensidad, duración y frecuencia del esfuerzo realizado (Linda S Pescatello, 2014; López Chicharro J and Fernández Vaquero A, 2006).

En la mayoría de los estudios publicados sobre los beneficios del ejercicio físico aeróbico en la ECV, se utiliza un entrenamiento continuo de moderada intensidad

(ECMI). El ejercicio aeróbico continuo se caracteriza por movilizar grandes masas musculares de una manera prolongada en el tiempo (30 a 60 minutos) y sin realizar pausas durante el mismo. En el ECMI, generalmente se prescriben intensidades entre el 40-50% del VO_2 pico (intensidad leve-moderada) y el 50-75% del VO_2 pico (intensidad moderada-alta) (Fletcher et al., 2013). El objetivo principal de ECMI es realizar períodos de ejercicio largos en estado estacionario favoreciendo el metabolismo oxidativo.

Los resultados positivos del uso del ECMI en los PRCV han sido respaldados por distintos ensayos clínicos que han mostrado mejorías significativas en la capacidad funcional (o aeróbica), con aumentos del 12% y el 31% del VO_2 pico (Taylor et al., 2004). En este contexto, durante muchos años el ECMI ha sido aceptado como el estándar de oro de los entrenamientos en pacientes con CI.

Sin embargo, desde hace algún tiempo, el entrenamiento interválico de alta intensidad, ha despertado un gran interés en la rehabilitación cardiaca debido a sus excelentes resultados en cuanto a parámetros pronóstico de morbi-mortalidad en pacientes con ECV (enfermedad arterial coronaria, insuficiencia cardíaca congestiva, arteriopatía periférica y síndrome metabólico) (Ito et al., 2016).

El método de entrenamiento interválico de alta intensidad, más conocido como HIIT por sus siglas en inglés "High Intensity Interval Training", permite cargas de esfuerzo superiores a las utilizadas cuando se trabaja a un ritmo constante. Este tipo de entrenamiento interválico se caracteriza por la realización de cortos períodos de tiempo con una alta intensidad de carga, $> 85\%$ del VO_2 pico (intervalos pico), seguidos de intervalos de recuperación activos (menor intensidad de carga), o intervalos de recuperación pasivos (sin carga). La breve duración de los intervalos lleva al paciente a ejercitarse a un nivel aeróbico con muy poca utilización del sistema glucolítico productor del lactato (glucólisis anaeróbica). De esta manera, se evitará la progresiva instauración rápida de acidosis metabólica y se impedirá que una exagerada activación del sistema simpaticoadrenérgico acentúe el trabajo cardiovascular ya de por sí sobrecargado (Daniels and Scardina, 1984). Por tanto, los breves intervalos de recuperación permitirán que el paciente pueda mantener estas cargas elevadas de trabajo, de una forma prolongada en el tiempo y sin riesgo significativo de complicaciones cardiovasculares (Guiraud et al., 2010).

3.3 Aplicación de entrenamiento interválico de alta intensidad en pacientes con cardiopatía isquémica.

Los beneficios del HIIT en pacientes con CI se han investigado desde hace más de dos décadas (Meyer et al., 1990). Existe abundante evidencia científica en cuanto a mejoras en el VO_2 pico, en la contractilidad miocárdica (Wisløff et al., 2007), en la eficiencia ventilatoria (Rocco et al., 2012), en la función endotelial (Tjønnå et al., 2008; Wisløff et al., 2007), en la sensibilidad a la insulina (Tjønnå et al., 2008), en la biogénesis mitocondrial (Little et al., 2011; Tjønnå et al., 2008; Wisløff et al., 2007) y en la calidad de vida (Conrads et al., 2015; Moholdt et al., 2012a, 2012b) entre otros.

En el año 2012, estos resultados llevaron a las Sociedades Europea, Americana y Canadiense a realizar una declaración conjunta con indicaciones para la prescripción de entrenamiento interválico en pacientes con ECV (Mezzani et al., 2013). Otros grupos de trabajo, se han planteado incluso, si debería convertirse en un entrenamiento habitual en ciertas ECV (Arena et al., 2013).

Un meta-análisis realizado por Pattyn y colaboradores en el año 2014 (Pattyn et al., 2014), que incluyó 9 estudios con 206 pacientes diagnosticados de CI con fracción de eyección del ventrículo izquierdo (FEVI) preservada y/o reducida, mostró un mayor aumento en el VO_2 pico tras un programa HIIT. Pattyn y colaboradores, encontraron una diferencia media ponderada en el VO_2 pico de $1,60 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ (IC 95% 0,18 a 3,02; $p = 0,03$).

Elliot y colaboradores en el año 2015 (Elliott et al., 2015), y tras analizar 6 estudios independientes con 229 pacientes diagnosticados de CI con FEVI preservado, encontraron una diferencia media ponderada en el VO_2 pico, a favor del grupo HIIT de $1,53 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ (IC 95% 0,84-2,23; $p = 0,0001$).

Liou y colaboradores en el año 2016 (Liou et al., 2016), obtuvieron resultados similares en su meta-análisis de 10 estudios con 472 pacientes (218 HIIT vs 254 ECMI), registrando una diferencia media ponderada en el VO_2 pico a favor del grupo HIIT de $1,78 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ (IC 95%; 0,45-3,11, $p = 0,009$).

El meta-análisis realizado por Gomes-Neto y colaboradores en el año 2017 (Gomes-Neto et al., 2017), con 12 estudios y 609 pacientes diagnosticados de CI, mostró igualmente la superioridad del grupo HIIT en comparación con el ECMI. La diferencia media ponderada del VO_2 pico fue de $1,3 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ (IC 95%: 0,6-1,9) en comparación con el grupo ECMI.

Un meta-análisis recientemente publicado por Hannan y colaboradores en el año 2018 (Hannan et al., 2018), con 17 estudios y 953 sujetos diagnosticados de enfermedad coronaria, confirma los resultados de las revisiones sistemáticas previas en cuanto a la superioridad del HIIT con respecto al ECMI. Hannan y colaboradores, encontraron una diferencia media ponderada en el VO_2 pico a favor del grupo HIIT de $1,15 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ (IC 95%: 0,76 a 1,55; $p < 0,0001$). Otra de sus conclusiones fue que las mejoras se producían en programas de más de 6 semanas, con mejoras significativas en cuanto al VO_2 pico en programas de entre 7 y 12 semanas de duración. Las intervenciones de > 12 semanas no mostraron mayores ganancias en la aptitud física y los programas de ≤ 6 semanas no dieron lugar a cambios significativos.

3.4 Disfunción del sistema nervioso autónomo: Recuperación de la frecuencia cardíaca post-ejercicio como factor pronóstico.

El control del sistema nervioso autónomo (SNA), afecta a funciones globales del aparato circulatorio. Algunas de estas funciones son el bombeo cardíaco (modificando la frecuencia y la fuerza de las contracciones cardíacas), la redistribución del flujo sanguíneo (hacia los distintos tejidos según sea necesario en cada momento) y el control de la presión arterial entre otros.

Aunque el impulso cardíaco es miogénico, la frecuencia cardíaca (FC) se encuentra estrechamente controlada por el SNA, a través de sus terminaciones nerviosas simpáticas y parasimpáticas localizadas en el corazón. Los transmisores liberados por los nervios del SNA, afectan al automatismo alterando las corrientes iónicas a través de las membranas de las células marcapaso. Durante el ejercicio, la FC aumenta debido a la inhibición del sistema nervioso parasimpático y la estimulación del sistema nervioso simpático, tras finalizar el esfuerzo estos cambios producidos por el SNA se invierten ayudando a disminuir la FC (Thayer and Lane, 2007). Las hormonas liberadas por la médula suprarrenal (adrenalina y noradrenalina), aunque son más lentas, también juegan un papel importante en el control de la FC, constatándose un aumento de la concentración de catecolaminas varias horas después de finalizar un ejercicio sostenido y de alta intensidad (Borresen and Lambert, 2008).

Tras un evento coronario acontecen una serie de trastornos en el sistema neurovegetativo. Se produce una disminución del tono vagal (parasimpático) y un aumento de la actividad simpática dando lugar a cambios como el aumento de la FC

en reposo, la disminución de la variabilidad de la FC, la incompetencia cronotrópica y/o la disminución de la recuperación de la frecuencia cardíaca (RFC) tras el ejercicio. Estos marcadores de disfunción autonómica cardiovascular han sido considerados como factores pronóstico de morbi-mortalidad tanto en la población general (Cole et al., 1999) como en los pacientes con ECV (Grad and Zdrenghea, 2014; La Rovere et al., 1998). En este sentido, la disfunción del SNA puede proporcionarnos información valiosa para la estratificación de riesgo cardiovascular de las ECV (Chen et al., 2016).

También se ha postulado que la disfunción del SNA puede tener un papel importante en el desarrollo de la enfermedad coronaria. A pesar de las investigaciones realizadas hasta la fecha, la base fisiopatológica de la enfermedad no está totalmente clarificada, habiéndose postulado, entre otros planteamientos patogénicos, una disfunción crónica del sistema nervioso autónomo (Thayer and Lane, 2007). Diferentes investigaciones han relacionado esta disfunción autonómica con el desarrollo de factores de riesgo cardiovascular tales como la hipertensión arterial, dislipemias y la diabetes mellitus (Grad and Zdrenghea, 2014). Así, Huang y colaboradores, establecieron una relación entre la RFC y la función endotelial, concluyendo que una RFC enlentecida predecía una disfunción endotelial, eventos cardiovasculares, así como un aumento de la mortalidad (Huang et al., 2004).

El análisis de la RFC es un método no invasivo y reproducible, que permite realizar una evaluación cuantitativa de la regulación autonómica cardíaca. La RFC después de un esfuerzo incremental presenta un patrón bifásico, con una caída rápida inicial a la que le sigue una caída lenta posterior. La fase rápida se refiere al primer minuto de recuperación (minuto 1) y se caracteriza por una disminución abrupta y rápida de la frecuencia cardíaca (Imai et al., 1994). La fase lenta, se refiere al período posterior a la fase rápida (minuto 2) (Peçanha et al., 2014). La recuperación de la frecuencia cardíaca en el primer minuto (RFC-1) después del ejercicio corresponde a la reactivación vagal (activación parasimpática), especialmente en los primeros 30 segundos, mientras que la recuperación posterior (minuto 2) se atribuye a una caída en la actividad simpática (Imai et al., 1994; Peçanha et al., 2014).

Hasta la fecha, no existe consenso sobre el momento y el método más apropiado para obtener los valores de RFC. La medición de la RFC-1 tras un ejercicio extenuante es el método más común empleado en nuestro entorno, considerándose clínicamente anormal una RFC-1 ≤ 12 lpm (Cole et al., 2000, 1999). Otras investigaciones, han mostrado un aumento de riesgo de morbi-mortalidad con una RFC-1 < 25 lpm (Jouven et al., 2005).

El grupo de Cole y colaboradores (Cole et al., 1999), realizaron un seguimiento durante 6 años a 2.428 pacientes que habían sido sometidos a una prueba de esfuerzo limitada por síntomas en cinta rodante (63% hombres con una edad media de 57 ± 12 años). El estudio logró mostrar que una RFC-1 ≤ 12 lpm es un fuerte predictor de mortalidad por cualquier causa, independientemente de la carga de trabajo alcanzada y la presencia o ausencia de defectos de perfusión en las pruebas de imagen. Documentaron que el riesgo de mortalidad por cualquier causa era el doble en pacientes con una RFC-1 ≤ 12 lpm.

Por otro lado, la medición de la RFC en pacientes coronarios durante el segundo minuto (RFC-2) de una recuperación pasiva en posición sentada y tras un ejercicio extenuante, también ha mostrado ser un predictor independiente de mortalidad cardiovascular y/o de mortalidad por cualquier causa. Valores inferiores a 22 lpm tras dos minutos de haber finalizado la prueba de esfuerzo, se han considerado clínicamente anormales. En el año 2001, Shetler y colaboradores (Shetler et al., 2001), publicaron un estudio acerca de la RFC en 2.193 pacientes con dolor torácico que habían sido sometidos a una ergometría, sugirieron que una RFC-2 post-esfuerzo $<$ de 22 lpm tiene una capacidad pronóstica de mortalidad mayor que la RFC-1. En este sentido, se han llevado a cabo estudios en sujetos sanos que también han confirmado el valor pronóstico de mortalidad para valores anormales de la RFC-2 post-esfuerzo (Cole et al., 2000).

Otros autores como Gayda y colaboradores (Gayda et al., 2012), llegaron a estudiar el valor pronóstico de la RFC en el minuto tres post-esfuerzo. Tras analizar a 4.097 pacientes con CI estable, concluyeron que valores inferiores a 46 lpm tras tres minutos post-esfuerzo pueden ayudar a identificar de manera independiente a pacientes con un mayor riesgo cardiovascular.

La realización de ejercicio físico en los PRCV ha demostrado mejoras en el equilibrio neurovegetativo con una mayor capacidad de recuperar la frecuencia cardiaca post-esfuerzo (Tsai et al., 2006), tanto en pacientes con FEVI normal como en aquellos con disfunción ventricular izquierda e insuficiencia cardiaca, donde este equilibrio es más precario (Coats et al., 1992). En este sentido, la RFC es un buen indicador de la efectividad de los PRCV, ya que puede servirnos como índice de calidad tras completar un programa de rehabilitación cardiaca (MacMillan et al., 2006).

Los estudios publicados sobre los beneficios del ejercicio físico con respecto a la RFC, utilizan ejercicios continuos de intensidad moderada (ECMI) mostrando mejoras en la RFC después de 8 (Hai et al., 2010) y 12 semanas de entrenamiento (Tsai et al.,

2005; Wu et al., 2006). En este sentido, Hai y colaboradores (Hai et al., 2010), realizaron un seguimiento prospectivo a 386 pacientes tras un infarto de miocardio. Todos fueron sometidos a una prueba de esfuerzo en cinta rodante limitada por síntomas al inicio y tras 8 semanas de entrenamiento físico. Tras un seguimiento prospectivo de 79 ± 41 meses, un 10,4% de los pacientes fallecieron por eventos cardíacos (n=40). El análisis de regresión multivariante de Cox reveló que una FEVI $\leq 30\%$, una FC de reposo inicial ≥ 65 lpm, una capacidad aeróbica ≤ 4 METs y una RFC-1 post-esfuerzo ≤ 12 lpm fueron predictores independientes de muerte cardíaca. Los pacientes que no lograron aumentar la RFC-1 por encima de 12 lpm tuvieron una mortalidad significativamente más alta (cociente de riesgos instantáneos 6,2, IC del 95%: 1,3-29,2, $p = 0,022$).

Los estudios que valoran las modificaciones de la RFC comparando los programas de ECMI con programas HIIT son muy limitados (Currie et al., 2013; Dimopoulos et al., 2006; Keteyian et al., 2014; Kim et al., 2015; Madssen et al., 2014; Moholdt et al., 2012b) y con resultados estadísticos muy heterogéneos. En el estudio de Dimopoulos (Dimopoulos et al., 2006) con una muestra aleatorizada de 29 pacientes, tan solo los que realizaron un ECMI tuvieron un aumento significativo en la RFC-1 ($15,0 \pm 9,0$ a $24,0 \pm 12$ lpm; $P = 0,02$), sin apreciar cambios en el grupo HIIT. Sin embargo, otras investigaciones (Kim et al., 2015; Moholdt et al., 2012b) han documentado un incremento significativo de la RFC-1 en ambos grupos de entrenamiento pero sin diferencias significativas entre grupos. Por último, otros estudios no apreciaron cambios de la RFC-1 en ninguna de las modalidades a pesar de que todos aumentaron de forma significativa la capacidad aeróbica y en mayor medida con el entrenamiento HIIT (Currie et al., 2013; Keteyian et al., 2014; Madssen et al., 2014).

3.5 Eficiencia mecánica en la enfermedad cardiovascular.

La eficiencia mecánica (EM) se refiere a la capacidad que tiene un individuo para transferir la energía que se consume en un trabajo externo (Layec et al., 2011). La mayoría de las investigaciones que estudian la eficacia del ejercicio físico en los PRCV, generalmente evalúan variables pronósticas asociadas a la morbi-mortalidad, como las descritas previamente (VO_2 pico y RFC). Pero existen muy pocas investigaciones que evalúen la EM, a pesar de que proporciona información muy valiosa sobre las adaptaciones biomecánicas y el uso de las diferentes fuentes de

energía durante el ejercicio físico y, por tanto, proporciona información de manera indirecta sobre la capacidad funcional de los pacientes.

Una EM disminuida, indica que se consume más energía durante una determinada carga de trabajo. Esta disminución de la EM podría ser debida a: 1) un mayor costo energético de la respiración durante el ejercicio; 2) una eficiencia alterada en la producción de ATP (relación de O₂ consumido con respecto al ATP producido) o 3) un mayor costo de ATP por contracción (relación de ATP consumido con respecto al trabajo externo) (Layec et al., 2011).

El ejercicio físico a intensidad moderada-vigorosa consigue mejorar de forma significativa el rendimiento muscular en sujetos no entrenados, previniendo la disminución de la EM. Además se ha observado que a mayor intensidad de ejercicio físico, mayor es el rendimiento muscular en el entrenamiento (Jabbour and Iancu, 2015). Estos cambios son probablemente el resultado de las adaptaciones del músculo esquelético relacionadas con la mejora metabólica, asociado con una mayor sensibilidad a la insulina (Nevill et al., 1996) y a mejoras en la fuerza muscular (Maffiuletti et al., 2013). Dado que el entorno metabólico y la función muscular pueden condicionar el rendimiento muscular y el perfil de energía muscular de un individuo, es posible que cualquier mejora en estos parámetros pueda predecir un aumento posterior en la EM (Jabbour and Iancu, 2015). Por lo tanto, la EM también puede ser un importante predictor de eficacia y proporcionar datos relevantes sobre el rendimiento y/o las adaptaciones del uso de energía en respuesta al entrenamiento terapéutico (Jabbour et al., 2017; Jabbour and Iancu, 2015).

Las investigaciones realizadas con respecto a la EM han sido fundamentalmente estudiadas en sujetos sin ECV y utilizando tanto entrenamientos continuos de moderada intensidad como entrenamientos interválicos de alta intensidad (Jabbour et al., 2017; Jabbour and Iancu, 2015). En nuestro conocimiento, no hay estudios que evalúen los cambios de la EM en respuesta a HIIT en pacientes con CI.

3.6 Seguridad de los entrenamientos interválicos de alta intensidad.

Aunque el ejercicio físico es útil para reducir el riesgo de ECV, su práctica también comporta un cierto riesgo cardiovascular. Las complicaciones más relevantes son la muerte súbita y el infarto agudo de miocardio. Estos eventos cardíacos agudos asociados con el ejercicio generalmente ocurren en individuos con enfermedad cardíaca estructural y/o en individuos habitualmente menos activos físicamente. Por

tanto, mantener una buena forma física a través de la actividad física regular puede ayudar a reducir los eventos (Thompson et al., 2007).

La incidencia de complicaciones cardiovasculares en la ECV relacionadas con el ejercicio durante el PRCV es baja. Se estima 1 paro cardíaco por 116.906 horas de ejercicio/paciente, 1 infarto de miocardio por 219.970 horas de ejercicio/paciente y 1 muerte súbita por cada 752.365 horas de ejercicio/paciente (Franklin et al., 1998; Vongvanich et al., 1996) (Franklin et al., 1998).

La seguridad de las sesiones interválicas de alta intensidad se ha valorado en la mayoría de los meta-análisis de los últimos 4 años, y la evidencia muestra que tanto las sesiones de alta intensidad como el entrenamiento de modera intensidad, son seguras y representan un bajo riesgo en la aparición de eventos cardiovasculares (Gomes-Neto et al., 2017; Hannan et al., 2018; Liou et al., 2016; Pattyn et al., 2014).

Destacar el estudio controlado y aleatorizado diseñado por Rognmo y colaboradores (Rognmo et al., 2012), con 4.846 pacientes con enfermedades coronarias, donde evaluaron el riesgo de eventos cardiovasculares durante la práctica de ejercicio de alta y moderada intensidad. Todos los pacientes realizaron ambos tipos de entrenamiento (HIIT y ECMI) y se analizaron 129.456 horas de ECMI y 46.364 horas de HIIT. Las incidencias durante las sesiones fueron de un paro cardíaco y muerte del paciente en una sesión de ECMI y dos paros cardíacos sin muerte en sesiones de HIIT. Los resultados indicaron que las tasas de eventos cardiovasculares durante el ECMI fueron de 1 por 129.456 horas y de 1 por 23.182 horas en el HIIT. Sus conclusiones fueron, que ambos tipos de ejercicio representaban un bajo riesgo de aparición de efectos adversos cardiovasculares durante las sesiones.

3.7 Calidad de vida tras los entrenamientos.

La calidad de vida relacionada con la salud (CVRS), hace referencia a la percepción sobre el estado de salud y su impacto en el funcionamiento físico, mental y social (Soto and Failde, 2004). Varios estudios han señalado que la CVRS en personas con cardiopatía isquémica es baja al ser comparadas con controles o con datos normativos mediante estudios transversales (Borowiak and Kostka, 2006). En este sentido, las personas con ECV suelen experimentar, no solo una reducción marcada en su capacidad física, sino que tiene efectos perjudiciales en sus actividades de la vida diaria y CVRS.

Todas las guías clínicas recomiendan incluir la evaluación de la calidad de vida relacionada con la salud (CVRS) de los pacientes con ECV, al ser ésta un factor predictivo independiente de morbi-mortalidad en personas con cardiopatía isquémica (Schenkeveld et al., 2010; Spertus et al., 2002). Por tanto, la valoración de la CVRS en las ECV se convierte en un marcador a tener en cuenta tanto para identificar a los enfermos con un elevado riesgo de resultados adversos, como para ser un indicador de la efectividad de nuestras actuaciones (Oldridge et al., 1991).

Uno de los objetivos prioritarios de los PRCV es mejorar la calidad de vida de los pacientes junto a la prevención secundaria de la enfermedad, y es por ello por lo que los PRCV incluyen pautas de actuación física, psicológica y de control de factores de riesgo. En este sentido, los PRCV han mostrado mejoras en las escalas de calidad de vida tras la participación en los mismos, independientemente del grupo de entrenamiento (ECMI vs HIIT) (Conraads et al., 2015; Gomes-Neto et al., 2017; Moholdt et al., 2012a).

4. JUSTIFICACION Y OBJETIVOS

4 JUSTIFICACIÓN Y OBJETIVOS DE LA INVESTIGACIÓN

4.1 Justificación de la investigación.

Existe suficiente evidencia científica que demuestra que el ejercicio físico consigue mejorar la capacidad funcional y la morbi-mortalidad de los pacientes con patología cardiovascular. Sin embargo, el tipo de ejercicio físico y la intensidad del mismo, con el que se obtienen mayores beneficios, es un tema controvertido.

Revisiones y meta-análisis recientes muestran que con la prescripción de HIIT (Entrenamiento Interválico de Alta Intensidad), se obtienen mejores resultados en determinados parámetros pronóstico de morbi-mortalidad (capacidad aeróbica, remodelación cardíaca, función endotelial, calidad de vida, etc.), y todo ello sin riesgo cardiovascular añadido.

4.2 Objetivos.

4.2.1 Objetivos principales:

1. Comparar el efecto de dos modalidades de entrenamiento aeróbico (ECMI vs HIIT) sobre la capacidad funcional (medida en $\text{ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$) en pacientes con cardiopatía isquémica.
2. Comparar los efectos de dos modalidades de entrenamiento aeróbico (ECMI vs HIIT) sobre la recuperación de la frecuencia cardíaca del primer y segundo minuto tras una prueba de esfuerzo hasta el agotamiento en pacientes con cardiopatía isquémica.
3. Comparar la influencia de dos modalidades de entrenamiento aeróbico (ECMI vs HIIT) en los valores de eficiencia mecánica en pacientes con cardiopatía isquémica.

4.2.2 Objetivos Secundarios:

1. Verificar la seguridad a la hora de aplicar entrenamiento físico de alta intensidad en pacientes con cardiopatía isquémica.
2. Conocer el impacto de ambos entrenamientos (ECMI vs HIIT) en la calidad de vida relacionada con la salud en pacientes con cardiopatía isquémica.

5. ARTICULOS

5 ARTÍCULOS PUBLICADOS

ARTÍCULO 1

Effect of High-Intensity Interval versus continuous exercise training on functional capacity and quality of life in patients with coronary artery disease: A randomised clinical trial. J Cardiopulm Rehabil Prev 2016;36(2):96-105.

<https://doi.org/10.1097/HCR.000000000000156>

ARTÍCULO 2

Effects of high-intensity interval versus continuous exercise training on post-exercise heart rate recovery in coronary heart-disease patients. Int J Cardiol. 2017;244:17-23.

<https://doi.org/10.1016/j.ijcard.2017.06.067>

ARTÍCULO 3

Mechanical efficiency of high versus moderate-intensity aerobic exercise in coronary heart disease patients: a randomized clinical trial. Cardiol J. 2019;26(2):130-137

<https://doi.org/10.5603/CJ.a2018.0052>

ARTICULO 1

Effect of Hight-Intensity Interval versus continuous exercise training on functional capacity and quality of life in patients with coronary artery disease: A randomised clinical trial. J Cardiopulm Rehabil Prev 2016;36(2):96-105. <https://doi.org/10.1097/HCR.000000000000156>

Effect of High-Intensity Interval Versus Continuous Exercise Training on Functional Capacity and Quality of Life in Patients With Coronary Artery Disease

A RANDOMIZED CLINICAL TRIAL

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■ **PURPOSE:** There is strong evidence that exercise training has beneficial health effects in patients with cardiovascular disease. Most studies have focused on moderate continuous training (MCT); however, a body of evidence has begun to emerge demonstrating that high-intensity interval training (HIIT) has significantly better results in terms of morbidity and mortality. The aim of this study was to compare the effects of MCT versus HIIT on functional capacity and quality of life and to assess safety.

■ **METHODS:** Seventy-two patients with ischemic heart disease were assigned to either HIIT or MCT for 8 weeks. We analyzed cardiopulmonary exercise test data, quality of life, and adverse events.

■ **RESULTS:** High-intensity interval training resulted in a significantly greater increase in $\dot{V}O_{2peak}$ (4.5 ± 4.7 mL·kg⁻¹·min⁻¹) compared with MCT (2.5 ± 3.6 mL·kg⁻¹·min⁻¹) ($P < .05$). The aerobic threshold (V_{T1}) increased by 21% in HIIT and 14% in MCT. Furthermore, there was a significant ($P < .05$) increase in the distance covered in the 6-minute walk distance test in the HIIT group (49.6 ± 6.3 m) when compared with the MCT group (29.6 ± 12.0 m). Both training protocols improved quality of life. No adverse events were reported in either of the groups.

■ **CONCLUSIONS:** On the basis of the results of this study, HIIT should be considered for use in cardiac rehabilitation as it resulted in a greater increase in functional capacity compared with MCT. We also observed greater improvement in quality of life without any increase in cardiovascular risk.

KEY WORDS

coronary artery disease

functional capacity

high-intensity interval training

quality of life

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In Europe, cardiovascular diseases cause 1.8 million deaths per year.¹ Exercise has a class I recommendation² for the management of these patients and results in a 15% to 31% reduction in mortality because of cardiac causes.³

Physical exercise increases functional capacity such as peak oxygen uptake ($\dot{V}O_{2\text{peak}}$), which is considered to be the best predictor of survival in cardiovascular disease.^{4,5} In their meta-analysis of 33 studies involving 84 323 individuals, Kodama et al⁶ concluded that a 3.5 mL·kg⁻¹·min⁻¹ increase in $\dot{V}O_{2\text{peak}}$ (1 metabolic equivalent or MET) is associated with a 13% reduction in the risk of all-cause mortality and a 15% reduction in cardiovascular events. Similarly, Gullati et al⁷ confirmed in their study with 5721 asymptomatic women that, for every increase in exercise capacity of 1 MET, the risk of death was reduced by 17%. In addition, patients with myocardial infarction who were followed up for 19 years, an increase of 1 MET was associated with an 8% to 14% reduction in mortality.⁸

The majority of studies published on the benefits of exercise in cardiovascular disease use moderate continuous training (MCT) at 60% to 80% of $\dot{V}O_{2\text{peak}}$. These studies have shown a significant improvement in functional capacity between 12% and 31% of $\dot{V}O_{2\text{peak}}$.⁹

Over the past decade, high-intensity interval training (HIIT) has raised great interest in the context of cardiac rehabilitation because of excellent results with regard to morbidity and mortality outcomes.^{10,11} High-intensity interval training consists of a repeating series of high-intensity (peak interval) exercises, alternating with periods of low-intensity exercise (recovery interval). These brief recovery intervals require the patient to perform aerobic exercise without requiring energy production by the lactate-producing glycolytic system for energy. This avoids prolonged acidosis and prevents the sympathoadrenergic system from increasing cardiovascular effort, as the heart is already overworked.¹² Therefore, patients can comfortably maintain these high-intensity workloads, for a prolonged period and without any significant risk of cardiovascular complications.^{12,13} Recent reviews and meta-analyses have shown that using HIIT results in improved outcomes for certain prognostic variables related to morbidity and mortality, such as aerobic capacity, left ventricular function, endothelial function, and quality of life, without any additional cardiovascular risk.^{10,11}

The principal objective of this study was to compare the effect of 2 exercise training protocols (MCT vs HIIT) on functional capacity and quality-of-life variables. Our hypothesis was that HIIT would increase $\dot{V}O_{2\text{peak}}$ more than MCT in stable patients with

coronary artery disease. Secondary outcomes were to determine the impact of the type of exercise on quality of life and to verify the safety of following these 2 exercise programs.

METHODS

Participants

A prospective, randomized clinical trial (NCT02168712) was conducted with patients referred by the Cardiac Rehabilitation Department who were diagnosed with stable New York Heart Association functional class I or II coronary artery disease with angina pectoris or myocardial infarction and no heart failure. To be included in the study, patients had to achieve a respiratory exchange ratio ≥ 1.10 during the initial cardiopulmonary exercise test (CPET). This respiratory exchange ratio value is often used as a criterion for achieving a maximum exercise effort.¹⁴ Patients who had residual ischemia (by electrocardiogram [ECG] criteria or angina symptoms), severe ventricular arrhythmias, uncontrolled hypertension, permanent pacemakers, or implanted cardiac defibrillators were excluded.

After signing an informed consent form, patients were randomized on a one-to-one basis to either the MCT or the HIIT group. The mode of exercise training was a cycle ergometer with 40 minutes per sessions, 3 days per week (total of 24 sessions over 2 months).

Patients entered the study within 6 weeks from the revascularization procedure. Clinical variables including the 6-minute walk test (6MWT) distance, selected CPET variables, and variables related to quality of life were recorded before and after the exercise training. Cardiopulmonary exercise tests were administered by staff blinded as to which exercise training group the patients were assigned.

CPET

All patients underwent exercise testing with a cycle ergometer (Ergoline900S, Ergoline GmbH, Bitz, Germany) including analysis of exhaled gases (UltimaCardiO₂, Medical Graphics Corporation, St Paul, Minnesota). The exercise test protocol was tailored to each patient's physical condition, with gradual increments of 10, 15, or 20 W/min. The same protocol was applied before and after the exercise training program. The objective of the exercise tests was to achieve a sustained effort for 8 to 12 minutes, with the aim of proper oxygen uptake ($\dot{V}O_2$) kinetics and maintaining a linear relationship between $\dot{V}O_2$, exercise workload and heart rate (HR).

A 12-lead ECG was continuously monitored, and blood pressure was measured every 3 minutes during the exercise tests. Exercise workloads in watts and metabolic, cardiac, ventilatory, and electrocardiographic parameters were analyzed. The ECG was continuously monitored during the first 5 minutes of recovery. Recorded HR was determined from the computerized test reports and was the average of the last 5 RR intervals.

The first (V_{T1}) and second (V_{T2}) ventilatory thresholds were considered to be indicators of the aerobic and anaerobic thresholds, respectively, and were determined after the ventilatory equivalent method described by Skinner et al.¹⁴ The $\dot{V}O_2$ in $\text{mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ and HR in $\text{beats}\cdot\text{min}^{-1}$ at V_{T1} were the parameters used to determine the MCT exercise intensity.

6MWT

We performed 2 consecutive 6MWT using a standardized protocol¹⁵ with the better of the 2 results being recorded. This process was used before and after the exercise training programs.

Steep Ramp Test

To design the HIIT program, we used the steep ramp test (SRT) protocol, according to the methodology described by Meyer et al.¹⁶ This exercise test protocol is composed of 2 minutes of free pedaling at 25 W followed by progressive 25-W increments every 10 seconds, maintaining a constant pedal cadence of between 50 and 60 rpm. The test was stopped when the patient could not maintain continuous pedal cadence of >40 rpm after encouragement to increase to 50 rpm and/or experienced hemodynamic and/or electrical alterations. The maximum exercise load achieved, as measured in watts, was the exercise parameter that was used to design the HIIT program for each patient.

MCT and HIIT Program Designs

The metabolic parameters obtained during the pre-training CPET were used to design the MCT program. Patients were asked to keep their training HR below the HR at V_{T1} during the first month. During the second month, the intensity of the exercise was adjusted, increasing to a training HR that corresponded to V_{T1} plus 10%.

The HIIT protocol used the methodology initially described by Meyer et al.¹⁶ and which was recently published by our group.¹⁷ In this type of exercise, the intensity was established using workload (watts), without taking HR into consideration as a measure for regulating the intensity of the exercise. The training workloads depended on the maximum workload achieved during the SRT. The intervals were designed as follows. In the first month of training, 20-second repetitions at an intensity corresponding to 50% of the maximum load reached with the SRT (peak intervals) were followed by 40-second recovery periods at 10%. In the second month of training, the intensity of exercise was adjusted using the results of a new SRT (Figure 1).

The total duration of both types of training was 40 minutes per session throughout the exercise program (including warm-up and cool-down). Table 1 summarizes the exercise time and intensity progression for both MCT and HIIT. Patients rated the peak level of exertion during each training session using the Borg Rating of Perceived Exertion Scale.¹⁸

Both types of exercise were reviewed and approved by the local Research Ethics Committee. Patients enrolled in the study participated in other activities established in our cardiac rehabilitation program that were aimed at managing psychological stress and learning about cardiac health habits. They were also taught to devise a home walking program for the days on which they did not have to attend sessions in the

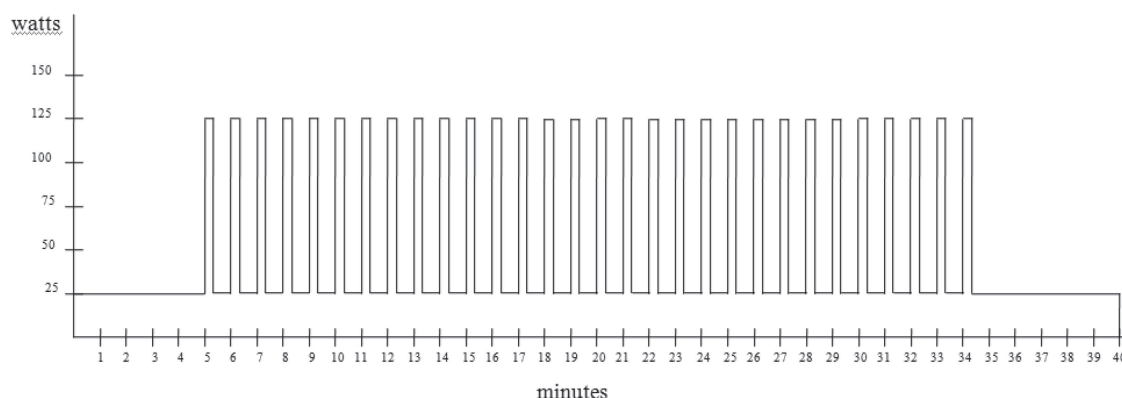


Figure 1. Interval training: 20-second repetitions at an intensity corresponding to 50% of the maximum workload reached with the steep ramp test, followed by 40-second intervals at 10%.

Table 1 • Program Designs for MCT and HIIT Groups

Week	Warm-Up Time and Intensity (MCT and HIIT)	Exercise Time and Intensity (MCT/HIIT)	Cool-Down Time and Intensity (MCT and HIIT)
1	12 min (25 W)	MCT: 15 min at V_{T_1} HIIT: 15 repetitions ^a	13 min (25 W)
2	10 min (25 W)	MCT: 20 min at V_{T_1} HIIT: 20 repetitions ^a	10 min (25 W)
3	7 min (25 W)	MCT: 25 min at V_{T_1} HIIT: 25 repetitions ^a	8 min (25 W)
4	5 min (25 W)	MCT: 30 min at V_{T_1} HIIT: 30 repetitions ^a	5 min (25 W)
5-8	5 min (25 W)	MCT: 30 min at ($V_{T_1} + 10\%$) HIIT: 30 repetitions ^b	5 min (25 W)

Abbreviations: HIIT, high-intensity interval training; MCT, moderate continuous training; SRT, steep ramp test.
^aIntervals of 50% (20 seconds) to 10% (40 seconds) of the maximum load reached in the first SRT.
^bIntervals of 50% (20 seconds) to 10% (40 seconds) of the maximum load reached in the second SRT.

hospital. The recommended intensity of walking was a perceived exertion of 11 to 13 on the Borg scale.

Safety of the Exercise Training Programs

To verify the safety of using this kind of aerobic exercise training, we made a daily record of any incidents or adverse effects that could limit the planned exercise. An incident was considered low if there were no repercussions and it was possible to start and/or restart training (eg, muscle overload, fatigue, muscular pain, and dyspnea without oxygen desaturation). A moderate incident was defined as one that limited the planned training (dyspnea with desaturation <94%, muscle injury, vasovagal conditions), and an incident was defined as severe if it was potentially life-threatening (ischemia, ventricular arrhythmia, hypertensive emergencies).

Quality of Life Questionnaires

A general quality of life (QOL) questionnaire (36-Item Short Form Health Survey [SF-36]) was given to the patients before and after the exercise training program. A disease-specific health-related QOL questionnaire, MacNew Heart Disease Health-related Quality of Life, was also administered before and after the exercise program.¹⁹

Statistical Analysis

Quantitative variables were described using means and standard deviations, and the qualitative variables were reported using frequency distributions. To evaluate the effect of each exercise protocol on the quantitative variables, pre- and postprogram values

were compared using Student's dependent samples *t* test. The effect was measured in absolute terms via the difference between the postprogram values and those obtained before training. These changes were described with the mean and standard deviation. Comparisons between the 2 training programs were made using Student's *t* test in the case of quantitative variables and using the χ^2 test of association or Fisher exact test for qualitative variables. All the comparisons were made using 2-tailed tests, and the level of significance was set at $P < .05$. The statistical analyses were done using R-3.0.1 for Windows (Microsoft Corporation, Redmond, Washington).

RESULTS

A total of 72 patients were included and studied (36 patients per group). At the start of the study, there were no significant differences between the groups with regard to clinical characteristics and medication use (Table 2).

Training Data

The intensity of exercise in the MCT group in the first month was $64.2\% \pm 8.5\%$ of the $\dot{V}O_{2peak}$ reached during the initial CPET (corresponding to the V_{T_1}) and $69.5\% \pm 8.7\%$ in the second month (corresponding to $V_{T_1} + 10\%$). The exercise workload applied at the peak intervals in the HIIT group using the Meyer et al methodology¹⁶ was $104.5\% \pm 22.2\%$ (first month) and $134.5\% \pm 29.7\%$ (second month) of the maximum load reached in the initial CPET corresponding to 50%

Table 2 • Patient Characteristics and Medication Use^a

	MCT (n = 36)	HIIT (n = 36)	P Value
Age, y	58 ± 11	58 ± 11	.82
Men	92	78	.21
Body mass index, kg/m ²	29.5 ± 4.1	29.6 ± 4.4	1.00
Waist circumference, cm	104 ± 9	104 ± 11	1.00
Hip circumference, cm	105 ± 8	104 ± 9	.88
Waist-to-hip ratio	0.99 ± 0.05	1.00 ± 0.07	.90
Cardiovascular risk factors			
Family history	47	46	1.00
Hypertension	57	65	.67
Diabetes mellitus	31	27	.88
Dyslipidemia	66	43	.09
History of smoking	81	73	.74
Active smoker	10	14	.64
Medical history			
Angina pectoris	50	43	.36
Myocardial infarction	50	57	.45
LVEF, %	59 ± 14	62 ± 11	.29
PCI	73	59	.35
CABG	15	22	.53
Conservative medical management	12	19	.44
Time from procedure to start of exercise program, d	54 ± 6	50 ± 4	.35
Medications			
β-Blockers	89	86	1.00
Calcium channel blockers	14	27	.27
ACE inhibitors	71	54	.20
Angiotensin receptor antagonists	20	19	1.00
Nitrates	11	11	1.00
Antiplatelet agents	97	97	1.00
Statins	94	100	.23
Antidiabetics	22	22	1.00

Abbreviations: ACE, angiotensin-converting enzyme; CABG, coronary artery bypass graft; HIIT, high-intensity interval training; LVEF, left ventricular ejection fraction; MCT, moderate continuous training; PCI, percutaneous coronary intervention.

^aContinuous data were reported as mean ± standard deviation; categorical data were reported as percentage.

of the SRT in both months. The resulting HR during the first and second months in the HIIT group was between V_{T1} and V_{T2} .

No significant differences were observed in perception of exercise between the HIIT and MCT groups during the first (Rating of Perceived Exertion, 11-13) and second (Rating of Perceived Exertion, 14-16) months of training. Adherence to the treatment sessions (the number of sessions attended compared with

the number of sessions scheduled) was 87.5% in the MCT group and 92% in the HIIT group. There was no significant difference between groups for adherence.

CPET and 6MWT

Results of testing for both groups before and after exercise training are summarized in Table 3. After 8 weeks of exercise training, both exercise programs significantly increased $\dot{V}O_{2peak}$, with a greater increase

Table 3 • CPET Variables and 6MWT Distance in Both Study Groups

	MCT Group			HIIT Group		
	Pretraining	Posttraining	Change	Pretraining	Posttraining	Change
CPET results						
Total exercise time, min	9.00 ± 2.02	10.1 ± 2.59	1.1 ± 1.8 ^c	7.80 ± 1.75	9.55 ± 2.26	1.7 ± 1.9 ^c
$\dot{V}O_2$ peak, mL·kg ⁻¹ ·min ⁻¹	20.3 ± 5.0	22.8 ± 6.5	2.5 ± 3.6 ^c	19.4 ± 4.7	24.0 ± 4.8	4.5 ± 4.7 ^{c,d}
$\dot{V}O_2$, % predicted	80 ± 17	89 ± 20	9.0 ± 13.2 ^c	80 ± 21	96 ± 19	16.5 ± 17.8 ^{c,d}
Resting HR, beats·min ⁻¹	61 ± 9	59 ± 8	-1.6 ± 8.2	66 ± 14	64 ± 10	-2.2 ± 10.0
Resting SBP, mm Hg	122 ± 18	116 ± 15	-5.6 ± 18.3	126 ± 15	123 ± 15	-3.1 ± 17.7
Resting DBP, mm Hg	74 ± 10	73 ± 9	-0.4 ± 11.3	76 ± 10	74 ± 8	-1.8 ± 11.0
Resting DP	7 368 ± 1 746	6 783 ± 1 388	-585 ± 1 614 ^a	8 333 ± 1 945	7 794 ± 1 421	-539 ± 1 727
Maximum HR, beats·min ⁻¹	118 ± 20	119 ± 21	1.0 ± 11.6	115 ± 14	126 ± 14	10.6 ± 11.7 ^{c,e}
Maximum SBP, mm Hg	171 ± 23	165 ± 26	-6.1 ± 22	171 ± 21	178 ± 23	7.2 ± 23.9 ^d
Maximum DBP, mm Hg	92 ± 12	89 ± 8	-3.0 ± 12.4	90 ± 11	92 ± 11	1.6 ± 10.9
Maximum DP	20 205 ± 4 880	20 098 ± 5 044	-107 ± 4 111	19 973 ± 4 099	22 312 ± 4 572	2 339 ± 4 386 ^{b,d}
Maximum HR, %	73 ± 14	73 ± 11	-0.2 ± 10.0	72 ± 10	77 ± 8	5.5 ± 8.7 ^{c,d}
Recovery HR at 1 min, beat·min ⁻¹	20 ± 9	21 ± 8	1.3 ± 8.0	15 ± 7	21 ± 7	5.8 ± 8.1 ^{c,d}
Maximum RER	1.12 ± 0.09	1.15 ± 0.10	0.03 ± 0.1	1.15 ± 0.09	1.19 ± 0.12	0.04 ± 0.1 ^a
Peak workload, W	109 ± 37	123 ± 41	13.1 ± 19.3 ^c	103 ± 38	129 ± 46	26.3 ± 23.5 ^{c,d}
HR at VT ₁ , beats·min ⁻¹	90 ± 14	89 ± 14	-0.9 ± 7.0	90 ± 11	93 ± 11	3.5 ± 9.2 ^{a,d}
$\dot{V}O_2$ at VT ₁ , mL·kg ⁻¹ ·min ⁻¹	12.6 ± 2.9	14.4 ± 3.5	1.8 ± 2.1 ^c	12.0 ± 2.6	14.5 ± 2.7	2.5 ± 3.0 ^c
Power at VT ₁ , W	55 ± 24	62 ± 27	7.9 ± 17 ^b	49 ± 22	65 ± 22	15.3 ± 16.1 ^c
HR at VT ₂ , beats·min ⁻¹	106 ± 17	107 ± 18	0.1 ± 7.0	102 ± 14	109 ± 14	6.9 ± 11.8 ^{a,d}
$\dot{V}O_2$ at VT ₂ , mL·kg ⁻¹ ·min ⁻¹	17.2 ± 4	19.1 ± 4.1	1.9 ± 2.9 ^b	17.0 ± 3.8	19.9 ± 3.9	2.9 ± 3.7 ^b
Power at VT ₂ , W	92 ± 38	106 ± 33	14.0 ± 15.5 ^c	88 ± 30	106 ± 28	17.2 ± 19.0 ^b
6MWT						
Distance, m	528 ± 96	558 ± 109	29.6 ± 12.0 ^c	531 ± 74	580 ± 80	49.6 ± 6.3 ^{c,d}

Abbreviations: BP, blood pressure; CPET, cardiopulmonary exercise test; DBP, diastolic blood pressure; DP, double product; HIIT, high-intensity interval training; HR, heart rate; MCT, moderate continuous training; RER, respiratory exchange ratio; SBP, systolic blood pressure; $\dot{V}O_2$, oxygen uptake; VT₁, first ventilatory threshold; VT₂, second ventilatory threshold; 6MWT, 6-minute walk test.
 Within-group differences: ^a*P* < .05; ^b*P* < .01; ^c*P* < .001.
 Between-group differences: ^d*P* < .05; ^e*P* < .001.

noted in the HIIT group (4.5 ± 4.7 mL·kg⁻¹·min⁻¹ vs 2.5 ± 3.6 mL·kg⁻¹·min⁻¹, for patients in the HIIT and MCT groups, respectively; *P* < .05). Both groups also showed a significant increase in the peak exercise workload achieved (MCT 13.1 ± 19.3 W vs HIIT 26.3 ± 23.5 W), with a significantly higher increase in the HIIT group (*P* < .001). A significant increase was observed in maximal HR in the HIIT group only (10.6 ± 11.7 beats·min⁻¹; *P* < .001). The $\dot{V}O_2$ and exercise workload at VT₁ and VT₂ significantly increased in both groups, but HR only increased in the HIIT group.

Thirty-two HIIT and 34 MCT patients achieved VT₁ on the first CPET, and 35 and 34 patients achieved it on the second, posttraining CPET. Concerning the achievement of VT₂, 20 HIIT and 25 MCT patients achieved it on the initial CPET. On the CPET after the training programs, 29 HIIT and 32 MCT patients achieved VT₂.

With regard to the HR recovery in the first minute after the exercise test, the only significant change was observed in the HIIT group (5.8 ± 8.1 ; *P* < .001).

Both groups showed significant (*P* < .001) increases in 6MWT distance (Table 4) after training, with a

Table 4 • Quality of Life Results in MCT and HIIT Groups^a

	MCT Group			HIIT Group		
	Pretraining	Posttraining	Change	Pretraining	Posttraining	Change
SF-36 ^a						
Physical functioning	73 ± 24	77 ± 23	4.3 ± 13.6	78 ± 15	83 ± 16	4.6 ± 13.3
Role physical	51 ± 43	59 ± 44	8.1 ± 51.4	49 ± 42	54 ± 45	4.4 ± 49.4
Body pain	67 ± 30	73 ± 25	5.8 ± 28.2	72 ± 23	74 ± 25	2.4 ± 26.2
General health	58 ± 19	62 ± 22	3.9 ± 14.8	58 ± 18	63 ± 19	5.0 ± 17.4
Vitality	62 ± 18	67 ± 18	4.1 ± 14.7	57 ± 19	63 ± 23	6.2 ± 22.4
Social functioning	83 ± 22	83 ± 22	0.6 ± 23.4	82 ± 19	89 ± 17	7.7 ± 24.0
Role emotional	73 ± 38	75 ± 40	2.9 ± 45.2	48 ± 44	73 ± 36	25.5 ± 47.9 ^c
Mental health	70 ± 20	73 ± 22	3.3 ± 14.6	64 ± 17	73 ± 18	9.3 ± 19.0 ^c
Self-reported health status	3 ± 1	2 ± 1	-0.6 ± 0.9 ^c	3 ± 1	2 ± 1	-0.9 ± 1.2 ^d
Physical health index	43 ± 11	46 ± 12	2.6 ± 7.3 ^b	47 ± 8	47 ± 7	-0.5 ± 7.6
Mental health index	48 ± 12	50 ± 14	1.6 ± 11.8	41.0 ± 12.4	49 ± 11	7.8 ± 14.0 ^c
MacNew						
Emotional domain	5.5 ± 1.1	5.7 ± 1.1	0.3 ± 0.8	5.3 ± 0.9	5.8 ± 0.9	0.5 ± 0.9 ^c
Physical domain	5.6 ± 0.9	5.9 ± 0.9	0.3 ± 0.7 ^b	5.5 ± 1.0	5.9 ± 1.0	0.4 ± 0.7 ^c
Social domain	5.7 ± 0.9	6.0 ± 0.8	0.4 ± 0.8 ^b	5.6 ± 0.9	6.0 ± 0.9	0.4 ± 0.7 ^c
Global domain	5.5 ± 0.9	5.8 ± 0.9	0.3 ± 0.7 ^b	5.3 ± 0.9	5.8 ± 0.9	0.5 ± 0.7 ^c

Abbreviations: HIIT, high-intensity interval training; MacNew, MacNew Heart Disease Health-related Quality of Life questionnaire; MCT, moderate continuous training; SF-36, 36-Item Short Form Health Survey.

^aAll data reported as mean ± standard deviation.

Within-group differences: ^b $P < .05$; ^c $P < .01$; ^d $P < .001$.

greater increase in distance for the HIIT group compared with the MCT group ($P < .05$).

Quality of Life

After the training program, scores in all domains of the MacNew questionnaire significantly improved in both groups except for the emotional domain in the MCT group. With regard to the SF-36 QOL questionnaire, significant increases in the role emotional, mental health, self-reported health status, and the mental health index were observed in the HIIT group (Table 4).

Safety of the Training Intervention

No incidents or adverse events were recorded that limited the ability of patients to perform the prescribed exercise in either of the training programs.

DISCUSSION

Recent studies have revealed that HIIT is more effective than MCT for improving functional capacity and other

variables predictive of cardiovascular risk.^{10,11,20-22} In our study, despite the increase in $\dot{V}O_{2peak}$ in both groups after 8 weeks of aerobic training, the improvement was significantly greater in the HIIT group. The mean increase in $\dot{V}O_{2peak}$ was $4.5 \pm 4.7 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ in the HIIT group and $2.5 \pm 3.6 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ in the MCT group. These results are important not only for the improved $\dot{V}O_{2peak}$ but also for the benefit that increased functional capacity has on survival. Since $\dot{V}O_{2peak}$ is considered to be the best predictor of survival in patients with cardiovascular diseases, HIIT may potentially contribute to the reduction of morbidity and mortality because its effect on increasing $\dot{V}O_{2peak}$.

The 24% increase (HIIT group) and the 12% increase (MCT group) in $\dot{V}O_{2peak}$ are similar to those reported by other authors,²¹ but are far from the results obtained by Wisloff et al,²⁰ who reported improvements in $\dot{V}O_{2peak}$ of 46% with HIIT and 15% with MCT. These greater differences in favor of the HIIT group could possibly be due to the fact that Wisloff's study was conducted on patients with heart failure and severe left ventricular dysfunction (average left ventricular ejection fraction $\approx 29\%$), with a lower baseline

functional capacity ($\dot{V}O_{2peak} = 13 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$) and the use of a different interval protocol compared with this study.

V_{T1} expressed in $\text{mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ increased in both groups after the exercise program, but the HR at V_{T1} in the HIIT group was significantly higher than in the MCT group. This finding reflects important peripheral and central adaptations to the exercise training as it allows patients to exercise longer at submaximal levels before the onset of fatigue and represents an improved aerobic capacity without increasing cardiovascular work.^{23,24} This shift in the V_{T1} toward increased $\dot{V}O_2$ could account for the increase ($P < .05$) in meters walked during the 6MWT after training in the HIIT group ($49.6 \pm 6.3 \text{ m}$) compared with the MCT group ($29.6 \pm 12 \text{ m}$).

On the other hand, an improvement in acidosis tolerance was observed in both training groups, with a shift of the V_{T2} closer to the $\dot{V}O_{2peak}$. This trend in the HIIT group could be due to a higher metabolic rate during exercise and a greater capacity for eliminating or buffering the lactate accumulated during incremental exercise.²⁵ This change in the anaerobic threshold provides a possibility of training at higher intensity without producing undesirable metabolic changes when exceeding the V_{T2} .²⁶

It is interesting to note that the maximum HR reached in the CPET after completing the exercise programs was significantly greater than at baseline testing in the HIIT group with no change in the MCT group. These findings in the HIIT group could be due to the fact that higher workloads were obtained after completing the program in the HIIT group ($103 \pm 38 \text{ W}$ vs $129 \pm 46 \text{ W}$) and were due to a significant increase in the exercise time on the second CPET ($7.80 \pm 1.75 \text{ minutes}$ vs $9.55 \pm 2.26 \text{ minutes}$; $P < .001$) and to an improved cardiovascular adaptation to exercise.

HR recovery in the first minute after maximum effort is considered by many to be predictive for future morbidity and mortality. A decrease in HR of $\leq 12 \text{ beats}\cdot\text{min}^{-1}$ during the first minute of recovery is considered abnormal.²⁷⁻²⁹ Improved HR recovery was observed only in the HIIT group, and this could be due to an increase in the vagal tone in patients in the HIIT group, as has been previously demonstrated.²⁸ These results suggest a greater contribution of the autonomic nervous system because of an increase in vagal tone that occurs after HIIT.²⁸ However, both the short- and long-term effects of HIIT on the autonomic nervous system are still unclear because of diversity in the results obtained in different studies.

Many of our results are similar to those reported by other authors, but it is difficult to compare them because of the different designs used for interval train-

ing programs. Different methods for determining the exercise intensity used during the peak and the recovery intervals include percentage of $\dot{V}O_{2peak}$,²⁰ percentage of $\dot{V}O_2$ reserve,³⁰ percentage of HR_{max} ,^{20,31} percentage HR reserve,³² or, as used in this study, percentage of workload.^{16,17} There are also differences between studies in the duration of the intervals, the number of peak and recovery periods per session, and the number of sessions per week.^{10,11,22} All of the above constitute important limitations because these variables significantly alter the total volume of training.^{10,11,22}

Our workgroup established the intensity of interval training exercise using exercise workload in watts as a percentage of the maximum workload achieved on the SRT. Our results show that the workloads applied in the peak intervals in this study were of high intensity and ranged between 104% and 134% of the maximum workload achieved during the initial CPET. Meyers et al²⁵ reported that using this methodology for the HIIT design, the exercise times during training at an intensity greater than 85% of the $\dot{V}O_{2peak}$ were prolonged and safe. This methodology described by Meyers et al²⁵ has been suggested as an alternative method for establishing the intensity of the short intervals,^{25,33} but we are aware that using it could be a limitation in our study because the SRT is not fully validated and is not a widely used test in cardiac rehabilitation.

Physiological improvement with both types of exercise training was accompanied by an improvement in QOL as measured by the MacNew and SF-36 questionnaires. Although no significant differences were observed between the 2 groups, the most analyzed domains in both questionnaires showed greater improvements in the HIIT group. All 3 domains in the MacNew questionnaire (emotional, physical, and social) demonstrated greater improvement in the HIIT group. This is a very important fact because it is related to adherence to exercise programs³⁴⁻³⁷ and it reflects good tolerance for and acceptability of the HIIT protocol.

In general, HIIT programs have been shown to be safe, although the number of studies is limited. As described in other studies,^{10,11,22,38} we observed good acceptability and tolerability by all of the patients in the HIIT group and no incidents or complications were recorded during the training program.

Although the absence of incidents in our study suggests that HIIT is a safe way to prescribe exercise and the data are reassuring, we cannot draw a clear conclusion that HIIT is safe. Further long-term studies are necessary in order for HIIT to be accepted as a standard methodology for exercise training in cardiac rehabilitation. We recommend that large-scale, randomized clinical trials be conducted to investigate the impact of

HIIT on morbidity and mortality in patients with cardiovascular diseases. Fortunately, 2 multicenter, randomized studies are already underway in Europe: the SAINTEX-CAD coronary artery disease study³⁹ and the SMARTEX-HF heart failure study.⁴⁰ The results from these studies will be an important advance in being able to make definitive recommendations regarding HIIT and the previously mentioned problems of patient safety and future morbidity and mortality risk.

CONCLUSIONS

The results of our study documented that HIIT in low-risk patients diagnosed with chronic ischemic heart disease resulted in a greater increase in functional capacity compared with MCT and favored the HIIT group in both maximal ($\dot{V}O_{2peak}$) and submaximal (VT_1 and VT_2) values. The acceptance and tolerability by patients, absence of adverse incidents, and its positive impact on the quality of life justify the use of HIIT as an alternative to standard exercise training protocols used in cardiac rehabilitation programs.

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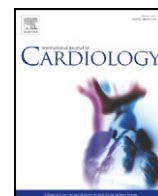
ARTICULO 2

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Effects of high-intensity interval versus continuous exercise training on post-exercise heart rate recovery in coronary heart-disease patients



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ABSTRACT

Background: Heart rate recovery (HRR) has been considered a prognostic and mortality indicator in both healthy and coronary patients. Physical exercise prescription has shown improvements in VO_2 peak and HRR, but most of the studies have been carried out applying continuous training at a moderate intensity, being very limited the use of protocols of high intensity interval training in coronary patients.

We aimed to compare the effects of a moderate continuous training (MCT) versus a high intensity interval training (HIIT) programme on VO_2 peak and HRR.

Methods: Seventy three coronary patients were assigned to either HIIT or MCT groups for 8 weeks. Incremental exercise tests in a cycloergometer were performed to obtain VO_2 peak data and heart rate was monitored during and after the exercise test to obtain heart rate recovery data.

Results: Both exercise programmes significantly increase VO_2 peak with a higher increase in the HIIT group (HIIT: 4.5 ± 4.46 ml/kg/min vs MCT: 2.46 ± 3.57 ml/kg/min; $p = 0.039$). High intensity interval training resulted in a significantly increase in HRR at the first and second minute of the recovery phase ($15,44 \pm 7,04$ vs $21,22 \pm 6,62$, $p < 0,0001$ and $23,73 \pm 9,64$ vs $31,52 \pm 8,02$, $p < 0,0001$, respectively).

Conclusions: The results of our research show that the application of HIIT to patients with chronic ischemic heart disease of low risk resulted in an improvement in VO_2 peak, and also improvements in post-exercise heart-rate recovery, compared with continuous training.

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1. Introduction

Coronary heart disease (CHD) continues to be the leading cause of morbidity and mortality in the developed countries, being the cause of approximately one third of all deaths in individuals over the age of 35 [1]. In spite of the research carried out to date, the pathophysiological basis of the disease is still not fully understood, with, among other pathogenic approaches, the chronic dysfunction of the autonomic nervous system being proposed as such a basis [2]. This has been implicated in

the development of cardiovascular risk factors such as hypertension, diabetes, and dyslipidemia, and has been directly linked with mortality caused by coronary artery disease [3].

The results of recent meta-analysis [4] have confirmed that the inclusion of exercise programmes in cardiac rehabilitation reduces cardiovascular mortality and hospital readmissions. The majority of the published research on the benefits of exercise for individuals with cardiovascular diseases have used constant load exercise (MCT) of between 60% and 80% of VO_2 peak. These studies have shown significant improvements in aerobic functional capacity (VO_2 peak) of between 12% and 31% [5]. In this context, for many years moderate continuous training (MCT) has been accepted as the gold standard [6]. However, for some time now, different teams have adopted a high-intensity interval training model (HIIT) as the most efficient with respect to objective adaptations of the majority of cardiac rehabilitation programmes in patients with coronary artery disease (CAD), congestive heart failure (CHF) and metabolic syndrome [7].

In recent years, various revisions and meta-analysis on the implementation of HIIT for CAD and CHF have been published [8–11]. Two

Abbreviations: CHD, coronary heart disease; HR, heart rate; HRR, heart rate recovery; MCT, moderate continuous training; HIIT, high intensity interval training; CAD, coronary artery disease; CHF, congestive heart failure; CPET, cardiopulmonary exercise test.

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of these studies [10,11] demonstrated in 260 patients with coronary heart disease the superiority of HIIT over continuous training with greater increases in VO_{2peak} . These findings are consistent with the results of previous meta-analysis, which compared HIIT with continuous training in patients with heart failure [12] and cardio-metabolic disease [13]. Recent studies [14,15] have even shown their effects on the diastolic dysfunction of the left ventricle that had not been effectively treated with drugs.

HIIT is usually defined as exercise of repeated intervals of a short to intermediate duration (e.g. 10 s to 5 min) completed at a higher intensity than the corresponding anaerobic threshold [16]. The exercise intervals are separated by low-intensity recovery times or rest which allow for partial recovery from the efforts of the previous interval [16].

The heart rate recovery (HRR) has been proposed in many studies as an indicator of prognosis and mortality, in that a slowing of the HRR after strenuous exercise is a predictor of mortality both in healthy subjects and in patients with CHD [3,17]. Meanwhile, other authors even consider that post-exercise HRR is a good indicator of cardiac rehabilitation programme effectiveness [18–20], it being a quality index to stratify patient risk upon completing a rehabilitation programme [21].

Post-exercise HRR can be divided into 2 phases: fast and slow. The quick phase refers to the first minute of recovery (<1 min) and characterises a period in which there is an abrupt and rapid decline of the HR [22,23]. The slow phase, meanwhile, refers to the period following the fast phase (≥ 2 min) [23–25]. HRR in the first minute after exercising corresponds to vagal reactivation, especially in the first 30 s [22], while later recovery (≥ 2 min) is likely attributed to a drop in sympathetic activity [26].

To date there exists no consensus regarding the most appropriate time and method to obtain HRR data. Since the publication of Cole et al.'s research [27,28] into men and women without cardiovascular disease, measuring the HRR in the first minute after exercise is the most common method employed, with a cut-off point of ≤ 12 bpm to consider a reading as clinically abnormal. Readings lower than 12 bpm were associated with mortality risk for any cause 2 times higher in the population group referred to [28]. Measuring HRR 2 min after exercise during passive recovery in a sitting position has also shown itself to be an independent predictor of cardiovascular mortality from all causes in a long series of coronary patients, moreover providing valuable information that can be used for risk stratification in this population group [29]. Readings lower than 22 bpm 2 min after exercise have been considered clinically abnormal [27,28]. Shetler et al. [30] suggested that a recovery of 22 bpm 2 min after exercise exceed in capacity the HRR 1 prognosis. Other studies carried out on healthy subjects confirmed the prognostic value of the HRR reading at 2 min post-exercise [27,31].

Training sessions in cardiac rehabilitation programmes which often use continuous exercises of moderate intensity have shown improvements in HRR after 8 [32] and 12 [33–37] weeks of training, the studies being more limited [38,39] which have valued modifications in the HRR employing HIIT protocols, compared with the continuous protocols of constant intensity.

Intermittent high-intensity exercise, which are matched to continuous for either energy expenditure or exercise duration, have shown improvements in different hemodynamic indicators at rest, cardiorespiratory fitness, endothelial functionality and morphology and function of the left ventricle [40–45].

The objective of this research was to compare the influence of 2 different exercise protocols (continuous and HIIT) when used with coronary patients as part of a cardiac rehabilitation programme on post-exercise heart-rate recovery readings.

2. Methods

2.1. Study population

A prospective, randomized clinical trial (NCT02168712) was conducted with patients referred by the Cardiac Rehabilitation Department who were diagnosed with stable

New York Heart Association functional class I or II coronary artery disease with angina pectoris or myocardial infarction and no heart failure. To be included in the study, patients had to achieve a respiratory exchange ratio ≥ 1.10 during the initial cardiopulmonary exercise test (CPET). This respiratory exchange ratio value is often used as a criterion for achieving a maximum exercise effort [46]. Patients who had residual ischemia (by electrocardiogram [ECG] criteria or angina symptoms), severe ventricular arrhythmias, uncontrolled hypertension, permanent pacemakers, or implanted cardiac defibrillators were excluded.

After signing an informed consent form, patients were randomized on a one-to-one basis to either the MCT or the HIIT group. The mode of exercise training was a cycle ergometer with 40 min per sessions, 3 days per week (total of 24 sessions over 2 months).

Patients entered the study within 6 weeks from the revascularization procedure. Selected CPET variables were recorded before and after the exercise training. Cardiopulmonary exercise tests were administered by staff blinded as to which exercise training group the patients were assigned.

Characteristics and medication use of the patients are shown in Table 1.

2.2. Cardiopulmonary exercise test (CPET)

All patients underwent exercise testing with a cycle ergometer (Ergoline900S, Ergoline GmbH, Bitz, Germany) including analysis of exhaled gases (UltimaCardiO2, Medical Graphics Corporation, St Paul, Minnesota). The exercise test protocol was tailored to each patient's physical condition, with gradual increments of 10, 15, or 20 W/min. The same protocol was applied before and after the Exercise training programme. The objective of the exercise tests was to achieve a sustained effort for 8 to 12 min, with the aim of proper oxygen uptake (VO_{2}) kinetics and maintaining a linear relationship between VO_{2} , exercise workload and heart rate (HR).

A 12-lead ECG was continuously monitored, and blood pressure was measured every 3 min during the exercise tests. Exercise workloads in watts and metabolic, cardiac, ventilatory and electrocardiographic parameters were analyzed. The ECG was continuously monitored during the first 5 min of recovery. Recorded HR was determined from the computerized test reports and was the average of the last 5 RR intervals.

Table 1

Patients' characteristics and medication use.

	MCT (n = 36)	HIIT (n = 37)	P
Age (years)	58 ± 11	58 ± 11	0.82
Men (%)	92	78	0.21
Body mass index (kg/m ²)	29.5 ± 4.1	29.6 ± 4.4	1.00
Waist circumference (cm)	104 ± 9	104 ± 11	1.00
Hip circumference (cm)	105 ± 8	104 ± 9	0.88
Waist to hip ratio	0.99 ± 0.05	1.00 ± 0.07	0.90
<i>Cardiovascular risk factors</i>			
Family history (%)	47	46	1.00
Hypertension (%)	57	65	0.67
Diabetes mellitus (%)	31	27	0.88
Dyslipidemia (%)	66	43	0.09
History of smoking (%)	81	73	0.74
Active smoker during programme (%)	10	14	0.64
Stroke (%)	9	5	0.67
Carotid disease (%)	3	3	1.00
Peripheral vascular disease (%)	9	8	1.00
Hyperuricaemia (%)	11	8	1.00
<i>Medical history</i>			
Angina pectoris (%)	50	43	0.36
Myocardial infarction (%)	50	57	0.45
LVEF (%)	59 ± 14	62 ± 11	0.29
Conservative (%)	12	19	0.44
PCI (%)	73	59	0.35
CABG (%)	15	22	0.53
<i>Drugs administered</i>			
Beta-blockers (%)	89	86	1.00
Calcium channel blockers (%)	14	27	0.27
ACE-inhibitors (%)	71	54	0.20
Angiotensin receptor antagonists (%)	20	19	1.00
Nitrates (%)	11	11	1.00
Anti-platelet agents (%)	97	97	1.00
Acenocoumarol (%)	11	5	0.43
Statins (%)	94	100	0.23
Ezetimibe (%)	6	3	0.61
Antidiabetics (%)	22	22	1.00

ACE: angiotensin converting enzyme; CABG: coronary artery bypass graft; HIIT: high-intensity interval training; LVEF: left ventricular ejection fraction; MCT: moderate continuous training; PCI: percutaneous coronary intervention.

HRR indices were calculated by subtracting first and second minute HR on recovery period from the maximal HR obtained during stress testing and designated as HRR-1 and HRR-2, respectively [28,47]. The relative change in HRR was determined as the decrease produced in HR at 1 and 2 min after finishing exercise expressed as a percentage of the peak HR (%HRR-1/HRpeak and %HRR-2/HRpeak, respectively). We also calculated the relative decrease in HR at 1 and 2 min post-exercise as a percentage of the increase produced from resting HR to peak HR (%HRR-1 / (HRpeak – HRrest) and %HRR-2 / (HRpeak – HRrest), respectively).

The first (VT1) ventilatory threshold were considered to be indicator of the aerobic threshold, and was determined after the ventilatory equivalent method described by Skinner et al. [46]. The VO_2 in ml/kg/min and HR in $\text{beats} \cdot \text{min}^{-1}$ at VT1 were the parameters used to determine the MCT exercise intensity.

2.3. Steep ramp test

To design the HIIT programme, we used the steep ramp test (SRT) protocol, according to the methodology described by Meyer et al. [48]. This exercise test protocol is composed of 2 min of free pedaling at 25 W followed by progressive 25-W increments every 10 s, maintaining a constant pedal cadence of between 50 and 60 rpm. The test was stopped when the patient could not maintain continuous pedal cadence of >40 rpm after encouragement to increase to 50 rpm and/or experienced hemodynamic and/or electrical alterations. The maximum exercise load achieved, as measured in watts, was the exercise parameter used to design the HIIT programme for each patient.

2.4. MCT and HIIT programme designs

The metabolic parameters obtained during the pretraining CPET were used to design the MCT programme. Patients were asked to keep their training HR below the HR at VT1 during the first month. During the second month, the intensity of the exercise was adjusted, increasing to a training HR that corresponded to VT1 plus 10%. The HIIT protocol used the methodology initially described by Meyer et al. [48] and which was recently published by our group [49]. In this type of exercise, the intensity was established using workload (watts), without taking HR into consideration as a measure for regulating the intensity of the exercise. The training workloads depended on the maximum workload achieved during the SRT. The intervals were designed as follows. In the first month of training, 20-second repetitions at an intensity corresponding to 50% of the maximum load reached with the SRT (peak intervals) were followed by 40-second recovery periods at 10%. In the second month of training, the intensity of exercise was adjusted using the results of a new SRT. The total duration of both types of training was 40 min per session throughout the exercise programme (including warm-up and cool-down). Table 2 summarizes the exercise time and intensity progression for both MCT and HIIT. Patients rated the peak level of exertion during each training session using the Borg Rating of Perceived Exertion Scale [50]. Both types of exercise were reviewed and approved by the local Research Ethics Committee. Patients enrolled in the study participated in other activities established in our cardiac rehabilitation programme that were aimed at managing psychological stress and learning about cardiac health habits. They were also taught to devise a home walking programme for the days on which they did not have to attend sessions in the hospital. The recommended intensity of walking was a perceived exertion of 11 to 13 on the Borg scale.

2.5. Safety of the exercise training programmes

To verify the safety of using this kind of aerobic Exercise training, we made a daily record of any incidents or adverse effects that could limit the planned exercise. An incident was considered low if there were no repercussions and it was possible to start and/or

restart training (e.g., muscle overload, fatigue, muscular pain, and dyspnea without oxygen desaturation). A moderate incident was defined as one that limited the planned training (dyspnea with desaturation <94%, muscle injury, vasovagal conditions), and an incident was defined as severe if it was potentially lifethreatening (ischemia, ventricular arrhythmia, hypertensive emergencies).

2.6. Statistical analysis

Quantitative variables were described using means and standard deviations. The normality of the data distribution was determined using the Kolmogorov Smirnov test. To evaluate the effect of each exercise protocol on the quantitative variables, pre- and post-programme values were compared using Student's dependent samples *t*-test. The effect was measured in absolute terms via the difference between the post-programme values and those obtained before training. These changes were described with the mean and standard deviation. Comparisons between the 2 training programmes were made using Student's *t*-test in the case of quantitative variables and using the χ^2 test of association or Fisher exact test for qualitative variables. All the comparisons were made using 2-tailed tests, and the level of significance was set at $p < 0.05$. The relationship between HRR and VO_2 peak was assessed by calculating Pearson correlation coefficients. All statistical tests were performed using commercially available software (SPSS, Version 19.0, Inc., Chicago, IL, USA).

3. Results

A total of 73 patients were included and studied (36 patients MCT group and 37 patients HIIT group). At the start of the study, there were no significant differences between the groups with regard to clinical characteristics and medication use.

3.1. Training data

The intensity of exercise in the MCT group in the first month was $64.2 \pm 8.5\%$ of the VO_2 peak reached during the initial CPET (corresponding to the VT1) and $69.5 \pm 8.7\%$ in the second month (corresponding to VT1 + 10%). The exercise workload applied at the peak intervals in the HIIT group using the Meyer et al. methodology [48] was $104.5 \pm 22.2\%$ (first month) and $134.5 \pm 29.7\%$ (second month) of the maximum load reached in the initial CPET corresponding to 50% of the SRT in both months. Adherence to the treatment sessions (the number of sessions attended compared with the number of sessions scheduled) was 87.5% in the MCT group and 92% in the HIIT group.

3.2. Cardiopulmonary exercise test

The exercise effort test results for both groups can be seen in Table 3. After 8 weeks of training, both exercise programmes significantly increased their VO_2 peak, with a greater increase in the HIIT group (4.5 ± 4.46 ml/kg/min vs 2.46 ± 3.57 ml/kg/min, for patients of the HIIT and MCT groups respectively, $p = 0.039$).

Both groups also showed a significant increase in the peak exercise workload achieved (MCT 13.13 ± 19.39 W vs HIIT 26.28 ± 23.52 W), with a significantly higher increase in the HIIT group ($p = 0.012$). A significant increase was observed in maximal HR in the HIIT group only (10.55 ± 11.74 $\text{beats} \cdot \text{min}^{-1}$; $p = 0.001$). The total time of the exercise effort test, as well as the VO_2 and exercise workload at VT1 significantly increased in both groups, but HR at VT1 only increased in the HIIT group (3.48 ± 9.23 ; $p = 0.030$).

3.3. Heart rate recovery

In Table 3, the heart-rate recovery values for both groups are reflected. With regard to the HR recovery in the first and second minute after the exercise test, the only significant change was observed in the HIIT group (15.44 ± 7.04 vs 21.22 ± 6.62 ; $p < 0.0001$ and 23.73 ± 9.64 vs 31.52 ± 8.02 ; $p < 0.0001$, respectively). Differences were observed in changes in HRR-1 (MCT: 1.27 ± 8.06 vs HIIT: 5.77 ± 8.06 ; $p = 0.021$) and in HRR-2 (MCT: 2.94 ± 9.16 vs HIIT: 7.78 ± 7.69 ; $p = 0.022$) between groups.

Table 2

Programme designs for MCT group or HIIT groups.

Week	Warm-up time and intensity (MCT and HIIT)	Exercise time and intensity	Cool-down time and intensity (MCT and HIIT)
1	12 min (25 W)	MCT: 15 min at VT1 HIIT: 15 repetition ^a	13 min (25 W)
2	10 min (25 W)	MCT: 20 min at VT1 HIIT: 20 repetition ^a	10 min (25 W)
3	7 min (25 W)	MCT: 25 min at VT1 HIIT: 25 repetition ^a	8 min (25 W)
4	5 min (25 W)	MCT: 30 min at VT1 HIIT: 30 repetition ^a	5 min (25 W)
4–8	5 min (25 W)	MCT: 30 min at (VT1 + 10%) HIIT: 30 repetition ^b	5 min (25 W)

MCT: moderate continuous training; HIIT: high intensity interval training; VT1: first ventilatory threshold.

^a 20-second repetitions at 50% of the maximum load reached with the first SRT (steep ramp test) followed by 40-second of recovery period at 10% of the first SRT.

^b 20-second repetitions at 50% of the maximum load reached with the second SRT followed by 40-second of recovery period at 10% of the second SRT.

Table 3
Cardiopulmonary exercise stress test variables and HRR-1 and HRR-2 values in MCT group vs HIIT group.

	MCT group			HIIT group		
	Pretraining	Posttraining	Change	Pretraining	Posttraining	Change
Total exercise time, (min)	9.00 ± 2.01	10.10 ± 2.58**	1.10 ± 1.78	7.80 ± 1.75	9.54 ± 2.25***	1.74 ± 1.91
VO ₂ peak, (ml/kg/min)	20.32 ± 5.03	22.78 ± 6.53***	2.46 ± 3.57	19.44 ± 4.69	23.94 ± 4.85***	4.50 ± 4.46†
Maximum HR, (bpm)	117.56 ± 19.57	118.53 ± 20.61	0.97 ± 11.58	115.36 ± 13.51	125.92 ± 14.04***	10.55 ± 11.74‡
Maximum SBP, (mm Hg)	171.03 ± 23.04	164.92 ± 26.37	-6.11 ± 21.72	170.75 ± 21.39	177.92 ± 23.06	7.16 ± 23.92†
Maximum DBP, (mm Hg)	92.47 ± 12.29	89.44 ± 8.26	-3.02 ± 12.38	90.14 ± 19.76	91.72 ± 10.75	1.58 ± 10.85
Maximum power, (W)	109.22 ± 37.21	122.47 ± 41.23***	13.13 ± 19.39	103 ± 37.71	129.29 ± 45.89***	26.28 ± 23.52†
Maximum RER	1.12 ± 0.09	1.15 ± 0.09	0.02 ± 0.12	1.14 ± 0.08	1.19 ± 0.11*	0.04 ± 0.11
VO ₂ at VT1, (ml/kg/min)	12.59 ± 2.88	14.37 ± 3.52***	1.77 ± 2.09	11.98 ± 2.64	14.48 ± 2.70***	2.50 ± 3.06
HR at VT1, (bpm)	90.32 ± 13.89	89.38 ± 14.12	-0.94 ± 7.00	89.64 ± 10.45	93.12 ± 10.81*	3.48 ± 9.23†
					p = 0.038	
Power at VT1, (W)	54.56 ± 24.25	62.50 ± 26.55**	7.94 ± 16.92	49.24 ± 22.33	64.55 ± 21.98***	15.30 ± 16.10
HRR-1, (bpm)	19.92 ± 8.79	21.19 ± 7.93	1.27 ± 8.06	15.44 ± 7.04	21.22 ± 6.62***	5.77 ± 8.06†
%HRR-1/HR _{peak} (%)	16.68 ± 6.44	17.93 ± 6.29	1.24 ± 7.18	13.37 ± 6.03	16.84 ± 4.94**	3.47 ± 6.54
HRR-2, (bpm)	28.46 ± 9.85	31.40 ± 11.94	2.94 ± 9.16	23.73 ± 9.64	31.52 ± 8.02***	7.78 ± 7.69†
%HRR-2/HR _{peak} (%)	24.02 ± 7.04	26.22 ± 7.64	2.19 ± 7.15	20.50 ± 7.74	25.00 ± 5.35***	4.49 ± 5.96

Abbreviations: HR: heart rate, SBP: systolic blood pressure, DBP: diastolic blood pressure, W: watos, RER: respiratory exchange ratio, VT1: ventilatory threshold 1, HRR-1: heart rate peak minus heart rate at 1 min of recovery, HR_{peak}: heart rate peak, HRR-2: heart rate peak minus heart rate at 3 min of recovery.

* Within-group difference <0.05.

** Within-group difference <0.01.

*** Within-group difference <0.001.

† Between-group difference <0.05.

‡ Between-group difference <0.01.

3.4. Relationship between HRR and Peak VO₂

Peak VO₂ showed significant correlation with HRR-1 ($r = 0.40$; $p < 0.001$) and %HRR-1/HR_{peak} ($r = 0.28$; $p = 0.014$), and with HRR-2 ($r = 0.43$; $p < 0.001$) and %HRR-2/HR_{peak} ($r = 0.26$; $p = 0.026$), for the whole group of patients pre-training. With regard to the post-training Peak VO₂ showed significant correlation with HRR-1 ($r = 0.38$; $p < 0.01$), and with HRR-2 ($r = 0.53$; $p < 0.001$) and %HRR-2/HR_{peak} ($r = 0.37$; $p < 0.01$), for the whole group of patients (Fig. 1).

3.5. Safety of the training intervention

No incidents or adverse events were recorded that limited the ability of patients to perform the prescribed exercise in either of the training programmes.

4. Discussion

The principle contribution of this study has been the verification of an improvement in the post-exercise heart-rate recovery (HRR1 and HRR2) associated with the group of patients that underwent training with HIIT methodology. In addition, a greater increase in post-exercise values of VO₂peak in the HIIT group was also recorded. Another interesting observation is that in the group of patients as a whole, we found a significant correlation of VO₂peak between HRR1 and HRR2.

In contrast to most previous research that analyzed only HRR1 [32–37], we measured the heart rate recovery in the 1 and 2 min post-exercise. Both points have shown associations with mortality risk, although the heart rate in min 2 post-exercise has proved to be the most powerful predictor [30], which suggests the need to add systematic evaluation of HRR2 in patients with cardiovascular disease. Considering that this was a maximal exercise test, we propose that in addition to the indices of HRR as absolute values (HR_{peak}-HR1 and HR_{peak}-HR2), it is perhaps preferable to also consider HRR as a percentage of the peak HR recorded during the graded cardiopulmonary test. Thus, HRR relative to HR_{peak} as a measure of HR recovery applicable to all subjects regardless of age is expressed. Similarly, only the HIIT group improved the %HRR1/HR_{peak} (%) (13.37 ± 6.03 to 16.84 ± 4.94 bpm; $p = 0.003$) and %HRR2/HR_{peak} (%) (to 20.50 ± 7.74 to

25.00 ± 5.35 bpm; $p < 0.0001$), with average post-exercise values of %HRR1/HR_{peak} (%) of 17.93% and 16.84% for MCT and HIIT groups respectively; and %HRR2/HR_{peak} (%) of 26.22% and 25.00% for MCT and HIIT groups, respectively.

Our study showed average HRR1 values (pre- and post-training) above the clinical cut-off point established at <12 bpm at min 1 post-exercise for a HRR anomaly to be considered. However, it should be noted that 16 of the 73 patients (21.9%) of our study did not reach a HRR-1 of 12 in the evaluation previous to the start of the exercise programme. Only 7 patients maintained their HRR1 below the limit of <12 bpm after the recovery period, emphasizing in this regard the effectiveness of HIIT, which reduced the number of patients below the clinical HRR1 limit by 81.8%. Although an HRR of <12 bpm in the 1st minute after exercise is the most commonly used index, some research has shown increases in mortality risk with HRR 1 of <25 bpm [51] and <22 bpm [52]. Different studies have shown improvements of heart-rate recovery with exercise training. Mahdavi Anari et al. [53] observed, after a 12-week training period, a significant improvement of the HRR-1 (13.76 ± 1.38 bpm to 17.07 ± 1.33 bpm). The improvement in recovery was similar in patients with coronary artery bypass graft or percutaneous transluminal coronary angioplasty. The results obtained in our HIIT group were similar in HRR-1 (15.44 ± 7.04 bpm to 21.22 ± 6.62 bpm). For their part, Ribeiro et al. [54] and Tiukinhoy et al. [55] also observed similar results in the improvement of HRR1 with an 8-week exercise programme. Thus, HRR is a useful indicator to stratify the patient risk after completing a rehabilitation programme.

Regarding the HRR-2 value, Cole et al. [28] proposed a normality limit of ≤ 42 beats. Based on this criterion, only 6 of our patients (8.2%) were above this limit before starting the exercise programme, it being reached by 13 patients (17.8%) at the end of it. While the MCT group managed to have 3 patients more under this limit upon completing the exercise programme, in the HIIT group, 4 new patients were incorporated, suggesting greater effectiveness in the HIIT modality. Unlike the many studies that have evaluated HRR1, those that have measured HRR-2 are scarcer, meaning that their established clinical criteria of normality are less powerful.

The later recovery (≥ 2 min) is likely attributed to a drop in sympathetic activity (reduced activation of peripheral muscle mechanoreceptors and chemoreceptors) and to humoral factors such as catecholamines [25,51,56–60], and, in contrast to that which occurs in the fast phase of the HRR (≤ 1 min), the slow phase (≥ 2 min) is clearly

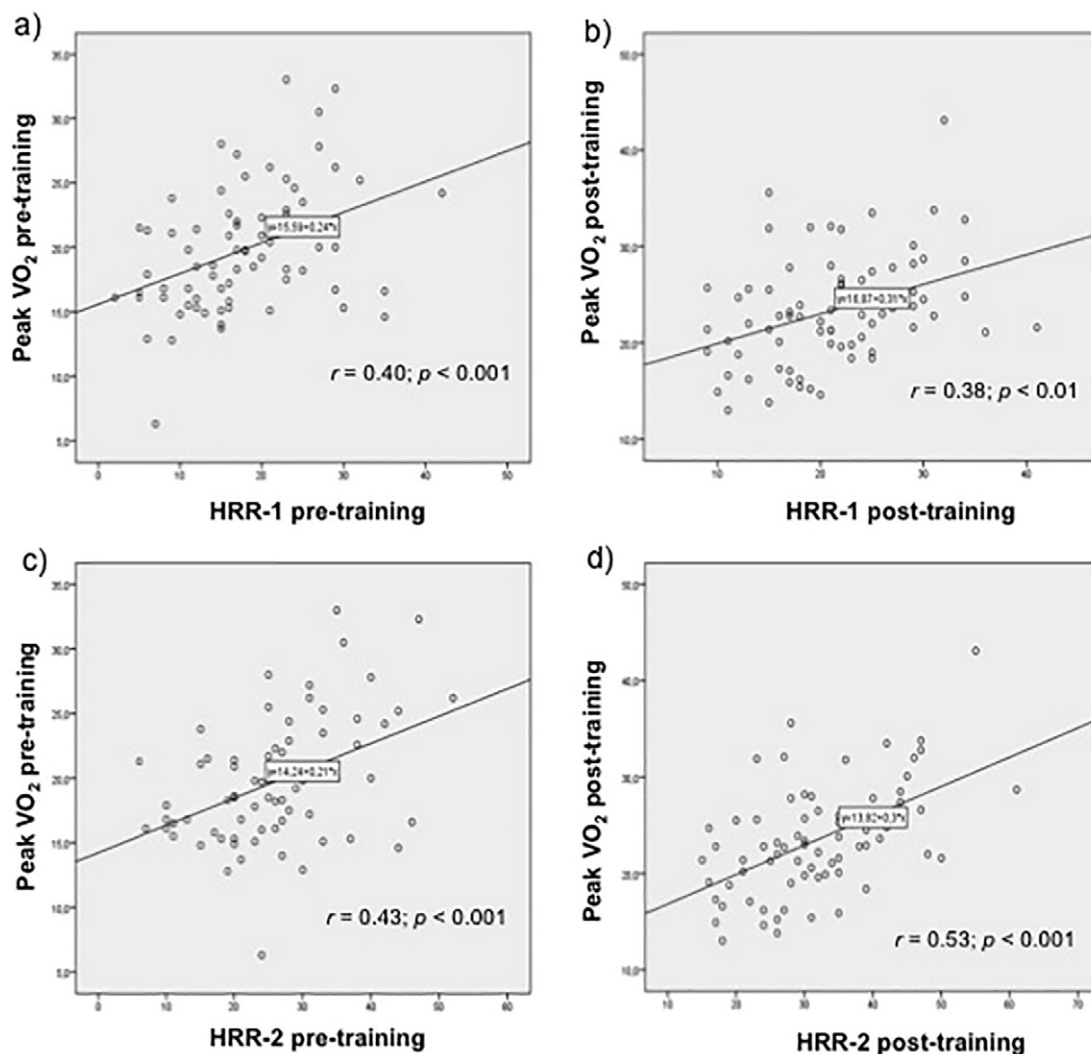


Fig. 1. Correlation between HRR-1 and HRR-2 plotted against Peak VO₂, pre- and post-training. a) HRR-1 pre-training values against Peak VO₂ pre-training. b) HRR-1 post-training values against Peak VO₂ post-training. c) HRR-2 pre-training values against Peak VO₂ pre-training. d) HRR-2 post-training values against Peak VO₂ post-training.

dependant on the intensity and duration of the previously performed exercise [22], conditioning the normalisation of the associated metabolic stress [25,61].

The intermittent high-intensity exercise (HIIT), which are matched to continuous for either energy expenditure or exercise duration, have shown improvements in different hemodynamic indicators at rest, cardiorespiratory fitness, endothelial functionality and morphology and function of the left ventricle [40–45]. However, Conraads et al. [62] observed in a large population of CAD patients similar improvements in exercise capacity and peripheral endothelial function following HIIT or moderate continuous training.

The physiopathological reason why an abnormal HRR is associated with a worse clinical prognosis is not clear. In accordance with Huang et al. [63], there exists a close relationship between HRR and the endothelial function; thus, any delay in the HRR might indicate endothelial dysfunction, and this alteration has proved to be a powerful predictor of global mortality in CHD [63]. Another factor that might contribute to HRR delay has been associated with an excessive pro-inflammatory state. In accordance with the recent concept of “cholinergic anti-inflammatory pathway”, immunity is coordinated by neural circuits that operate reflexively, and this well established neural circuit terminates excessive pro-inflammatory cytokine responses, preventing immune-mediated damage [64,65]. Therefore, a fall in parasympathetic activity can result in a pro-inflammatory response, thereby increasing

morbidity and mortality [2,66,67]. Similarly, Youn et al. [68] confirmed that a slowing of post-exercise HRR was linked to an exaggerated pro-inflammatory response, being an independent predictor variable in patients with heart failure.

Different studies have shown that HIIT training improves VO₂peak values in patients to a greater extent with respect to continuous load training [38,43,45]. Also of note in our research was that VO₂peak improved in both groups, but more so ($p < 0.05$) in the HIIT group. Other investigations [62] showed no differences in VO₂peak improvement using HIIT vs aerobic continuous training in patients with coronary artery disease. In the HIIT protocol of our study, the training intensity was established using the workload in watts as a percentage of the maximum workload reached in the SRT. The workloads applied were high intensity with a range of 104% and 134% of the maximum load reached during the initial effort test (CPET). Meyers et al. [69] noted that using this methodology for the HIIT design, exercise time at an intensity higher than 85% VO₂peak during prolonged training was prolonged, which justifies physiological adaptations to those associated with the improvement of the VO₂peak.

In our study, we found a significant correlation between the VO₂peak values of the entire group with HRR-1 ($r = 0.40$; $p < 0.001$) and HRR-2 ($r = 0.43$; $p < 0.001$), thereby confirming the relation between VO₂peak and HRR suggested by the authors [70–74]. Our group [75] also found a significant correlation between VO₂peak

(ml/kg/min) and HRR3 ($r = 0.36$; $p < 0.001$) in adult physically active men. Together, this data indicates that cardiorespiratory fitness is linked to HRR.

Maximum heart rate increased with training in the HIIT group, with changes in the continuous training (MCT) group not being found. This response seems to be related to the high workload achieved in the HIIT group in the effort test after the training programme. Underlying these functional improvements, cellular adaptations including rate of Ca^{2+} cycling and Ca^{2+} sensitivity of the cardiomyocytes were demonstrated in animal models following HIIT.

The two groups of our study improved VO_2 and the load (W) associated with VT1, with no differences between them. Similar results were found in other research studies [40,76–78], while in others, greater improvements in VO_2 associated to VT with HIIT were obtained [39,79]. The different protocols used may justify the lack of concordance in the results. Looking at HR related to VT, this factor only increased in the HIIT group, reflecting peripheral metabolic adaptations that allow for the sustaining of a greater workload in VT1.

In line with the increase of VO_2 peak, the maximum load reached (W_{max}) increased significantly more ($p = 0.012$) in the HIIT group, reflecting an improvement in the base-acid balance with peak loads.

Additionally, HIIT seems to be a safe exercise modality and did not differ in frequency or magnitude of cardiovascular adverse events during exercise training as compared with continuous training, as was shown previously [77].

Although it is a randomized study, we studied a small number of patients. It would be necessary large-scale, randomized clinical trials to investigate clinical end-points.

5. Conclusions

The results of our research show that the application of HIIT to patients with chronic ischemic heart of low risk resulted in an improvement in VO_2 peak, and also improvements in post-exercise heart-rate recovery, compared with continuous training (which showed no significant changes). Given the observed inverse relationship between the values of VO_2 peak and post-exercise HR recovery rates with all-cause mortality in these patients, the results of our study argue for giving preference to the interval high intensity training during the rehabilitation programme in low-risk coronary patients.

Conflicts of interest

The authors report no relationships that could be construed as a conflict of interest.

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ARTICULO 3

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Mechanical efficiency of high versus moderate intensity aerobic exercise in coronary heart disease patients: A randomized clinical trial

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Abstract

Background: Mechanical efficiency (ME) refers to the ability of an individual to transfer energy consumed by external work. A decreased ME, could represent an increased energy cost during exercise and may, therefore, be limited in terms of physical activity. This study aimed to compare the influence of two different exercise protocols: moderate continuous training (MCT) versus high intensity interval training (HIIT), as part of a cardiac rehabilitation program on ME values among coronary patients.

Methods: One hundred and ten coronary patients were assigned to either HIIT or MCT groups for 8 weeks. Incremental exercise tests in a cycle ergometer were performed to obtain VO_{2peak} . Net energy expenditure (EE) and ME were obtained at intensities corresponding to the first (VT_1) and second (VT_2) ventilatory thresholds, and at VO_{2peak} .

Results: Both exercise programs significantly increase VO_{2peak} with a higher increase in the HIIT group (2.96 ± 2.33 mL/kg/min vs. 3.88 ± 2.40 mL/kg/min, for patients of the MCT and HIIT groups, respectively, $p < 0.001$). The ME at VO_{2peak} and VT_2 only significantly increased in the HIIT group. At VT_1 , ME significantly increased in both groups, with a greater increase in the HIIT group ($2.20 \pm 6.25\%$ vs. $5.52 \pm 5.53\%$, for patients of the MCT and HIIT groups, respectively, $p < 0.001$).

Conclusions: The application of HIIT to patients with chronic ischemic heart disease of low risk resulted in a greater improvement in VO_{2peak} and in ME at VT_1 , than when MCT was applied. Moreover, only the application of HIIT brought about a significant increase in ME at VT_2 and at VO_{2peak} . (Cardiol J 2019; 26, 2: xx–xx)

Key words: coronary artery disease, cardiopulmonary exercise test, high interval training, mechanical efficiency, energy expenditure

Introduction

Mechanical efficiency (ME) refers to the ability of an individual to transfer energy consumed by external work. Most studies that assess the

efficiency of the different cardiac rehabilitation exercise programs evaluate the modification of the cardiovascular risk factors, quality of life and clinical variables associated with the prognosis of morbidity and mortality (i.e. VO_{2peak}), but there

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is very little research that evaluates ME, even though it provides important information concerning biomechanical adaptations and the use of the energy sources associated with clinical training and therefore the functional capacity of patients.

A decreased ME, which indicates that more energy is consumed at a given work output, could represent an increased energy cost of breathing during exercise, an altered efficiency in ATP production (ATP produced per O₂ consumed), or a higher ATP cost of contraction (ATP consumed per work output) [1]. Therefore, individuals with lower ME values should be less efficient in respect to performance and may therefore be limited in terms of physical activity [2]. Consequently, the evaluating ME may be valuable for the detection of muscle dysfunction and the assessment of any subsequent adaptations in response to training [3].

The results of a recent meta-analysis [4] have confirmed that the inclusion of exercise programs in cardiac rehabilitation reduces cardiovascular mortality and hospital readmissions in coronary artery disease (CAD) patients. For many years moderate continuous training (MCT) has been accepted as the gold standard [5]. However, recent evidence suggests that high intensity interval training (HIIT) may be a better modality for the improvement of aerobic exercise capacity [6]. Recently, with CAD patients, a superiority has been demonstrated of HIIT over MCT with greater increases in VO_{2peak}, as well as the recuperation rates of post-exercise heart rate. This constitutes an emerging prognostic variable of heart disease [7, 8].

Several studies have demonstrated that HIIT results in significant increases in muscle performance in untrained males. These adaptations are likely the result of skeletal muscle adaptations related to metabolic improvement associated with strengthening of muscle. Given that metabolic environment and muscle function may condition muscle performance and muscle energy profile of an individual, it is possible that any improvement in these parameters may be predictive of a subsequent increase in ME [2]. Therefore, ME may also be an important predictor of efficacy and may provide relevant data regarding performance and energy use adaptations in response to training [2].

Studies in young adults and older individuals [3] have reported significant increases in ME in response to HIIT. Considering that HIIT demonstrated a multitude of physiological adaptations that were correlated with performance and health benefits [9, 10], it was hypothesized that this form of exercise may promote greater improvements in ME among CAD patients.

This study aimed to compare the influence of two different exercise protocols (MCT vs. HIIT) as part of a cardiac rehabilitation program on ME values among coronary patients.

Methods

Study population

This is a unicentric, prospective and randomized clinical trial in patients with stable CAD, which was registered on clinicaltrials.gov (NCT02168712). All patients underwent exercise testing with a cycle ergometer including analysis of exhaled gases.

The main study inclusion criteria were: 1) Stable New York Heart Association functional class I or II CAD with angina pectoris or myocardial infarction and no heart failure; 2) No change in medication during the study; 3) Included between 6 and 12 weeks following the cardiac event, elective percutaneous coronary intervention, or coronary artery bypass grafting; 4) Achieve the first (VT₁) and second (VT₂) ventilatory thresholds in the initial and final (cardiopulmonary exercise test [CPET]) and 5) Achieve a respiratory exchange ratio ≥ 1.10 in both CPET. Patients who had residual ischemia (by electrocardiogram criteria or angina symptoms), severe ventricular arrhythmias, uncontrolled hypertension, permanent pacemakers, or implanted cardiac defibrillators were excluded.

Patients were randomized on a one-to-one basis to either the MCT or the HIIT group. The mode of exercise training was a cycle ergometer with 40 min per session, 3 days per week (total of 24 sessions over 2 months).

Selected CPET variables and ME measurement were recorded before and after the exercise program. ME (expressed as a percentage) was calculated during an incremental maximal cycling test at stages corresponding to VT₁, VT₂ and VO_{2peak}. CPET were administered by staff who were unaware of the exercise training group the patients were assigned.

The study complies with the Declaration of Helsinki and was approved by the Local Ethics Committees, and written informed consent was obtained from each participant.

Characteristics and medication use of the patients are shown in Table 1.

Cardiopulmonary exercise test

The test was performed on an electro-mechanically braked cycle ergometer (Ergoline900S). The cycling position, which is known to affect

Table 1. Patient characteristics and medication use.

	MCT (n = 53)	HIIT (n = 57)	p
Age [years]	58.3 ± 9.5	57.6 ± 9.8	0.752
Men	42 (79.2%)	50 (87.7%)	0.234
Body mass index [kg/m ²]	27.8 ± 3.7	29.1 ± 3.9	0.909
Waist circumference [cm]	98.7 ± 8.9	101 ± 14.3	0.879
Hip circumference [cm]	102.1 ± 6.8	103.5 ± 8.1	0.353
Cardiovascular risk factors:	3.9%	11.3%	
Family history	47.2%	42.1%	0.743
Hypertension	47.1%	49.1%	1.000
Diabetes mellitus	24.5%	25.4%	1.000
Dyslipidemia	52.8%	58.8%	0.743
Smoking	73.6%	82.3%	0.754
Stroke	5.6%	3.5%	1.000
Peripheral vascular disease	7.8%	5.7%	1.000
Hyperuricemia	3.9%	11.3%	1.000
Heart disease factors:			
LVEF [%]	60.3 ± 9.7	61.2 ± 10.1	0.622
Intervention:			
Conservative	9.4%	8.8%	1.000
PCI	79.3%	82.4%	0.531
CABG	11.3%	8.7%	0.429
Drugs administered:	21.6%	20.7%	
Beta-blockers	90.1%	86.8%	1.000
Calcium channel blockers	13.2%	19.3%	0.684
ACE-inhibitors	88.2%	81.1%	0.897
Angiotensin receptor antagonists	17.6%	16.9%	1.000
Nitrates	15.6%	7.5%	0.497
Antiplatelet agents	97.3%	97.4%	1.000
Acenocoumarol	9.4%	5.4%	0.596
Statins	96.7%	100.0%	0.828
Ezetimibe	5.6%	5.3%	1.000
Antidiabetics	21.6%	20.7%	1.000

ACE — angiotensin converting enzyme; CABG — coronary artery bypass graft; HIIT — high-intensity interval training; LVEF — left ventricular ejection fraction; MCT — moderate continuous training; PCI — percutaneous coronary intervention

energy expenditure, was standardized by adopting a top bar position. Saddle height was adjusted according to the participant's leg length and knee flexion was between 20 and 30 degrees. Toe-clips were used and participants were instructed to stay seated during the test. Patients were required to maintain a constant pedal cadence between 50 and 70 revolutions per minute.

An individualized exercise protocol was performed in all patients and was tailored to each patient's physical condition, with gradual increments of 10, 15, or 20 W/min. Required exercise time was between 6 and 12 min in order to

respect the proper kinetics of oxygen consumption (VO_2) and to maintain a linear relationship between VO_2 , exercise workload and heart rate (HR) during CPET. The same protocol was applied before and after the exercise training program. Throughout the test, patients were kept under continuous 12-lead electrocardiographic-monitoring, and blood pressure was established every 3 min.

VO_2 was determined breath by breath using an automated system (UltimaCardiO2, Medical Graphics Corporation, St. Paul, Minnesota, USA). The gas analysers were calibrated before each test.

Table 2. Program designs for moderate continuous training (MCT) group or high intensity interval training (HIIT) group.

Week	Warm-up time and intensity (MCT and HIIT)	Exercise time and intensity	Cool-down time and intensity (MCT and HIIT)
1	12 min (25 watts)	MCT: 15 min at VT ₁ HIIT: 15 repetition (*)	13 min (25 watts)
2	10 min (25 watts)	MCT: 20 min at VT ₁ HIIT: 20 repetition (*)	10 min (25 watts)
3	7 min (25 watts)	MCT: 25 min at VT ₁ HIIT: 25 repetition (*)	8 min (25 watts)
4	5 min (25 watts)	MCT: 30 min at VT ₁ HIIT: 30 repetition (*)	5 min (25 watts)
4–8	5 min (25 watts)	MCT: 30 min at VT ₁ + 10% HIIT: 30 repetition (**)	5 min (25 watts)

*20-second repetitions at 50% of the maximum load reached with the first steep ramp test (SRT) followed by 40-second of recovery period at 10% of the first SRT; **20-second repetitions at 50% of the maximum load reached with the second SRT followed by 40-second of recovery period at 10% of the second SRT; VT₁ — first ventilatory threshold

The VT₁ and VT₂ were determined following the method of ventilatory equivalents described by Skinner et al. [11]. VT₁ corresponds to an increment of the VE/VO₂ ratio without an increased VE/VCO₂ ratio, and with an increased concentration of oxygen fraction (PetO₂). VT₂ corresponds to an increment of the VE/VCO₂ ratio and a fractional decrease in the concentration of CO₂ (PetCO₂).

Training interventions

MCT-Program Designs. To design the intensity prescription in MCT-program, the HR reached at VT₁ were used and obtained during the pre-training CPET. During the second month, the intensity of the exercise was adjusted, increasing to a training HR that corresponded to VT₁ plus 10% [7, 8].

HIIT-Program Designs. To design the HIIT-program, the steep ramp test (SRT) protocol was used according to the methodology described by Meyer et al. [12] and described by the present work group in several articles [7, 8]. The maximum exercise load achieved (watts), was the exercise parameter used to design the HIIT-program for each patient. In the first month of training, 20-s repetitions at an intensity corresponding to 50% of the maximum load reached with the SRT (peak intervals) were followed by 40-s recovery periods at 10%. In the second month of training, the intensity of exercise was adjusted using the results of a new SRT.

The total duration of both modalities of training was 40 min per session throughout the exercise program (including warm-up and cool-down). Table 2

summarizes the exercise time and intensity progression for both MCT and HIIT. Patients enrolled in the study participated in other activities established in this cardiac rehabilitation program that were aimed at managing psychological stress and learning about cardiac health habits. They were also taught to devise a home walking program for the days on which they did not have to attend sessions in the hospital. The recommended intensity of walking was a perceived exertion of 11 to 13 on the Borg Scale.

Energy consumption and mechanical efficiency calculations

VO_{2net} was obtained by subtracting resting VO₂ from total VO₂ at each exercise stage. The net energy expenditure (EE) in watts was calculated as follows [13]: $(4.94 \times \text{RER} + 16.04) \times (\text{VO}_{2\text{net}}, \text{ in mL/min}) \times 60^{-1}$. ME was also calculated in net terms as follows [14]: $\text{work produced in Watts} \times (\text{EE net, in Watts}^{-1}) \times 100^{-1}$. EE and ME were obtained at intensities corresponding to VT₁, VT₂ and at VO_{2peak}. This method allowed a comparison of these variables in terms of relative exercise intensity [3].

Safety of the exercise training programs

To verify the safety of using this kind of aerobic exercise training, a daily record was made of any incidents or adverse effects that could limit the planned exercise.

Statistical analysis

Quantitative variables were described using means and standard deviations. The normality of

the data distribution was determined using the Kolmogorov-Smirnov test. To evaluate the effect of each exercise protocol on the quantitative variables, pre- and post-program values were compared using the Student dependent samples *t*-test. The effect was measured in absolute terms via the difference between the post-program values and those obtained before training. These changes were described with the mean and standard deviation. Comparisons between the two training programs were made using the Student *t* test in the case of quantitative variables and using the χ^2 test of association or Fisher exact test for qualitative variables. All comparisons were made using two-tailed tests, and the level of significance was set at $p < 0.05$. All statistical tests were performed using commercially available software (SPSS, Version 22.0, Inc., Chicago, IL, USA).

Results

A total of 110 patients were included and studied (53 patients in MCT-group and 57 patients in HIIT-group). At the start of the study, there were no significant differences between the groups with regard to clinical characteristics or medication use (as shown in Table 1).

Training data

The intensity of exercise in the MCT-group in the first month was $62.9\% \pm 7.6\%$ of the VO_{2peak} reached during the initial CPET (corresponding to the VT_1) and $69.8\% \pm 8.8\%$ in the second month (corresponding to $VT_1 + 10\%$). The exercise workload applied at the peak intervals in the HIIT-group using the Meyer et al. [12] methodology was $108.3\% \pm 20.7\%$ (first month) and $126.1\% \pm 27.8\%$ (second month) of the maximum load reached in the initial CPET, corresponding to 50% of the SRT in the first and second month. The resulting HR during first and second month in HIIT-group was between VT_1 and VT_2 .

Cardiopulmonary exercise test

The exercise effort test results for both groups can be seen in Table 3. After 8 weeks of training both exercise programs significantly increased their VO_{2peak} , the peak exercise workload achieved and the total time of the exercise effort test with a greater increase in the HIIT-group ($p < 0.05$).

The VO_2 at VT_1 and VT_2 significantly increased in both groups, with a significantly higher increase in the HIIT-group ($p < 0.05$). The power at VT_1 significantly increased in both groups, with a

greater increase in the HIIT-group ($p < 0.01$), but the power at VT_2 only significantly increased in HIIT-group ($p < 0.001$).

Energy expenditure and mechanical efficiency values

Energy expenditure determined at VT_1 , VT_2 and at VO_{2peak} (Table 3) increased significantly post-training compared to baseline values in both groups but with a significantly higher increase in the HIIT-group.

Mechanical efficiency measured at VT_1 , VT_2 , and at VO_{2peak} is reported in Table 3. At VT_1 , ME significantly increased in both groups, with a greater increase in the HIIT-group ($p < 0.01$). The ME at VO_{2peak} and VT_2 only significantly increased in the HIIT-group ($p < 0.001$).

Safety of the training intervention

No incidents or adverse events were recorded that limited the ability of patients to perform the prescribed exercise in either training program.

Discussion

According to available research, this study is the first to examine ME changes in response to 8 weeks of HIIT in patients with CAD. The most relevant finding of the present research was a greater increase in ME of the HIIT-group over MCT-group in intensities related to VT_1 , and a significant increase in the ME at VO_{2peak} and VT_2 in the HIIT-group alone.

Exercise carried out at an intensity greater than VT_2 necessitated an increase of energy contribution of the glycolytic pathway, even when oxidative energetic provision is predominant. Glycolytic activation disturbs the internal cell environment of the muscles involved in the exercise. This means that the mechanism of the excitement-contraction is negatively affected, progressively contributing to the onset of muscular fatigue. This process is related to the muscular capacity to work, and therefore negatively affects mechanical efficiency.

HIIT is a training system that has as its main objective the improvement of VO_{2peak} , but due to the relative high intensity which is applied ($> VT_2$), it is also the cause of improvements related to glycolytic metabolism in type II muscular fibres. This provides an improvement in energetic efficiency, in the development of strength and in resistance to fatigue, meaning an improvement in ME.

A relatively high cost of ATPs for muscular contraction is the main cause of the low ME ob-

Table 3. Cardiopulmonary exercise stress test variables in moderate continuous training (MCT) group versus high intensity interval training (HIIT) group at maximal intensity, VT₁ and VT₂.

	MCT group			HIIT group		
	Pretraining	Posttraining	Change	Pretraining	Posttraining	Change
Total exercise time [min]	8.32 ± 1.73	9.67 ± 2.10***	1.35 ± 1.03	8.29 ± 1.69	10.23 ± 2.34***	1.93 ± 1.24 [†]
VO ₂ peak [mL/kg/min]	19.50 ± 5.26	22.47 ± 5.71***	2.96 ± 2.33	18.90 ± 4.63	22.78 ± 5.75***	3.88 ± 2.40 [†]
Maximum HR [bpm]	119.19 ± 16.56	123.58 ± 17.84**	4.39 ± 10.97	118.98 ± 16.55	126.47 ± 16.24***	7.49 ± 10.18
Maximum power [W]	114.52 ± 33.94	132.64 ± 41.24***	18.11 ± 16.11	115.78 ± 37.17	153.07 ± 43.99***	38.86 ± 20.11 [†]
Maximum RER	1.18 ± 0.08	1.19 ± 0.08	0.01 ± 0.09	1.16 ± 0.08	1.16 ± 0.07	0.01 ± 0.08
EE [W]	420.81 ± 153.41	501.15 ± 165.91***	80.34 ± 63.94	423.78 ± 148.93	534.82 ± 190.53***	111.03 ± 77.69 [†]
ME [%]	25.61 ± 4.98	24.91 ± 4.09	-0.70 ± 4.14	24.84 ± 5.99	26.98 ± 5.41***	2.14 ± 3.97 [†]
VO ₂ at VT ₁ [mL/kg/min]	10.97 ± 2.74	12.05 ± 2.85***	1.08 ± 1.64	10.40 ± 1.97	12.34 ± 2.45***	1.94 ± 1.42 [†]
HR at VT ₁ [bpm]	86.13 ± 10.38	85.26 ± 10.80	-0.86 ± 5.68	87.09 ± 10.30	89.49 ± 11.20***	2.40 ± 6.42 [†]
Power at VT ₁ [W]	49.18 ± 18.57	59.94 ± 21.23***	10.76 ± 11.55	49.73 ± 18.32	73.64 ± 19.30***	23.91 ± 10.63 [†]
RER at VT ₁	0.87 ± 0.06	0.86 ± 0.06	0.01 ± 0.05	0.88 ± 0.06	0.85 ± 0.06 [†]	0.02 ± 0.07
EE [W] at VT ₁	166.96 ± 74.74	192.41 ± 77.15***	25.45 ± 42.64	155.44 ± 59.27	207.02 ± 70.45***	51.58 ± 45.79 [†]
ME [%] at VT ₁	24.57 ± 5.94	26.78 ± 7.15 [†]	2.20 ± 6.25	24.61 ± 7.93	30.14 ± 8.27***	5.52 ± 5.53 [†]
VO ₂ at VT ₂ [mL/kg/min]	15.39 ± 4.12	17.09 ± 4.34***	1.69 ± 2.01	14.64 ± 3.76	17.13 ± 4.19***	2.49 ± 1.94 [†]
HR at VT ₂ [bpm]	103.11 ± 15.30	103.92 ± 16.00	0.81 ± 7.30	101.81 ± 13.21	106.11 ± 14.24**	4.29 ± 8.25 [†]
Power at VT ₂ [W]	87.34 ± 30.79	99.49 ± 33.36	12.15 ± 14.53	86.26 ± 30.34	114.08 ± 32.18***	27.82 ± 13.30 [†]
RER at VT ₂	1.03 ± 0.06	1.02 ± 0.08	-0.01 ± 0.07	1.02 ± 0.07	1.00 ± 0.06 [†]	-0.02 ± 0.07
EE [W] at VT ₂	294.74 ± 116.70	338.35 ± 124.08***	43.61 ± 57.51	285.37 ± 114.51	353.76 ± 132.99***	68.38 ± 61.30 [†]
ME [%] at VT ₂	26.76 ± 5.97	27.01 ± 5.17	0.25 ± 4.94	26.32 ± 7.09	29.55 ± 7.12***	3.23 ± 4.95 [†]

*Within-group difference < 0.05; ** Within-group difference < 0.01; *** Within-group difference < 0.001; †Between-group difference < 0.05; ‡Between-group difference < 0.01; HR — heart rate; W — watts; RER — respiratory exchange ratio; VT₁ — ventilatory threshold 1; VT₂ — ventilatory threshold 2; EE — energy expenditure; ME — mechanical efficiency; VT — ventilatory threshold

served in many patients with a cardiovascular pathology [1]. In this context, the improvement in ME (a lower cost of ATPs for the same muscular effort applied) is essentially determined by the improvement of ATP consumption from myosin-ATPase and noncontractile processes related to ion transport associated with the contraction-relaxation cycle (mainly calcium ATPase and to a lesser extent due to Na-K-ATPase). Therefore, any improvement of one of these processes would explain the fall in energy cost of contraction at any exercise intensity level (e.g. VT_1 , VT_2 , VO_{2peak}) [1].

The energy required to sustain a given bicycle workload has been previously shown to be correlated with body mass [15, 16]. In the present study, bodyweight decreases in the same proportion in the two training groups during the intervention period, which rules out body mass as an influential factor in the observed modification of ME in the HIIT-group.

A lower O_2 for the same production of power during the bicycle workload could be the result of: 1) A lower ATP cost of the muscular contraction for the same production of effort (an improvement in muscle contraction efficiency); and/or 2) A lower VO_2 for the same level of ATP oxidative resynthesis (an improvement in mitochondrial efficiency). HIIT was able to increase VO_{2peak} , maximum load (W_{max}) and ME to a greater extent, especially by improving the internal cell environment of the muscles active during exercise. However, some authors are of the opinion that the typical short-term adaptations to endurance training such as increased oxygen delivery [17], muscle capillarization and mitochondrial content [18], among others, have a limited impact on ME, meaning that improvements in muscle motor function cannot be excluded as a key element in the improvement of ME.

Moreover, type II muscle fibres have been demonstrated to be substantially less efficient than type I fibres during cycling, as reflected by higher VO_2 in performing exercise at a given power output [19]. Training in aerobic resistance, such as the one employed in the two groups of this study, especially reinforces the oxidative capacity of type I fibres, being able to sustain greater exercise intensity (greater levels of applied resistance). This fact would result in a greater ME.

In athletes HIIT improvement in “metabolic stability” (e.g. reduced changes in concentrations of muscle metabolites such as ADP, AMP, inosine-monophosphate, creatine, inorganic phosphate, and H^+ for a given ATP turnover) may be crucial to limit muscle fatigue, VO_2 slow component, and ME impairment occurring at heavy and severe ex-

ercise intensities, particularly through a decrease in the ATP use/power output ratio [20]. Although HIIT in coronary patients are of a less demanding nature from a metabolic point of view, the attainment of partial biochemical muscular adaptations which contribute to the improvement in “metabolic stability” may be speculated upon, and with it ME.

Mechanical inefficiency is mainly related to inactivity and it seems that the exercise intolerance promoted by the disease makes the patients less physically active, with a detraining effect on their peripheral muscles [21]. Lower ME indicates that more energy is consumed at a given work output. Therefore, individuals with lower ME values should be less efficient with respect to performance and may therefore be limited in terms of physical activity [2]. Consequently, an improvement in ME in patients with central limitation (cardiac), will contribute to an improvement in exercise capacity.

Different studies have shown greatest VO_{2peak} improvements in HIIT respect to continuous load training [7, 8, 22]. In the present research, both exercise programs significantly increased their VO_{2peak} , with a greater increase in the HIIT-group (difference between group: $p < 0.05$).

In line with the increase of VO_{2peak} , the maximum load reached increased significantly more in the HIIT-group ($p < 0.001$), reflecting an improvement in the base-acid balance with peak loads.

The two groups of this study improved VO_2 and the load (W) associated with VT_1 and VT_2 , with greater improvements in HIIT. Similar results were found in other research studies [23, 24], however other authors have not observed differences associated to the modality of training [7, 8, 25, 26]. While in research conducted by Moholdt and Rognmo the different protocols used may justify the lack of concordance in the results, in previous studies [7, 8], in which a trend for a greater improvement was found in VO_2 and W associated with VT_1 , the greater number of patients included in the study meant that the trend had a statistical significance. Physiological variables associated with VT_2 were observed — not an usual occurrence in clinical trials with cardiac patients. HIIT constitutes a training method with a clear objective of improvement in oxidative or aerobic status, but on attaining intensities greater than VT_2 , it significantly improves the glycolytic and lactate clearance processes.

Focus on HR related to VT_1 and VT_2 , this factor only increased in the HIIT-group, reflecting peripheral metabolic adaptations that allow for sustaining a greater workload. The same results were observed previously [8] suggesting that the

HR associated with ventilatory thresholds are perhaps not a valid variable reflecting an adaptation to exercise.

Additionally, HIIT seems to be a safe exercise modality and did not differ in frequency or magnitude of cardiovascular adverse events during exercise training as compared with MCT, as was shown previously [7].

Conclusions

The results of the present research show that the application of HIIT to patients with chronic ischemic heart disease of low risk resulted in a greater improvement in VO_2 peak and in ME at VT_1 , than when MCT was applied. Moreover, only the application of HIIT brought about a significant increase in ME at VT_2 and at VO_2 peak.

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6. DISCUSION

6 DISCUSIÓN

Todos los meta-análisis de los últimos años han objetivado que el HIIT es más eficaz que el ECMI a la hora de mejorar la capacidad funcional aeróbica y otras variables predictoras de riesgo cardiovascular (Arena et al., 2013; Cornish et al., 2011; Rognum et al., 2004; Smart et al., 2013; Wisløff et al., 2007), en pacientes con enfermedad coronaria.

Los cambios objetivables se pueden agrupar en variables obtenidas en esfuerzo máximo durante una prueba de esfuerzo, variables de carácter submáximo, índices de recuperación después de la realización de la prueba de esfuerzo, eficiencia mecánica, indicadores de calidad de vida y registro de incidencias durante el programa de ejercicio físico.

6.1 Cambios en variables máximas en una ergoespirometría después de completar un programa de entrenamiento aeróbico (ECMI vs HIIT).

6.1.1 VO₂ pico.

En nuestro estudio (Jaureguizar et al., 2016), a pesar de que el VO₂ pico aumentó en ambos grupos tras 8 semanas de entrenamiento aeróbico, la mejoría fue significativamente mayor en el grupo que entrenó a alta intensidad. Tras la aleatorización de 72 pacientes con CI, el aumento medio del VO₂ pico fue de $4,5 \pm 4,7$ ml·kg⁻¹·min⁻¹ en el grupo HIIT y de $2,5 \pm 3,6$ ml·kg⁻¹·min⁻¹ en el grupo ECMI (diferencias entre grupo p<0,05). Resaltar que al aumentar el tamaño muestral (110 pacientes) aplicando el mismo protocolo de entrenamiento, la diferencia entre grupos en la mejora del VO₂ pico se mantuvo a favor del HIIT (Villegas-Jaureguizar et al., 2018).

Estos resultados son de gran interés, no solo por el aumento de la condición física o capacidad funcional del paciente sino por el beneficio potencial que representa este incremento del VO₂ pico en la supervivencia de los pacientes como factor pronóstico (Kodama et al., 2009). Por tanto y debido a que el VO₂ pico es considerado como el mejor factor predictivo de supervivencia en pacientes con ECV, el HIIT podría contribuir en mayor medida a la reducción de la morbi-mortalidad.

Los mecanismos implicados en la superioridad de HIIT con respecto a ECMI no están del todo aclarados, habiéndose propuesto, entre otras justificaciones, la mayor activación de la proteína 1 α coactivadora (PGC-1 α) debido a la mayor intensidad de

ejercicio aplicada. [Bartlett 2012]. Esta proteína es considerada como la principal reguladora de la biogénesis mitocondrial del músculo esquelético, teniendo una implicación directa en la mejora del VO_2 pico (Little et al., 2011).

El incremento en la capacidad funcional (VO_2 pico) del 24% en el grupo HIIT y del 12% en el grupo ECMI, son similares a los mostrados por otros autores (Rognmo et al., 2004), pero quedan lejos de los resultados obtenidos por Wisløff y colaboradores (Wisløff et al., 2007) con mejoras del 46% en el HIIT y del 15% en el ECMI. Estas diferencias pueden ser debidas a que en el estudio de Wisløff y colaboradores, participaron pacientes con insuficiencia cardiaca y disfunción severa del ventrículo izquierdo (29%), con una capacidad funcional basal más deteriorada (VO_2 pico de $13 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$).

Resulta difícil comparar nuestros resultados con los aportados por otros autores debido a las diferencias en la metodología aplicada para diseñar los entrenamientos interválicos. Así, se han aplicado diferentes métodos de control de la intensidad aplicada en el intervalo y/o recuperación basadas en: % de VO_2 pico (Rognmo et al., 2004), en % del VO_2 de reserva (Warburton et al., 2005), en % de FC máxima (Madssen et al., 2014), en % de la FC de reserva (Keteyian et al., 2014) o, como el aplicado por nuestro grupo de trabajo, basado en el % de carga (Currie et al., 2013; Jaureguizar et al., 2016; Meyer et al., 1990; Villeda-Beitia-Jaureguizar et al., 2018). También existen diferencias en la duración de los intervalos (segundos y/o minutos), en el número, en el tipo de recuperación entre ellos (recuperaciones activas o pasivas) y en cuanto al número de sesiones por semanas. Toda esta heterogeneidad en el diseño de los protocolos HIIT puede constituir una limitación importante a la hora de comparar resultados debido a que la manipulación de estos parámetros altera de manera significativa la respuesta fisiológica (% del VO_2 de los entrenamientos) y como consecuencia de ello las adaptaciones alcanzadas (Cornish et al., 2011).

Nuestro grupo de trabajo estableció la intensidad de los entrenamientos interválicos bajo un control de carga (vatios) obtenido de un porcentaje de la carga máxima alcanzada en una prueba de esfuerzo en rampa denominada "Steep Ramp Test" (SRT). Nuestros resultados demuestran que las cargas aplicadas en los intervalos fueron de alta intensidad, al estar estas comprendidas entre 104% y 134% de la carga máxima alcanzada en la cicloergoespirometría inicial. Estudios previos (Meyer et al., 2012) demostraron que con esta metodología para el diseño de HIIT, los tiempos de estancia a una intensidad mayor del 85% de VO_2 pico durante los entrenamientos, eran suficientemente prolongados.

La mayoría de los estudios que comparan HIIT frente a ECMI, igualando el gasto de energía o la duración del ejercicio, han mostrado mejoras no solo en capacidad funcional (VO_2 pico), sino también en diferentes indicadores hemodinámicos de reposo como la función endotelial, así como cambios favorables en la función y/o morfología del ventrículo izquierdo (Moholdt et al., 2012a; Munk et al., 2009; Rognmo et al., 2004; Warburton et al., 2005; Wisløff et al., 2007). Sin embargo, otros autores (Conraads et al., 2015) observaron mejoras similares tanto en la capacidad de ejercicio como en la función endotelial tras aplicar HIIT o ECMI. Según los autores, una posible explicación de estos resultados contradictorios a los mostrados en estudios previos, podría ser que en el grupo HIIT las cargas aplicadas en los intervalos no fueron muy bien toleradas y por tanto, la intensidad real del ejercicio fue ligeramente menor que la intensidad prescrita (88% de la FC máxima en lugar de 90-95%). Por otro lado, los pacientes del grupo ECMI toleraron muy bien los entrenamientos, incluso entrenaron a intensidades superiores a las prescritas (80% de FC máxima en lugar de 70-75%). Esta escasa diferencia en cuanto a la intensidad de los entrenamientos (88% del HIIT frente al 80% en ECMI) podría justificar la ausencia de diferencias significativas obtenidas entre ambos protocolos.

Meta-análisis publicados posteriormente continúan demostrando la superioridad del HIIT frente al entrenamiento continuo de intensidad moderada en cuanto a la mejora de la condición física aeróbica en pacientes con cardiopatía isquémica (Elliott et al., 2015; Gomes-Neto et al., 2017; Hannan et al., 2018; Liou et al., 2016; Pattyn et al., 2014). No obstante, esas diferencias se minimizan en algunos estudios o incluso desaparecen cuando en el sub-análisis se comparan protocolos isocalóricos (Gomes-Neto et al., 2017).

6.1.2 Carga máxima.

En línea con el aumento del VO_2 pico, también pudimos comprobar que la carga máxima alcanzada aumentó significativamente más en el grupo HIIT tras 8 semanas de entrenamiento (ECMI $13,1 \pm 19,3$ vatios vs HIIT: $26,3 \pm 23,5$ vatios; diferencias entre grupos $<0,05$). A medida que aumentó el tamaño muestral la diferencia entre grupos se hizo cada vez más significativa (diferencias entre grupos $p<0,01$) (Vilhelbeitia-Jaureguizar et al., 2018).

La capacidad de alcanzar una mayor carga de trabajo en la prueba de esfuerzo, es decir, de aumentar el tiempo de estancia en la misma hasta el agotamiento, depende de múltiples factores, algunos centrales y otros periféricos. En nuestro caso, se constataron adaptaciones musculares periféricas significativas que llevaron a mejoras en el segundo umbral ventilatorio, aproximando en términos relativos la intensidad asociada al VT_2 con la carga máxima. Una parte de esa adaptación se basa en una mejora del equilibrio ácido-base que se va a reflejar en la tolerancia al esfuerzo cerca de la carga máxima. La intensidad aplicada en el HIIT supera a la carga de trabajo correspondiente al VT_2 , asociándose a mejoras en la capacidad buffer muscular y sanguíneo permitiendo tolerar mayores desequilibrios en el balance ácido-base y con ello prolongar el tiempo hasta la fatiga (Peña et al., 2013).

Además, la mejora de la obtención de energía por la ruta oxidativa (VO_2 pico), debida a cambios centrales (función cardíaca) y periférica (aumento de capilaridad muscular y activación de enzimas oxidativas) posibilita que la implicación del metabolismo glucolítico se retrase para la misma intensidad de esfuerzo y con ello que la alteración del medio interno celular en los tejidos musculares activos en el ejercicio ocurra a mayores intensidades de ejercicio.

6.1.3 Frecuencia cardíaca máxima.

En nuestro primer estudio (Jaureguizar et al., 2016), la FC máxima alcanzada en la ergoespirometría tras finalizar el programa de entrenamiento fue mayor que la inicial en el grupo de HIIT (115 ± 14 lpm vs 126 ± 14 lpm; $p<0,001$), sin apreciar cambios en el grupo de ECMI (118 ± 20 vs 119 ± 20 lpm; $p=0,58$). Sin embargo, en el tercer estudio (Vilhelbeitia-Jaureguizar et al., 2018) la FC máxima alcanzada en la ergoespirometría post-programa fue mayor que la inicial con ambos protocolos sin

apreciar diferencias entre HIIT (119 ± 17 lpm vs 126 ± 16 lpm; $p < 0,001$) y ECMI (119 ± 17 vs 124 ± 18 ; $p < 0001$).

Hay que tener en cuenta que la principal limitación para alcanzar la frecuencia cardíaca máxima en estos pacientes no es habitualmente central, sino periférica. Dado que las mayores adaptaciones con el entrenamiento en estos pacientes se sitúan a nivel del músculo esquelético, la fatiga periférica se retrasará y por tanto se podrá alcanzar una mayor intensidad de ejercicio y con ello acercarse al techo de la respuesta cronotrópica del paciente. Las adaptaciones celulares en los cardiomiocitos ligadas al ejercicio, incluidas la velocidad del ciclo del Ca^{2+} y la sensibilidad al Ca^{2+} son factores que pueden contribuir también en la respuesta de la frecuencia cardíaca.

Con los resultados de nuestros estudios, no podemos afirmar que el entrenamiento HIIT se asocie en mayor medida que el entrenamiento continuo de moderada intensidad, a mayores incrementos de los valores de la frecuencia cardíaca máxima en una prueba de esfuerzo incremental.

6.2 Cambios en variables submáximas en una ergoespirometría después de completar un programa de entrenamiento aeróbico (ECMI vs HIIT).

El entrenamiento de resistencia aeróbica, además de mejorar el VO_2 pico asociado al máximo nivel de esfuerzo del paciente, así como la intensidad máxima tolerada y, en algunos casos, la frecuencia cardíaca máxima, también mejora variables fisiológicas vinculadas a intensidades submáximas de ejercicio. Estas variables tienen la ventaja de que no dependen de la voluntad del paciente de continuar el esfuerzo, ya que acontecen a intensidades bien toleradas, y por consiguiente sus valores suelen ser más objetivos. También constituyen herramientas muy útiles tanto para comprobar la eficacia de los programas de ejercicio, como sobre todo para poder individualizar la carga de trabajo en los programas de rehabilitación cardíaca.

6.2.1 Umbral ventilatorio 1 (VT₁).

En nuestro trabajo, ambos grupos de entrenamiento aumentaron tanto el VO₂ (ml kg⁻¹ min⁻¹) como la carga (vatios) asociados al primer y segundo umbral ventilatorio (VT₁ y VT₂) con mayores incrementos a favor del HIIT. El mayor número de pacientes incluidos a lo largo del estudio (Vilhelbeitia-Jaureguizar et al., 2018), dio como resultado que la tendencia del valor estadístico del VT₁ aumentase a favor del HIIT (Grupo HIIT: 1,9 ± 1,4 ml kg⁻¹ min⁻¹; Grupo ECM 1,0 ± 1,6 ml kg⁻¹ min⁻¹; diferencias entre grupos p<0,05). Estos resultados, reflejan adaptaciones al entrenamiento especialmente a nivel periférico o muscular, posibilitando a los pacientes realizar más trabajo a un nivel submáximo antes de entrar en fatiga, representando en suma una mejora de la capacidad aeróbica sin acentuar el trabajo cardiovascular (Arena et al., 2013; Myers and Ashley, 1997). En este sentido, este cambio del VT₁ hacia intensidades y/o cargas superiores, justifica el aumento observado en los metros recorridos durante la prueba de los seis minutos caminando (6MWD) (Jaureguizar et al., 2016). Así, una vez finalizado el PRCV, la mejora se produjo en los pacientes de ambos grupos de entrenamiento, pero con una diferencia entre grupos a favor del HIIT (Grupo HIIT: 49,6 ± 6,3 metros; Grupo ECMI 29,6 ± 12 metros; p<0,05). El aumento de la distancia recorrida en el test de 6MWD refleja especialmente las adaptaciones metabólicas que se producen tras un programa de entrenamiento físico.

Los trabajos de investigación que analizan los cambios asociados al VT₁ son escasos y estadísticamente muy heterogéneos, ya que la mayoría de los estudios que comparan ECMI frente a HIIT se centran en el VO₂ pico. Las investigaciones llevadas a cabo por Currie y Keteyian, muestran resultados similares a los nuestros (Currie et al., 2013; Keteyian et al., 2014). Sin embargo, otros autores no han observado diferencias asociadas entre ninguna de las modalidades de entrenamiento (Moholdt et al., 2012a; Rognum et al., 2012). Esta falta de concordancia podría estar justificada por los diferentes protocolos y/o metodologías utilizadas, así como por el número de pacientes incluidos en los estudios. A favor de nuestros resultados estaría la mayor potencia estadística con una muestra de 110 pacientes entrenados (Vilhelbeitia-Jaureguizar et al., 2018).

6.2.2 Umbral ventilatorio 2 (VT₂).

Por otra parte, también se pudo objetivar una mejora de la tolerancia a la acidosis en ambos grupos de entrenamiento, produciéndose un desplazamiento del segundo umbral ventilatorio (VT₂) hacia valores más cercanos del VO₂ pico. El mayor número de pacientes incluidos a lo largo del estudio (Vilhelbeitia-Jaureguizar et al., 2018), dio como resultado que la tendencia del valor estadístico aumentase a favor del HIIT (Grupo HIIT: $2,4 \pm 1,9$ ml·kg⁻¹·min⁻¹ Grupo ECM $1,6 \pm 2,0$ ml·kg⁻¹·min⁻¹; diferencias entre grupos <0,05). Esta mejora, podría ser debida a una mayor tasa metabólica durante estos entrenamientos (mejora de los procesos glucolíticos) y a una mayor capacidad para eliminar o tamponar los protones (H⁺) acumulados durante el ejercicio incremental (Meyer et al., 2012). Este cambio en el segundo umbral ventilatorio, posibilita a los pacientes a entrenar a intensidades más elevadas y seguras, sin producir los cambios metabólicos indeseables y vinculados a la fatiga, al superar la intensidad correspondiente al VT₂ (Díaz-Buschmann et al., 2014).

En este sentido, no hemos encontrado ninguna evidencia respecto al VT₂ relacionado con el HIIT en pacientes con ECV para poder comparar resultados.

6.3 Cambios en la frecuencia cardiaca de recuperación tras una ergoespirometría después de completar un programa de entrenamiento aeróbico (ECMI vs HIIT).

Otra de las principales aportaciones de este estudio fue constatar que la mejora de la recuperación de la frecuencia cardiaca del primer y segundo minuto tras una prueba de esfuerzo incremental hasta el agotamiento (RFC-1 y RFC-2), estaba asociada al grupo de pacientes que entrenaron con la metodología HIIT (Vilhelbeitia-Jaureguizar et al., 2017).

6.3.1 Recuperación de la frecuencia cardiaca al minuto de iniciar la recuperación (RFC-1).

Los resultados solo mostraron mejoras (recuperaciones más rápidas) en el grupo HIIT (pre-programa: $15,4 \pm 7,0$ lpm; post-programa: $21,2 \pm 6,6$ lpm; $p < 0,001$), sin apreciar cambios significativos en el grupo ECMI. Estos hallazgos sugieren que el HIIT es más efectivo modificando el balance simpático-vagal del ritmo cardiaco hacia un

incremento del tono parasimpático, lo cual se ha asociado hacia un mejor pronóstico en estos perfiles de pacientes cardíacos.

Nuestro estudio mostró que los pacientes incluidos en ambas modalidades de entrenamiento (ECMI vs HIIT), partían de unos valores promedios de RFC-1 (pre y post entrenamiento) superiores al punto de corte clínico establecido como normal (>12 lpm). Sin embargo, hay que resaltar que 16 de los 73 pacientes incluidos en nuestro estudio (21,9%) no llegaron a una RFC-1 de 12 lpm en la valoración previa al inicio del programa de ejercicio. Tras finalizar el programa de ejercicio, tan solo 7 pacientes mantuvieron su RFC-1 por debajo del límite de <12 lpm, destacando en este sentido la eficacia del HIIT que redujo en un 81,8% el número de pacientes por debajo de este límite clínico patológico. De acuerdo con esto, la RFC-1 podría ser un buen indicador de la efectividad de los PRCV, así como para estratificar el riesgo del paciente.

Diferentes investigaciones han mostrado mejoras de los índices de recuperación de la frecuencia cardíaca con el entrenamiento aeróbico. Mahdavi Anari y colaboradores, observaron que después de un periodo de entrenamiento de 12 semanas, la RFC-1 mejoraba significativamente (de $13,7 \pm 1,3$ lpm a $17,0 \pm 1,3$ lpm) (Mahdavi Anari et al., 2015). Estos cambios favorables con respecto a la mejora del índice de RFC-1 ocurrieron de manera similar tanto en los pacientes sometidos a una revascularización percutánea como a una revascularización quirúrgica. Por otro lado, las investigaciones llevadas a cabo por Ribeiro y Tiuhinhoy también observaron resultados similares en la mejora de la RFC-1 tras 8 semanas de ejercicio físico programado (Ribeiro et al., 2012; Tiuhinhoy et al., 2003).

Sin embargo, los estudios que valoran las modificaciones de la RFC-1 comparando los programas de ECMI con programas HIIT son muy limitados y con resultados estadísticos muy heterogéneos. Así, en el estudio de Dimopoulos y colaboradores, tan solo mejoraron la RFC-1 los pacientes que realizaron un ECMI, sin apreciar cambios en el grupo HIIT (Dimopoulos et al., 2006). Otras investigaciones (Kim et al., 2015; Moholdt et al., 2012b) documentaron un incremento significativo de la RFC-1 en ambos grupos de entrenamiento pero sin diferencias significativas entre grupos. Otros estudios en cambio, no apreciaron cambios de la RFC-1 en ninguna de las modalidades (Currie et al., 2013; Keteyian et al., 2014; Madssen et al., 2014). Esta falta de concordancia en los resultados podría estar justificada por los diferentes protocolos y metodologías utilizadas.

6.3.2 Recuperación de la frecuencia cardiaca al segundo minuto de iniciar la recuperación (RFC-2).

En contraste con la mayoría de las investigaciones previas llevadas a cabo en HIIT, donde únicamente analizan la RFC-1 tras un ejercicio extenuante (Giallauria et al., 2006; Hai et al., 2010; Tsai et al., 2005; Wu et al., 2006), nosotros también analizamos la RFC-2 post-esfuerzo. Ambos índices (RFC-1 y RFC-2), han mostrado tener una relación directa con la morbi-mortalidad cardiovascular, aunque la RFC-2 post-ejercicio parece tener una capacidad pronóstico mayor que la RFC-1 (Shetler et al., 2001). Por esta razón, sugerimos la necesidad de añadir de manera sistemática la valoración de la RFC-2 post-esfuerzo en pacientes con ECV.

La fase lenta de la recuperación cardiaca (RFC-2) se atribuye a una disminución de la actividad simpática (activación reducida de los mecanorreceptores y quimiorreceptores de los músculos periféricos) y a factores humorales como las catecolaminas (Jouven et al., 2005; Kannankeril et al., 2004; Perini et al., 1989). A diferencia de lo que ocurre en la fase rápida de la RFC (≤ 1 min), la fase lenta (≥ 2 min) depende claramente de la intensidad y la duración del ejercicio realizado (Hart et al., 2006; Imai et al., 1994), condicionando la normalización del estrés metabólico asociado (Al Haddad et al., 2012; Perini et al., 1989).

Los resultados de nuestro estudio tan solo apreciaron cambios de la RFC-2 en el grupo de pacientes que entrenaron con la metodología HIIT (pre-programa $23,7 \pm 9,6$ lpm; post-programa $31,5 \pm 8,0$ lpm; $p < 0,001$), sin apreciar cambios en el grupo ECMI. Estos resultados sugieren que los entrenamientos HIIT adquieren una mayor capacidad para normalizar el estrés metabólico asociado al ejercicio físico (Al Haddad et al., 2012).

Aunque una RFC-2 de < 22 lpm, es el valor más utilizado para considerarlo como clínicamente anormal (Shetler et al., 2001), algunas investigaciones han mostrado aumentos del riesgo de mortalidad con un RFC-2 de < 42 lpm (Cole et al., 1999). De acuerdo con este último criterio (RFC-2 ≤ 42 lpm), tan solo 6 de nuestros pacientes (8,2%) estaban por encima de este límite antes de comenzar el programa de ejercicios, y lo alcanzaron 13 pacientes (17,8%) tras finalizarlo. Mientras que el grupo ECMI logró tener 3 pacientes más por debajo de este límite (RFC-2 ≤ 42 lpm), en el grupo HIIT se incorporaron 4 pacientes nuevos, sugiriendo una mayor efectividad de la metodología HIIT. A diferencia del gran número de estudios que han analizado la RFC-

1, los que han investigado la RFC-2 son muy escasos lo que significa que no hay un punto de corte claro establecido como normal desde un punto de vista clínico.

Los trabajos de investigación que analizan la modificación de la RFC-2 comparando los programas de ECMI con programas HIIT son muy limitados. Tan solo hemos encontrado un estudio (Currie et al., 2013) en el cual no se aprecian cambios en la RFC-2. Posiblemente esta discordancia con nuestros resultados sea debida al menor número de pacientes incluidos en el estudio de Currie y colaboradores (7 pacientes en cada grupo), y nuevamente al protocolo HIIT aplicado.

Teniendo en cuenta que para el cálculo del índice de la RFC-1 y RFC-2 partíamos de una prueba de esfuerzo máxima (criterio de inclusión del ensayo: coeficiente respiratorio $\geq 1,10$), propusimos que además de medir estos índices en valores absolutos (FC pico - RFC-1 y FC pico - RFC-2), era también adecuado medirlo como un porcentaje de la FC pico, registrándolo tanto en el primer minuto como en el segundo minuto de la recuperación (%RFC-1/FC pico vs %RFC-2/FC pico). Expresar los resultados de la RFC en valores relativos a una FC pico, podría ser aplicable a todos los sujetos independientemente de la edad. En este sentido y, al igual que sucedió en valores absolutos, tan sólo el grupo HIIT mejoró el índice de RFC relativo a la FC pico, tanto en el primer minuto (de $13,3 \pm 6,0\%$ a $16,8 \pm 4,9\%$; $p = 0,003$) como en el segundo minuto (de $20,5 \pm 7,7$ a $25,0 \pm 5,3$; $p < 0,0001$). Los valores medios post-entrenamiento en el primer minuto fueron de $16,8\%$ y $17,9\%$ para el grupo HIIT vs ECMI respectivamente y en el segundo minuto fueron de $25,0\%$ y $26,2\%$ para el grupo HIIT vs ECMI respectivamente. En este sentido podemos destacar la eficacia del HIIT independientemente de la edad en cuanto a mejoras del equilibrio neurovegetativo.

La razón fisiopatológica por la cual una RFC anormal se asocia con un peor pronóstico clínico no está clara. De acuerdo con Huang y colaboradores, existe una estrecha relación entre el tono autonómico y la función endotelial, demostrando como una actividad parasimpática disminuida y un tono simpático incrementado, puede conducir a largo plazo a una disfunción endotelial (Huang et al., 2004). Estos autores, comprobaron que una respuesta pobre de la RFC predecía una disfunción endotelial, eventos cardiovasculares y aumento de la mortalidad global. Por lo tanto, la RFC-1 y RFC-2 pueden ser indicadores útiles para estratificar el riesgo de los pacientes después de completar un programa de rehabilitación. Otro factor que podría contribuir al retraso de la RFC se ha asociado con un estado pro-inflamatorio excesivo. De acuerdo con un concepto reciente de "vía antiinflamatoria colinérgica", la inmunidad está coordinada por circuitos neuronales que operan de manera refleja. Este circuito

neuronal, si está bien establecido, evita las respuestas excesivas de citoquinas proinflamatoria, previniendo el daño tisular mediado por el sistema inmunitario (Borovikova et al., 2000; Tracey, 2009). Por consiguiente, un descenso en la actividad parasimpática puede dar como resultado una respuesta pro-inflamatoria exagerada y un aumento de la morbi-mortalidad (Haensel et al., 2008). El trabajo de Youn y colaboradores, confirmó que el enlentecimiento de la RFC post-esfuerzo se asociaba con una respuesta pro-inflamatoria exagerada, siendo una variable independiente predictora de eventos cardiovasculares en insuficiencia cardiaca (Youn et al., 2016).

Otra observación interesante de nuestro estudio, fue la correlación significativa obtenida en todos nuestros pacientes entre las variables VO_2 pico ($ml \cdot kg^{-1} \cdot min^{-1}$) y la RFC-1 ($r = 0,40$; $p < 0,001$) y/o RFC-2 ($r = 0,43$; $p < 0,001$), confirmando así la relación entre VO_2 pico y RFC sugerida por otros autores (Carnethon et al., 2005; Darr et al., 1988; Heffernan et al., 2007; Hirsh et al., 2006; Vicente-Campos et al., 2014). Se ha propuesto que esta relación puede ser debida a la vinculación entre una mejor capacidad aeróbica y una recuperación más temprana de la homeostasis intracelular lo que se traduciría en una reducción de los impulsos simpáticos desde los receptores periféricos musculares (Carnethon et al., 2005; Darr et al., 1988; Heffernan et al., 2007; Hirsh et al., 2006; Vicente-Campos et al., 2014). En cualquier caso, todos los estudios muestran que la aptitud cardiorrespiratoria está relacionada con la RFC.

6.4 Eficiencia mecánica.

En nuestro conocimiento, este estudio es el primero en examinar los cambios en la eficiencia mecánica (EM) tras 8 semanas de entrenamiento HIIT en pacientes con cardiopatía isquémica. El hallazgo más relevante del presente estudio fue un mayor incremento en la EM del grupo HIIT con respecto al grupo ECMI en intensidades relacionadas con VT_1 ($5,5 \pm 5,5\%$ vs $2,2 \pm 6,2\%$, $p < 0,01$). Sin embargo, la EM en la intensidad correspondiente a VT_2 y en máximo esfuerzo (VO_2 pico), solo aumentó significativamente en el grupo de HIIT ($p < 0,001$).

El ejercicio físico realizado a intensidades cercanas o superiores al VT_2 supone la necesidad de aumentar la contribución de energía a través de la vía glucolítica, aún cuando el suministro de energía oxidativa siga siendo el predominante. La activación glucolítica provoca alteraciones en el medio interno celular de los músculos implicados en el ejercicio que hacen que el mecanismo de la excitación-contracción del musculo se vea afectado negativamente, lo que va a afectar de forma negativa a la capacidad de trabajo muscular y por lo tanto a la eficiencia mecánica.

El HIIT es un tipo de entrenamiento que tiene como principal objetivo mejorar el VO_2 pico, pero debido a que las intensidades aplicadas son relativamente altas ($> VT_2$), también inducen mejoras relacionadas con el metabolismo glucolítico de las fibras musculares tipo II. Esto proporciona una mejora en la eficiencia energética, tanto en el desarrollo de la fuerza como en la resistencia a la fatiga, lo que significa una mejora en EM.

La causa principal de la baja EM observada en los pacientes con ECV parece ser el coste de ATPs relativamente alto para una determinada intensidad de contracción muscular (Layec et al., 2011). En este contexto, la mejora en la EM y, por lo tanto, un menor costo de ATP para el mismo esfuerzo muscular aplicado, está esencialmente determinado por la mejora del consumo de ATP de la miosina-ATPasa y de procesos "no contráctiles" relacionados con el transporte iónico asociado al ciclo de contracción-relajación (principalmente Calcio ATPasa y, en menor medida, Na-K-ATPasa). Por lo tanto, cualquier mejora de uno de estos procesos, podría explicar el menor costo energético necesario para una contracción a cualquier intensidad del ejercicio (VT_1 , VT_2 y VO_2 pico) (Layec et al., 2011).

Estudios previos han mostrado que la energía consumida para mantener una determinada carga de trabajo en cicloergómetro está correlacionada con la masa corporal (Berry et al., 1993; Cotes, 1969; Lafortuna et al., 2004). Lafortuna y

colaboradores (Lafortuna et al., 2004), encontraron niveles más bajos de la EM en una población adulta y obesa en comparación con individuos con normopeso. En nuestro estudio, ambos grupos de entrenamiento disminuyeron el peso corporal en la misma proporción durante el período de intervención, lo que descarta que el peso corporal sea un factor influyente en la modificación observada de la EM en el grupo HIIT.

Un menor consumo de O_2 para la misma producción de potencia durante el pedaleo en bicicleta, podría ser el resultado de: 1) un menor costo de ATP por cada contracción muscular para la misma producción de fuerza (es decir, una mejora en la eficiencia de la contracción del músculo); y/o 2) un consumo de O_2 más bajo para la misma tasa de resíntesis oxidativa de ATP (es decir, una mejora en la eficiencia mitocondrial) (Layec et al., 2011). Nuestro estudio comprobó como el HIIT fue capaz de aumentar el VO_2 pico, la carga máxima y la EM en mayor medida que el ECMI, especialmente al mejorar el entorno celular interno de los músculos activos durante el ejercicio. Sin embargo, algunos autores opinan que las adaptaciones típicas a corto plazo de estos entrenamientos, como es la mejora en el aporte de oxígeno (Bonne et al., 2014), en la capilarización muscular y en el contenido mitocondrial (Hoppeler et al., 1985), entre otros, tienen poco impacto en la EM, lo que significa que las mejoras en la función motora muscular no pueden excluirse como un elemento clave en la mejora de la EM.

Además, se ha demostrado que las fibras musculares tipo II son sustancialmente menos eficientes que las fibras tipo I durante el ciclismo, tal y como se refleja en un mayor VO_2 durante la realización de un ejercicio a una determinada potencia (Coyle et al., 1992). El entrenamiento en resistencia aeróbica, como el empleado en los dos grupos de este estudio, refuerza especialmente la capacidad oxidativa de las fibras de tipo I, pudiendo mantener una mayor intensidad de ejercicio (mayor nivel de resistencia) y como resultado de ello una mayor ME.

Grassi y colaboradores (Grassi et al., 2015), comprobaron cómo atletas sometidos a un programa HIIT, mejoraban la “estabilidad metabólica”, con disminución de los metabolitos musculares [ADP, AMP, Inosinamonofofato, creatina, fosfato inorgánico, H^+ , etc.] para un volumen de ATP dado. Esta mejora en la “estabilidad metabólica” puede ser crucial para limitar la fatiga muscular, el componente lento de VO_2 y el deterioro de la EM que ocurre a intensidades elevadas de ejercicio, especialmente debido a una disminución del ATP consumido por el trabajo realizado (Grassi et al., 2015). En este sentido, aunque las intensidades aplicadas en nuestro programa para los pacientes coronarios del grupo HIIT eran de una naturaleza menos

exigente desde un punto de vista metabólico, se puede especular que la obtención de adaptaciones bioquímicas parciales en el músculo puedan contribuir a la mejora de la "estabilidad metabólica", y con ello a una mejora en la EM.

La ineficiencia mecánica se relaciona principalmente con la inactividad, y parece que la intolerancia al ejercicio promovida por la enfermedad hace que los pacientes sean menos activos físicamente, con un efecto de desacondicionamiento de los músculos periféricos (Høydal et al., 2007). Una EM disminuida, indica que se consume más energía durante una determinada carga de trabajo. Por lo tanto, los individuos con una baja EM son menos eficientes con respecto al rendimiento y en consecuencia podrán estar limitados en términos de actividad física (Jabbour and Iancu, 2015). Por consiguiente, una mejora en la EM en pacientes con una limitación central (cardíaca), contribuirá a una mejora en la capacidad de ejercicio.

6.5 Calidad de vida.

Las mejoras fisiológicas de ambos entrenamientos fueron acompañadas por una mejora en la calidad de vida medida por los cuestionarios SF-36 y MacNew. Aunque no se observaron diferencias significativas entre ambos grupos tras finalizar el programa de 8 semanas, los dominios analizados en los cuestionarios mostraron mayores mejoras en el grupo de HIIT. De los 3 dominios del cuestionario MacNew (emocional, físico y social) el HIIT tuvo un grado mayor de significación ($p < 0,01$) que el ECMI ($p < 0,05$). Este es un hecho muy importante porque está relacionado con el cumplimiento de los programas de ejercicio (Gibala 2007, Bartlett 2011) y refleja una buena tolerancia y aceptabilidad del protocolo HIIT.

Los mecanismos implicados por los que el HIIT obtiene mejores resultados en determinados parámetros de la calidad de vida con respecto al ECMI, no están del todo aclarados. Algunos autores (Klocek et al., 2005) sugieren que este hecho, es debido a las mayores adaptaciones fisiológicas alcanzadas en los HIIT. En este sentido, el aumento de la capacidad aeróbica, así como la mejora en la eficiencia mecánica de nuestro grupo de pacientes que entrenaron con la metodología HIIT, podría justificar una mayor tolerancia al ejercicio y un aumento de la capacidad para hacer frente a las demandas físicas de la actividad diaria y con ello, a una mejora del estado psicosocial.

6.6 Seguridad.

En general los programas de entrenamiento HIIT han demostrado ser seguros, aunque el número de investigaciones es aun limitado. Al igual que otros autores (Arena et al., 2013; Cornish et al., 2011; Guiraud et al., 2010; Smart et al., 2013), hemos podido evidenciar una buena aceptación y tolerancia entre todos los pacientes del grupo HIIT, sin implicar un riesgo añadido ya que no se registró durante nuestro programa de entrenamiento ninguna incidencia ni eventos adversos cardiovasculares.

En esta línea, todos los meta-análisis de los últimos años confirman la seguridad de los programas de entrenamiento HIIT [Mezzani 2012, Arena 2013, Pattyn 2014, Elliot 2015, Liou 2015, Gomes-Neto 2017], pero sería adecuado llevar a cabo grandes ensayos clínicos aleatorizados a corto y largo plazo que investiguen su impacto en cuanto a la morbi-mortalidad en pacientes con ECV.

7. CONCLUSIONES

7 CONCLUSIONES

La aplicación de un programa de entrenamiento basado en HIIT mejora la capacidad funcional, tanto a nivel de esfuerzo máximo (VO_2 pico) como a nivel de esfuerzo submáximo (VT_1 y VT_2), en mayor cuantía que un programa de entrenamiento tipo ECMI, en pacientes con cardiopatía isquémica.

La aplicación de un programa de entrenamiento tipo HIIT mejora los índices de recuperación de la frecuencia cardiaca del primer y segundo minuto tras una prueba de esfuerzo hasta el agotamiento, en comparación con la aplicación de un entrenamiento basado en ECMI, que no mostró cambios significativos.

La aplicación de un programa de entrenamiento tipo HIIT en pacientes con cardiopatía isquémica consigue mayores mejoras en la eficiencia mecánica a intensidades correspondientes a VT_1 , VT_2 y VO_2 pico, en comparación con la aplicación de ECMI.

La ausencia de incidencias o complicaciones, su buena aceptación y tolerancia, junto a su mayor impacto en los test de calidad de vida, refuerzan la eficiencia y eficacia de los programas basados en HIIT en pacientes con CI de bajo riesgo.

8. BIBLIOGRAFIA

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