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TESIS DOCTORAL

Rehabilitación cardiaca en pacientes con cardiopatías congénitas

PRESENTADA POR

Ana Úbeda Tikkanen

Directora

Olga Arroyo Riaño

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Mª OLGA ARROYO RIAÑO, JEFA DE SECCIÓN DE REHABILITACIÓN INFANTIL DEL HOSPITAL GENERAL UNIVERSITARIO "GREGORIO MARAÑÓN" Y PROFESORA ASOCIADA DEL DEPARTAMENTO DE MEDICINA FÍSICA Y REHABILITACIÓN. HIDROLOGÍA MÉDICA DE LA UNIVERSIDAD COMPLUTENSE DE MADRID,

INFORMA que Doña **ANA ÚBEDA TIKKANEN**, ha realizado bajo mi dirección el trabajo titulado: **"REHABILITACION CARDIACA EN PACIENTES CON CARDIOPATIAS CONGÉNITAS"**

Este trabajo presentado en formato de publicaciones, de las que ella es coautora, se ha desarrollado con rigor metodológico, tras la realización de tres publicaciones en revistas de reconocido prestigio en el tema y de gran difusión, como demuestra su alto factor de impacto (15,20; 0,948 y 4,125). En ellas revisa aspectos destacables como son:

La rehabilitación infantil, supra especialidad en pleno auge, con importante demanda socio-sanitaria, en la población de cardiopatías congénitas infantiles. Tema novedoso, que requiere previamente de una revisión exhaustiva de todos los aspectos relacionados con los programas, que es lo que se realiza en el primer artículo donde se analizan las respuestas fisiopatológicas al ejercicio de los pacientes con cardiopatías congénitas y la calidad de las distintas pruebas utilizadas para la cuantificación del mismo, estableciendo la que se considera el gold estándar.

El segundo paso es la revisión de los programas de rehabilitación cardiaca (fase II) aplicados a la población pediátrica, el análisis de su calidad y la evidencia de su utilidad, que en este momento se puede considerar sugestiva, pero no definitiva. Es lo que se realiza en la segunda publicación.

En la tercera se aplica el hipotético mejor de los programas a una muestra de pacientes con cardiopatía congénita, pero que ya han llegado a la edad adulta, comprobando, como en el resto de las cardiopatías, que una actividad física frecuente y moderada, mejora la capacidad de ejercicio de los pacientes.

Es por todo ello que esta línea de investigación completa el abordaje de prevención y tratamiento de la discapacidad en la población de cardiopatías congénitas infantiles, abriendo un nuevo campo a la especialidad de Rehabilitación, que repercutirá en la

mejora de la calidad de vida percibida, que, a su vez, debe acompañar al aumento de supervivencia.

Por ello, y porque se entiende que reúne todos los requisitos formales exigibles a una Tesis Doctoral para que pueda ser presentada y defendida públicamente para optar al Grado de Doctor por esta Universidad, lo firmo en Madrid a cinco de junio de dos mil catorce.

Fdo. Dra. Olga Arroyo Riaño

DEDICATORIA

ESTA TESIS ESTA DEDICADA:

A mis padres y hermanos que siempre apoyaron mis sueños.

A todos aquellos amigos y mentores que me ayudasteis en mi camino.

AGRADECIMIENTOS

Deseo expresar mi más profundo agradecimiento a todas las personas que han dispuesto parte de su tiempo y dedicación a la elaboración de esta tesis doctoral:

En primer lugar, mi más amplio agradecimiento a la Dra. Olga Arroyo Riaño, Directora de mi tesis, maestra y amiga. Ella me abrió las puertas a la rehabilitación infantil, y ha sido siempre una fuente inagotable de inspiración y apoyo, incluso en la distancia.

Al Dr. Jonathan Rhodes que me introdujo en el fascinante mundo de la fisiología del ejercicio en los pacientes con cardiopatía congénita, y ha sido una pieza clave en mi trayectoria investigadora, ha sido un excepcional Co-director de tesis en funciones.

Al Dr. Enrique Maroto que apoyó mis primeros pasos en el mundo de la investigación y la innovación en la cardiología infantil.

Dos grandes mentores, el Dr. Pedro del Nido y la Dra. Donna Nimec, apoyan incondicionalmente mi proyecto actual, sin ellos me sería muy difícil seguir con mi sueño.

Agradecer a todos aquellos amigos y compañeros que han compartido, inspirado y apoyado este increíble viaje en algún momento, en especial a Paula.

Y por último a mis padres, que me han enseñado el valor del trabajo y el sacrificio, y sin los que todo esto no habría sido posible.

ABREVIATURAS Y ACRÓNIMOS

TOF: Tetralogía de Fallot

VSD o CIV: Comunicación interventricular

ASD o CIA: Comunicación interauricular

CoA: Coartación de aorta

TGA: Transposición de las grandes arterias

EPOC: Enfermedad pulmonar obstructiva crónica

NYHA: New York Heart Association

CIF: Clasificación internacional de la función

IMC: Índice de masa corporal

CR o RER: Coeficiente respiratorio

UA o VAT: Umbral anaeróbico

$pVO_{2\text{-}abs}$: Consumo de oxígeno en l/min

$pVO_{2\text{-}perkg}$,: Consumo de oxígeno en ml/min/kg

$pVO_{2\text{-}\%pred}$: Porcentaje predicho del consumo de oxígeno

PO_2: Pulso de oxígeno

FC: Frecuencia cardiaca

RESUMEN

a) Introducción

Los avances médicos y quirúrgicos de los últimos años son responsables del aumento de la supervivencia de los pacientes con cardiopatías congénitas. Sin embargo este incremento de la longevidad de esta población, frecuentemente se acompaña de complicaciones e incluso secuelas, que repercutirán en su pronóstico vital y su calidad de vida.

Los programas de Rehabilitación Cardiaca en cardiopatías adquiridas del adulto, están sólidamente estructurados, validados y ampliamente difundidos, habiendo demostrado su capacidad para aumentar la capacidad de ejercicio, disminuir la morbi-mortalidad y el gasto sanitario, y mejorar la calidad de vida.

Una de las consecuencias más frecuentes de las cardiopatías congénitas, es la disminución de la capacidad de ejercicio, hecho fundamental, ya que en estos pacientes este valor es utilizado como marcador pronóstico. Cuanto menor la capacidad de ejercicio, mayor es el riesgo de hospitalización o de muerte.

En la bibliografía, se describen distintos métodos de medición de la capacidad de ejercicio en los pacientes con cardiopatías congénitas. El método óptimo, será aquel que nos aporte más información, nos permita cuantificar el efecto de una intervención con terapias físicas o medicación, y nos aporte un valor clínico medible y reproductible.

La intervención rehabilitadora, como programa integral en pacientes con cardiopatía congénita, considerando que en ocasiones la discapacidad es multiorgánica, podría ser de gran utilidad en esta población. Y específicamente la rehabilitación cardiaca, encaminada a mejorar la tolerancia al ejercicio, tendría un incuestionable valor. Paradójicamente, son pocos los estudios realizados hasta el momento acerca de la efectividad de dicha intervención y consecuentemente realizados con programas muy variados y heterogéneos. De ahí el interés en definir el programa de rehabilitación cardiaca indicado en estos pacientes.

La capacidad de ejercicio en pacientes con cardiopatía congénita ya se ha mencionado que suele estar disminuida comparada con la de sujetos sanos y que esta disminución tiene un valor pronóstico negativo. Una pregunta importante a responder es si la reversibilidad de esta disminución de la capacidad de ejercicio es posible. Es decir, si una intervención terapéutica dirigida a aumentar la actividad física puede mejorar la capacidad de ejercicio, o está limitada debido a las alteraciones fisiológicas y anatómicas de base que presentan estos pacientes.

b) Objetivos e hipótesis

Un programa de rehabilitación que incluya ejercicio físico resultará beneficioso para los pacientes con cardiopatías congénitas, tanto en el momento de su instauración o prescripción, como a medio y largo plazo.

Los objetivos fueron:

Hacer una revisión exhaustiva de las diferentes modalidades de pruebas de esfuerzo, determinar cuál es la que presenta mayores propiedades instrumentales y definir qué variables de la prueba son las más relevantes para valorar la capacidad de ejercicio de las cardiopatías congénitas.

Estudiar la estructura y desarrollo de los programas de rehabilitación cardiaca aplicados a pacientes pediátricos con cardiopatías congénitas hasta el momento y los resultados obtenidos

Determinar la relación entre la actividad física y la capacidad de ejercicio en adultos con cardiopatía congénita para objetivar la reversibilidad de la intolerancia al ejercicio

c) Resultados

De los sistemas de cuantificación del ejercicio, la prueba de esfuerzo con análisis metabólico, es la el método de valoración que mayora riqueza de información aporta, acerca de la interacción de sistema cardiovascular y el musculoesquelético.

En la revisión sistemática de la literatura, se incluyeron 16 estudios acerca de programas de rehabilitación cardiaca en pacientes con cardiopatía congénita. De ellos se deduce que esta intervención, parecen tener un efecto beneficioso sobre la población y entraña bajo riesgo, aunque se siguen necesitando estudios con un mayor número de pacientes y con cuantificación más precisa de los efectos de la intervención. La estructura de los programas era muy variable.

Por último, se realizó un estudio retrospectivo en 156 adultos con cardiopatías congénitas dónde se estudió la relación entre la capacidad de ejercicio y la actividad física que realizaban en el momento de inicio del estudio y el cambio de los mismos con el paso del tiempo al termino del mismo. Se observó una relación significativa entre la capacidad de ejercicio y la actividad física y el índice de masa corporal, así como entre el cambio de actividad física y el cambio de consumo de oxígeno.

d) Conclusiones

La prueba de esfuerzo con análisis metabólico es la forma más objetiva y detallada de medir la capacidad de ejercicio en las cardiopatías congénitas.

Las variables más importantes a considerar son: el consumo pico de oxígeno, el pulso de oxígeno, la frecuencia cardiaca, el umbral anaeróbico y el coeficiente respiratorio.

La disminución de capacidad de ejercicio en las cardiopatías congénitas, no se debe sólo a la patología de base, sino a un estilo de vida sedentario. Se ha demostrado la reversibilidad de esta intolerancia al esfuerzo.

Los pacientes con cardiopatía congénita se podrían beneficiar de un programa de rehabilitación cardiaca

La evidencia científica de la eficacia de los programas de rehabilitación cardiaca en cardiopatías congénitas infantiles es limitada.

La composición idónea de este tipo de programa en cardiopatías congénitas está aún por definir.

Se deben de realizar estudios clínicos para determinar específicamente el beneficio, la estructura y desarrollo óptimo de dichos programas.

SUMMARY

a) Introduction

Increased survival has been observed in the congenital heart disease population due to advances both in the medical and in the surgical fields. However this increase in life expectancy is frequently accompanied by complications and sequels that will impact prognosis and quality of life of patients with congenital heart disease.

Cardiac rehabilitation programs in adults with acquired heart disease have a defined structure, have been validated and are widely used. They have been shown to increase exercise capacity and quality of life as well as decrease morbidity, mortality and healthcare costs.

One of the most frequent consequences we find in congenital heart disease is decreased exercise capacity, fact of vital importance due to the prognostic implication it has: the lower the exercise capacity the higher the risk of hospitalization and/or death.

We describe different exercise capacity measurement techniques. The best one being the one that most information provides, that allows us to quantify the effect of an intervention and that gives us clinically relevant and reproducible data.

The rehabilitation intervention as an integral part of management of congenital heart disease, understood as a multisystemic disability, could be very helpful in this patient population. More specifically cardiac rehabilitation targeting improvement of exercise capacity could have profound implications in this patient population.

Surprisingly few studies haves been performed to assess the effectiveness of these interventions, and therefore their programs are variable and heterogeneous. Definition of the structure and the composition of cardiac rehabilitation programs in these patients are warranted.

As mentioned previously exercise capacity in congenital heart disease patients tends to be decreased compared to healthy subjects, this decreased exercise capacity can have negative prognostic implications. An important question to be answered is whether his

decreased exercise capacity is reversible. More specifically, would an intervention that increases physical activity improve exercise capacity, or is exercise capacity limited due to anatomic and physiologic alterations found in this population.

b) Objectives and hypothesis

A rehabilitation program that includes exercise training would benefit patients with congenital heart disease, both at the time of the program as well as in the mid and long term.

Our objectives were:

To perform an extensive review of all exercise testing modalities, determine which provides the most objective quantification of exercise capacity and define the most important variables to analyze.

To study the structure and contents of cardiac rehabilitation programs applied to pediatric patients with congenital heart disease performed up until 2011 as well as analyzing the outcomes

To determine the relationship between physical activity and exercise capacity in adults with congenital heart disease to prove the reversibility of exercise intolerance in this patient population

c) Results

Of all exercise capacity measurement techniques, the metabolic stress testing is the one that provides the richest source of information regarding the cardiopulmonary and musculoskeletal systems.

The systematic review included 16 studies of cardiac rehabilitation in pediatric patients with congenital heart disease. We can conclude that this intervention seems to have beneficial effects in this population and is of low risk. However more studies, with a

higher number of patients and more precise outcomes are needed. The structure of these programs was variable.

Lastly, we performed a retrospective study on 156 adults with congenital heart disease who had undergone two metabolic stress tests, where we determined the relationship between exercise capacity and physical activity performed at the first test as well as change in exercise capacity related to change in physical activity.

We observed a significant relationship between exercise capacity and physical activity, exercise capacity was also related to BMI. A change in physical activity was also shown to be related to a change in exercise capacity.

d) Conclusions

- Metabolic stress testing is the most objective and detailed method to measure exercise capacity in congenital heart disease.
- The most important variables to analyze are: Peak oxygen consumption, oxygen pulse, heart rate, anaerobic threshold and respiratory exchange rate
- Decreased exercise capacity in congenital heart disease is not entirely caused by their underlying condition, but also to a sedentary lifestyle. We have proven the reversibility of exercise intolerance.
- Patients with congenital heart disease might benefit from a cardiac rehabilitation program.
- Scientific evidence on the efficacy of pediatric rehabilitation programs in congenital heart disease children is promising but limited.
- The ideal composition of these types of programs is yet to be determined.
- Clinical studies to determine the benefit, structure and optimal development of these programs should be performed.

Contents

I. INTRODUCCIÓN

1.1 Cardiopatía congénita

Se define como cardiopatía congénita, a cualquier defecto del corazón o de los grandes vasos, que está presente desde el nacimiento y su incidencia es de 4-8 por cada 1000 recién nacidos vivos. Numerosos avances, tanto en el campo médico como el quirúrgico, han contribuido a incrementar la supervivencia de los pacientes con cardiopatía congénita siendo reseñable, que desde hace tan solo un par de años por primera vez en la historia, el número de pacientes adultos con cardiopatías congénitas ha sobrepasado al de los niños.[1, 2]

Sin embargo este aumento de la supervivencia, se acompaña también de un aumento en las complicaciones y/o comorbilidades de esta población, lo que hace que disminuya su calidad de vida respecto a la población general.[3-7]

Las cardiopatías congénitas, se pueden clasificar según las alteraciones anatómicas o fisiológicas que se producen en el sistema cardiovascular:

Anatómicas: cardiopatías simples (Ej. comunicación interauricular) o complejas (Ej. Tetralogía de Fallot compuesta por una combinación de defectos simples: comunicación interventricular, acabalgamiento de la aorta, estenosis pulmonar e hipertrofia del ventrículo derecho).

Fisiológicas: cianosantes, con saturación de oxígeno disminuida (Ej. Tetralogía de Fallot) o no cianosantes, si la saturación de oxígeno es normal (Ej. comunicación interauricular).

Aunque a nivel de recomendación de ejercicio, también se manejan los conceptos de cardiopatía progresiva, reparables quirúrgicamente o en tratamiento anticoagulante.[8, 9]

1.2 Fisiología del ejercicio en la población sana

La función principal del sistema cardiopulmonar es la de proporcionar un flujo sanguíneo (y de oxígeno) acorde a las demandas metabólicas del cuerpo.

En los individuos sanos, durante el ejercicio físico, se producen una serie de respuestas fisiológicas en cadena en diversos sistemas para poder hacer frente al incremento de las necesidades metabólicas del organismo. Dichas adaptaciones se observan en la Tabla 1.

Cardiovasculares
Aumento de la frecuencia cardíaca (cronotropismo), de la velocidad de conducción del estímulo (dronotropismo) y de la fuerza de contracción (inotropismo).
Modificación de las resistencias vasculares periféricas: redistribución del flujo sanguíneo: vasodilatación en zonas musculares activas y vasoconstricción en zonas inactivas
Incremento del retorno venoso por la contracción muscular y el aumento de la presión intratorácica negativa
Aumento de las catecolaminas circulantes, el péptido natriurético auricular, el sistema renina-angiotensina-aldosterona y la hormona antidiurética
Respiratorias
Aumento de la ventilación y la vasodilatación pulmonar según la intensidad del ejercicio, con optimización de la relación ventilación/perfusión
Aumento de la capacidad de difusión del oxígeno
Musculoesqueléticas
Vasodilatación local
Incremento de la temperatura
Aumento de la extracción de oxígeno

Tabla 1. Respuestas fisiológicas agudas al ejercicio[10]

Para que el ejercicio sea óptimo se requiere por lo tanto la integridad del eje cardiopulmonar y del sistema musculoesquelético (Fig.1).

La actividad física implica un aumento de la demanda metabólica y por lo tanto del consumo de O_2. Cualquier alteración en estos sistemas que repercuta, en última instancia, en la capacidad de transporte de oxígeno en sangre, en la extracción del mismo y/o su utilización a nivel muscular, limitará la capacidad de ejercicio del paciente.[11, 12]

Los cambios fisiológicos fundamentales, incluyen una triplicación de la frecuencia cardiaca, un incremento del 50% del volumen sistólico y una caída entre un 50-60%, de la resistencia vascular pulmonar y periférica, lo que en conjunto incrementa aproximadamente cinco veces el gasto cardiaco.[13, 14] El incremento del gasto cardiaco se acompaña de un aumento de la precarga y las presiones sistólicas y de la arteria pulmonar. [13, 14]

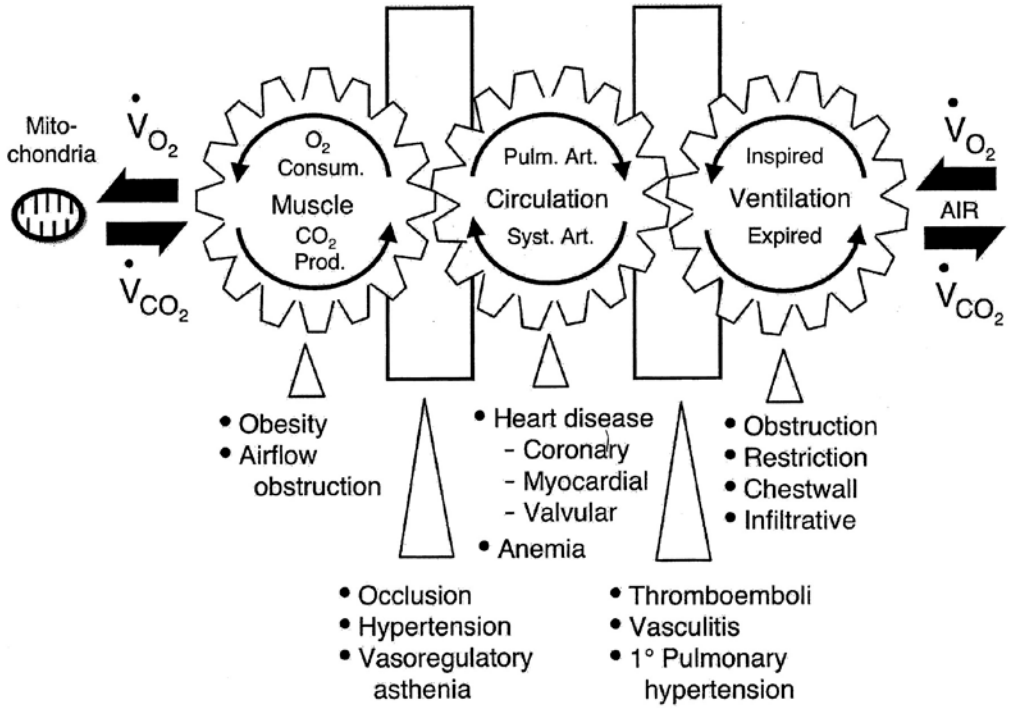

Fig.1. Alteraciones de los distintos sistemas que pueden afectar al intercambio gaseoso[15]

1.3 Fisiología del ejercicio en la cardiopatía congénita

En las cardiopatías congénitas estos mecanismos de respuesta al esfuerzo están alterados, aunque a diferentes niveles, según el tipo de patología:

Ej. un paciente con corazón univentricular al que se realiza cirugía paliativa de Fontan, consistente en la conexión de las dos venas cavas a la arteria pulmonar, carece de una "bomba" pulmonar competente al usar el único ventrículo funcional como bomba sistémica, lo que implica que la circulación pulmonar es "pasiva" y la distribución sanguínea pulmonar es diferente a la de un paciente sano. Esto va a limitar la cantidad de sangre que puede atravesar el pulmón en un momento dado y por lo tanto el volumen sistólico[16]. Ej. Los pacientes con Tetralogía de Fallot, tienen alteraciones congénitas o adquiridas del lecho vascular pulmonar, de manera que no se produce la disminución de la resistencia vascular de forma normal[17]. Otros pacientes con cardiopatía congénita compleja presentan disfunción del nodo sinusal y consecuentemente una respuesta cardiaca anormal con el ejercicio.[17]

Además diversos estudios han sugerido una alteración intrínseca del músculo periférico en pacientes con cardiopatías congénitas, similar a las "miopatías" observadas en adultos con insuficiencia cardiaca, a la que se hace en parte responsable de la alteración de la utilización/extracción de oxígeno.[18, 19]

De todas las circunstancias reseñadas, se deduce globalmente una menor capacidad de ejercicio, de origen multifactorial, en cualquier tipo de cardiopatía congénita, y con mayor limitación cuanto más compleja es la misma. [20-24] (Fig. 2)

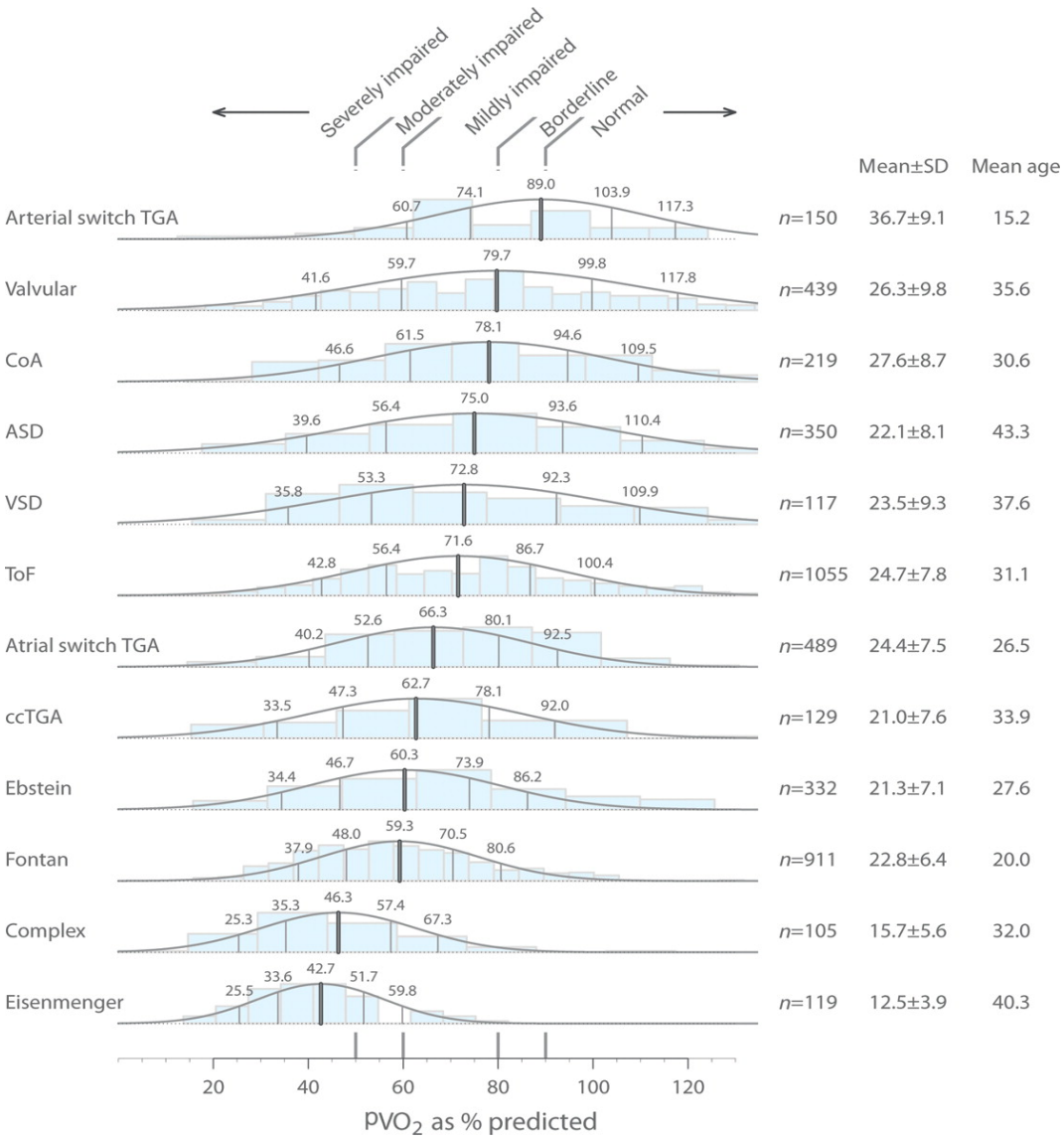

Fig. 2. Capacidad de ejercicio en pacientes con cardiopatías congénitas (Kempney et al)[22]: TGA: Transposición de las grandes arterias, CoA: Coartación de aorta, ASD: Comunicación interauricular, VSD: Comunicación interventricular, TOF: Tetralogía de Fallot, ccTGA: Transposición de las grandes arterias congénitamente corregidas. pVO_2: Consumo de oxígeno pico

Habiendo encontrado en distintos estudios una relación directa entre la capacidad de ejercicio y el riesgo de hospitalización o de mortalidad.[20, 25-27]

No sólo tienen una alteración objetiva de la capacidad de ejercicio, también la tienen perceptiva. En un estudio de Diller et al.[26] se objetivó que la clasificación funcional de la New York Heart Association (NYHA) no era fiable en pacientes con cardiopatías congénitas[28] donde pacientes con cardiopatía congénita asintomáticos (NYHA I) tenían

una capacidad de ejercicio objetiva parecida a la de pacientes con cardiopatía adquirida moderadamente sintomáticos con NYHA III.

1.4 Cuantificación del ejercicio

La evaluación de la capacidad de ejercicio del paciente con cardiopatía congénita, puede proporcionar una valiosa información del sistema cardiopulmonar y explicar qué factores pueden estar contribuyendo a limitar la capacidad de su participación en actividades físicas habituales[12]. Ya se ha reseñado con anterioridad que la cuantificación subjetiva no suele ser objetiva en esta población.[26]

La mayoría de las pruebas clínicas utilizadas por el cardiólogo pediátrico valoran al paciente en reposo, y aunque sean útiles, no predicen necesariamente la respuesta del sistema cardiovascular a las necesidades del ejercicio, ni le proporcionan información al médico acerca de la capacidad real del paciente de llevar a cabo actividades físicas.

La evaluación de la capacidad de ejercicio del niño o adolescente implica unos desafíos únicos debidos al tamaño y madurez del paciente. Además, los cambios que acontecen en los sistemas cardiopulmonares y musculoesqueléticos durante la infancia complican la interpretación de los datos. [29]

Para obtener dicha información se debe hacer una valoración de la capacidad de ejercicio, para la cual existe una gran variedad de pruebas.

1.5 Discapacidad en el niño con cardiopatía congénita

El paciente con cardiopatía congénita, presenta en conjunto una serie de característica clínicas que le hacen susceptible de presentar no solo la limitación de su propio proceso cardiológico, sino una discapacidad múltiple, por la serie de posibles alteraciones fisiológicas, comorbilidades y complicaciones acompañantes a la evolución natural de la enfermedad y a las sucesivas cirugías.

Dicha situación en el entorno rehabilitador es abordada siguiendo el modelo socio biopsicosocial de la CIF: Clasificación Internacional del Funcionamiento[30] aprobada en el 2001 que incluye el Funcionamiento y la Discapacidad asociado a las condiciones de salud. Esta clasificación presenta un lenguaje unificado y estandarizado para la descripción de la salud y los aspectos relacionados con ella como son la educación y el bienestar.

El concepto de funcionamiento y discapacidad en la CIF (Fig.3) hace referencia a:

- *Funciones corporales*: funciones fisiológicas y estructuras corporales.
- *Actividades*: realización individual de una tarea o acción.
- *Participación*: acto de involucrarse en una situación vital.

E incluye Factores Contextuales de dos tipos:

- *Factores Ambientales:* Lo constituyen el ambiente físico y social en el que las personas viven y desarrollan sus vidas.
- *Factores Personales:* Constituyen el trasfondo particular de la vida de una persona, familia y su estilo de vida.

La CIF tiene una aplicación práctica no solo a *nivel clínico* para valoración de necesidades, homogeneización de tratamientos y evaluación de resultados en rehabilitación, sino a nivel *educativo*, para la valoración de necesidades y adaptaciones escolares. A nivel de *políticas sociales* para la planificación de sistemas de seguridad social y de compensación. A nivel de i*nvestigación* para medir resultados, calidad de vida y factores ambientales relacionados con la salud, y a nivel de estadística para recogida y registro de datos.

Específicamente en cardiopatías congénitas la estructura corporal alterada es el sistema cardiovascular y las funciones corporales implicadas, las cardiopulmonares, neurológicas, musculo esqueléticas, de aparato digestivo y psicológicas, como a continuación se desarrollan.

1.6 Comorbilidad en cardiopatías congénitas

En la población con cardiopatías congénitas se encuentran frecuentemente complicaciones que no sólo afectan a la capacidad de ejercicio, sino también a su nivel de funcionamiento o discapacidad. Se describen agrupadas por sistemas:

Neurológicas: relacionadas con *factores innatos* si la cardiopatía forma parte de un síndrome genético Ej. La trisomía 21 o la deleción 22q11. También se ha observado que el cerebro del neonato con cardiopatía tiene características comunes al de un prematuro en el momento del nacimiento, así como alteraciones de la circulación cerebral fetal intraútero, de ahí que haya empezado a coger fuerza la teoría de que el neurodesarrollo puede ya estar alterado a nivel fetal.[4, 31, 32] Otros *factores adquiridos* también pueden afectar al neurodesarrollo, por la hipoxia cerebral mantenida, que además aumentará la viscosidad sanguínea favoreciendo infecciones a nivel cerebral, la parada circulatoria hipotérmica, los tromboembolismos secundarios a arritmias o la disfunción ventricular, entre otros.[33] [5]

La expresividad clínica varía desde alteraciones sutiles neurocognitivas como alteraciones de las funciones ejecutivas o de procesamiento de información, déficits de atención o problemas de aprendizaje, a manifestaciones neuromotoras como epilepsia, infartos cerebrales o trastornos del movimiento. De hecho la cirugía cardiaca es una de las principales-etiologías de infarto cerebral en niños.[5, 34, 35]

Pulmonares: Las cirugías repetidas pueden dar lugar a alteraciones restrictivas de la vía aérea o a parálisis diafragmáticas secundarias a una lesión del nervio frénico.[3] Recientemente se ha demostrado la relación entre la disminución de la capacidad vital forzada y la capacidad de ejercicio.[36, 37] En pacientes con insuficiencia cardiaca y congestión pulmonar también se ha comprobado afectación de la pequeña vía aérea. El desarrollo de hipertensión pulmonar, frecuente en algunos de los defectos cardiacos, afecta directamente a la cantidad de sangre circulante por los pulmones y a su contenido de oxígeno.[38]

Digestivas: Las alteraciones de la deglución son relativamente frecuentes en esta población lo que puede desembocar en aspiraciones e ingesta calórica insuficiente.

Estos problemas se han relacionado con los síndromes genéticos y la ventilación invasiva.[39, 40] También es conocida la malabsorción y la falta de apetito como síntoma de desarrollo de insuficiencia cardiaca.

Músculo-esqueléticas: Dentro de las alteraciones extracardíacas más comunes de los pacientes con cardiopatías congénitas, se incluyen las alteraciones del tejido conectivo, hipotonías, desviaciones del raquis y deformidades de la caja torácica.[41] También está descrito un tipo de miopatía, similar al hallado en pacientes con insuficiencia cardiaca crónica, así como un desacondicionamiento muscular global. También se pueden encontrar alteraciones del tono muscular secundarias a alteraciones neurológicas.[42, 43]

Psicológicas: se han evidenciado un gran número de problemas psicológicos en estos pacientes entre los que cabe destacar la ansiedad y la depresión hasta en un tercio de los pacientes. Otros desajustes psicológicos-que se han visto son problemas de internalización y una afectación de las relaciones sociales.[44, 45]

Globalmente y de manera sumatoria, cualquiera de estas alteraciones puede afectar la capacidad de ejercicio del niño y van a contribuir negativamente aumentando la discapacidad del paciente.

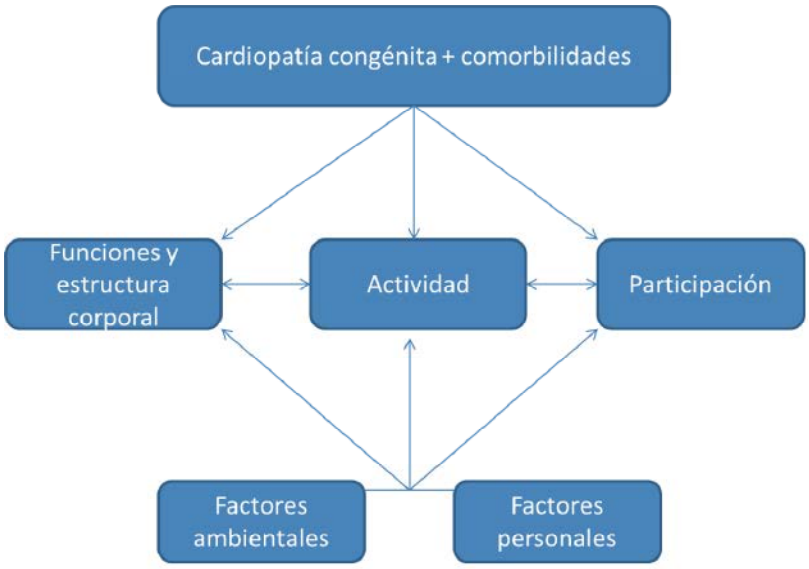

Fig. 3 La discapacidad en la cardiopatía congénita

1.7 Programas de rehabilitación cardiaca

Los beneficios de la actividad física en la población general ya han sido ampliamente demostrados. Se ha relacionado con una disminución de la mortalidad y de incidentes cardiovasculares[46-49], así como con beneficios a nivel respiratorio, musculoesquelético y metabólico[50-52], como se observa en la Tabla 2. Beneficios parecidos se deberían obtener en los pacientes con cardiopatía congénita aunque todavía no han sido suficientemente demostrados.

Cardiovasculares
Hipertrofia cardíaca concéntrica
Reducción de la demanda de oxígeno miocárdico
Aumento del volumen minuto
Aumento del tono vagal y disminución de los niveles de catecolaminas (aumento de la vasodilatación y control de la presión arterial, disminución de la frecuencia cardíaca basal)
Aumento del flujo coronario
Estabilización del endotelio
Incremento de la fibrinólisis
Respiratorios
Aumento de fuerza muscular inspiratoria
Aumento de la capacidad pulmonar total y de la capacidad vital
Musculoesqueléticos
Aumento del tamaño y el número de la fibras musculares IIa
Aumento de la vascularización
Aumento de la capacidad oxidativa y el número mitocondrial

Metabólicos
Mejora del perfil lipídico
Mejora del metabolismo de los hidratos de carbono: mejora de la utilización de la insulina
Disminución de los factores inflamatorios
Favorecimiento de la reducción de peso: evita la obesidad
Psicológicos
Reducción de la ansiedad y el estrés
Favorecimiento del control de la depresión
Ayuda al control del sueño y el manejo del estrés
En la calidad de vida
Mejora de la fuerza y la resistencia muscular
Mejora de la funcionalidad
Disminución del riesgo de muerte, mejor control de las enfermedades crónicas
Mejora de la imagen personal y las relaciones sociales

Tabla 2. Beneficios del ejercicio en la población general [10]

Los niveles de actividad física en los pacientes con cardiopatía congénita es menor que la recomendada por las distintas guías clínicas[53] y comparada con la población sana.[29, 54]

El objetivo de la rehabilitación es precisamente la prevención, diagnóstico y tratamiento de la discapacidad. ¿Se puede ofrecer a estos pacientes alguna intervención más específica que disminuya el impacto que tenga la enfermedad en su vida?

Los programas de rehabilitación cardiaca en adultos con cardiopatías adquiridas se empezaron a desarrollar a partir de los años 70, y han demostrado ampliamente que no

sólo mejoran la capacidad de ejercicio, los síntomas de ansiedad y depresión y calidad de vida, sino que también disminuyen la morbimortalidad y el gasto sanitario de esta población.[55, 56] De hecho en todos los países del primer mundo está protocolizada la intervención rehabilitadora al menos en pacientes que han sufrido un infarto cardiaco o en los que se ha realizado una cirugía cardiaca.[56, 57] A pesar de ello menos de un 10% de todos los pacientes que se beneficiarían de esta intervención la reciben.[58]

En pacientes con insuficiencia cardiaca, a pesar de haber demostrado su efectividad, están mucho menos implantados.[59]

Los programas de rehabilitación de la cardiopatía adquirida constan de tres fases bien diferenciadas:

- *1ª Fase o período agudo*, que incluye el post-operatorio agudo: El objetivo de esta fase es que el paciente consiga la mayor independencia posible antes del alta, así como evitar complicaciones del encamamiento prolongado.
- *2ª Fase o periodo post-agudo*: es lo que común y específicamente se conoce como el programa de "rehabilitación cardiaca". Se inicia a los dos meses de la intervención o evento agudo y dura aproximadamente 3 meses. Incluye reentrenamiento al esfuerzo con monitorización telemétrica, educación, manejo de factores de riesgo cardiovascular y terapia de relajación en un ambiente hospitalario.
- *3ª Fase o fase de mantenimiento*: se trata de realizar un programa de ejercicio de mantenimiento, con supervisión de forma crónica.

Estos programas de rehabilitación, rara vez se ofertan a los niños con cardiopatías congénitas y tampoco están diseñados para cubrir sus necesidades específicas.[60]

1.8 Hipótesis de trabajo y justificación de la unidad temática

La mayor supervivencia de los pacientes con cardiopatías congénitas, genera la necesidad de que su calidad de vida sea similar a la de la población general.

Los programas de rehabilitación en general y específicamente aquellos que incluyan alguna modalidad de ejercicio físico resultarían beneficiosos para estos pacientes, tanto en el momento de su instauración o prescripción, como a medio y largo plazo.

Por ello los objetivos de la unidad temática, han sido:

Conocer las respuestas fisiopatológicas de los pacientes con cardiopatías congénitas ante el ejercicio, así como hacer una revisión exhaustiva de las diferentes modalidades de pruebas de esfuerzo, determinar cuál es la que presenta mayores propiedades instrumentales y definir qué variables de dicha prueba de esfuerzo son las más relevantes para valorar la capacidad de ejercicio en esta población de pacientes. Se realiza la revisión, análisis y crítica de los diferentes métodos y medidas de cuantificación.

Los beneficios aportados por los programas de rehabilitación cardiaca en cuanto a la adaptación al ejercicio y la estructura ideal de este tipo de intervención sigue sin estar definido en estos pacientes, en contraste con los programas bien estructurados y consensuados para la población de adultos con cardiopatía adquirida. Se estudia la estructura y desarrollo de los programas de rehabilitación cardiaca aplicados a pacientes con cardiopatías congénitas hasta el momento, y los resultados obtenidos.

Estudiar la respuesta de adultos con cardiopatía congénita con determinada capacidad de ejercicio a la actividad física diaria y valorar la capacidad de la misma para modificar la situación a lo largo del tiempo, partiendo de la base de que el conocimiento de la respuesta a esta actividad en adultos, puede ser de utilidad para el diseño y aplicación en niños con similar patología de base.

Se considera prioritario conocer la respuesta a estas preguntas para poder optimizar la intervención a estos pacientes.

1.9 Presentación de los artículos

Los tres artículos derivados de la hipótesis de la tesis, siguiendo la línea argumental y la cimentación para las conclusiones son:

Artículo 1. Rhodes J, Ubeda A, Jenkins K. Exercise testing and training in children with congenital heart disease. Circulation 2010;122:1957-1967. ANEXO I

Artículo 2. Ubeda Tikkanen A, Rodriguez Oyaga A, Arroyo Riaño O, Maroto Álvaro E, Rhodes J. Paediatric cardiac rehabilitation in congenital heart disease: a systematic **review**. Cardiol Young 2012;22:241-250. ANEXO II

Artículo 3. Ubeda Tikkanen A, Opotowsky A, Landzberg M, Bhatt A, Rhodes J. Physical Activity Improves Exercise Capacity in Adults with Congenital. Int J Cardiol. 2013 12;168(5):4685-91. ANEXO III

Artículo 1. *Exercise testing and training in children with congenital heart disease*

Es una revisión por invitación de la revista Circulation. Se realiza un exhaustivo análisis de las respuestas fisiopatológicas de los pacientes con cardiopatías congénitas ante el ejercicio. Se revisan los distintos tipos de pruebas utilizados para medir la capacidad de ejercicio, se describen los métodos y se establece el que se considera con mayores propiedades para la cuantificación de la capacidad de ejercicio en cardiopatías congénitas. Por último, se realiza la descripción de los programas de rehabilitación cardiaca aplicables a pacientes infantiles con cardiopatías congénitas.

Artículo 2*: Paediatric cardiac rehabilitation in congenital heart disease: a systematic review*

Se trata de una revisión sistemática y clasificación de la evidencia científica existente en el momento actual acerca de los estudios de programas de rehabilitación cardiaca infantil publicados entre Enero de 1981 y Noviembre de 2010. Es una profundización y ampliación de la revisión de programas de rehabilitación cardiaca infantil del artículo número 1.

Artículo 3: *Physical Activity is Associated with Improving Aerobic Exercise Capacity over Time in Adults with Congenital Heart Disease*

Se trata de un estudio retrospectivo cuya finalidad es objetivar la relación entre la capacidad de ejercicio en las cardiopatías congénitas del adulto con el ejercicio físico realizado, para intentar demostrar la reversibilidad de la disminución de dicha situación observada en esta población.

II. OBJETIVOS

Por lo anteriormente expuesto, creemos importante plantear:

- La revisión de las respuestas fisiológicas al ejercicio en las cardiopatías congénitas.
- El estudio de las medidas de cuantificación de la capacidad de ejercicio y descripción del que reúna mayores propiedades.
- La determinación de qué variables de la prueba de esfuerzo, son las más relevantes para el estudio.
- La revisión de la evidencia de la calidad metodológica, eficacia y riesgo/beneficio de los programas de rehabilitación cardiaca en pacientes con cardiopatía congénita así como propuesta de la estructura de dichos programas.
- La objetivación de la reversibilidad de la disminución de la capacidad de ejercicio en pacientes con cardiopatía congénita.

III. MATERIAL Y MÉTODOS

3.1 Articulo1: Exercise testing and training in patients with congenital heart disease

Circulation 2010; 122:1957-1967

Factor de impacto de la revista en 2013: 15.20

Revisión por invitación de la revista Circulation, se trata de una revisión por expertos de la literatura existente sobre la capacidad de ejercicio en la cardiopatía congénita, la cuantificación de dicha capacidad, las variables relevantes determinadas por estas pruebas y los programas de rehabilitación cardiaca hechos hasta el momento.

3.2 Artículo 2: Paediatric cardiac rehabilitation in congenital heart disease: a systematic review

Cardiol Young 2012;22:241-250

Factor de impacto: 0.948

Palabras claves de la estrategia de búsqueda fueron: *heart, cardiac, rehabilitation, exercise, lung, human, infant, child, adolescent*. Las bases de datos consultadas para la búsqueda de los estudios fueron: MEDLINE/PubMed, EMBASE, Cardiosource Clinical Trials Database, and Cochrane Library. Adicionalmente se obtuvieron estudios a partir de la bibliografía de los estudios obtenidos.

Criterios de inclusión: estudios que incorporaban un programa de rehabilitación cardiaca estructurado con un componente de reentrenamiento al esfuerzo en pacientes con cardiopatías congénitas menores de 18 años o revisiones de dichos tipos de estudio. Sólo se incluyeron estudios realizados entre Enero de 1981 y Noviembre del 2010.

Criterios de exclusión: estudios que no fueran escritos en inglés, francés, castellano o italiano. También se excluyeron estudios de programas de rehabilitación sin un componente de reentrenamiento al esfuerzo.

Clasificación de la evidencia: Dos revisores independientes (AUT y ARO) clasificaron los estudios de acuerdo al Centro de Medicina Basado en la Evidencia de Oxford.[61] Cuando la asignación de ambos autores no coincidía, se discutía el estudio y se acordaba el nivel de evidencia científica.

3.3 Artículo 3: Physical Activity is Associated with Improving Aerobic Exercise Capacity over Time in Adults with Congenital Heart Disease

Int J Cardiol. 2013 12;168 (5):4685-91

Factor de impacto: 4.125

Criterios de inclusión: adultos con cardiopatías congénitas mayores de 21 años de edad, que completaron al menos dos pruebas de esfuerzo con análisis de gases entre Enero del 2006 y Julio del 2011 en el Boston Children's Hospital. Las pruebas tenían que ser de esfuerzo máximo (CR > 1,09), con un intervalo de tiempo entre ellas de 6-24 meses. Se excluyeron pacientes embarazadas durante o entre las pruebas, pacientes que se sometieron a intervenciones cardiacas percutáneas o procedimientos quirúrgicos que pudieran afectar la capacidad de ejercicio entre las pruebas, así como aquellos que sufrían un proceso agudo en el momento de la prueba. Para el estudio, se utilizaron las dos primeras pruebas que cumplieran con estos criterios.

Prueba de esfuerzo cardiopulmonar: se realizó ciclo-ergometría con un protocolo de rampa, con monitorización electrocardiográfica y análisis de los gases espirados ($CardiO_2$ exercise testing system, Medical Graphics, Minneapolis, Minnesota). Los cálculos y valores predictivos se hallaron utilizando las ecuaciones de Wasserman et al.[11]

Valoración de la actividad física: La actividad física de los pacientes se cuantificó a partir de la historia clínica del paciente y se clasificó en:

1) Sedentario: Actividad física mínima, Ej. "Tiene una bicicleta estática en casa pero no la utiliza".

2) Ocasional: Actividad física de intensidad ligera, o moderada (actividad que obliga al paciente a sudar o respirar fuerte) <2 veces a la semana y/o <40 minutos por sesión. Ej. "Ha hecho ejercicio de forma regular en la cinta rodante durante unos 10-20 minutos alrededor de 3 veces por semana."
3) Frecuente: ejercicio de intensidad al menos moderada ≥ 2 veces durante ≥ 40 minutes, Ej. "Ahora va al gimnasio dos horas al día lunes, miércoles y viernes."
4) Indeterminado: no había información suficiente para poder clasificar al paciente.

Los cambios en los niveles de actividad física descritos anteriormente (sedentario, ocasional, frecuente) entre la primera y la segunda prueba de esfuerzo también se clasificaron como: sin cambios, aumento, o disminución de la actividad física.

Dos investigadores (AUT, JR) clasificaron, de forma independiente, la frecuencia y la existencia o no de cambios en la actividad en 50 sujetos para cuantificar la variabilidad inter-observador, siendo el valor de Kappa para la clasificación de la actividad física 0.79; y para los cambios en la actividad física entre pruebas fue 0.66, algo más baja pero seguía siendo aceptable.

El valor porcentual del consumo de oxígeno esperado ($pVO_{2\text{-}\%pred}$) se calculó mediante la mediana, siendo para pacientes con fisiología univentricular 56.5% y biventricular 66.7%.

A los pacientes con $pVO_{2\text{-}\%pred}$ por encima de este valor, se consideró que tenían una capacidad de ejercicio "por encima de la media" para su fisiología subyacente, y aquellos con $pVO_{2\text{-}\%pred}$ por debajo de este valor se clasificaron como capacidad de ejercicio "por debajo de la media". Se investigó la proporción de pacientes con capacidades de ejercicio por encima y por debajo de la media en la segunda prueba de esfuerzo.

Análisis estadístico: La variable principal de interés fue el cambio del pVO_2 a lo largo del tiempo, se incluyó el cambio del pVO_2 absoluto ($pVO_{2\text{-}abs}$ en l/min), el pVO_2 ajustado por peso ($pVO_{2\text{-}perkg}$, en ml/min/kg) así como el porcentaje predicho de pVO_2 ($pVO_{2\text{-}\%pred}$). Otras variables secundarias analizadas fueron el cambio en la frecuencia cardiaca máxima, el pulso de oxígeno y la pendiente VE/VCO_2.

Las variables continuas se presentaron como media ± SD y las variables categóricas como porcentajes. Debido a que las características de los grupos de actividad física sedentario y ocasional eran similares, se combinaron para formar un único grupo en la mayoría de los análisis. La relación entre las variables categóricas de actividad física y las variables individuales de las pruebas de esfuerzo, se analizaron con el ANOVA o el test de Kruskal-Wallis. Se utilizaron pruebas de t pareada para comparar los valores iniciales y finales para las variables de la prueba de esfuerzo con distribución normal (Wilcoxon rank sum test para las distribuciones no-normales).

Dada la variabilidad de tiempo entre las pruebas de esfuerzo de cada paciente también se analizó la relación entre los predictores de interés y el cambio de las variables de la prueba de esfuerzo ajustado por año (Ej. $\Delta pVO_{2perkg/\,año}$). Se realizó una regresión lineal donde el cambio del parámetro de ejercicio de interés (Ej. $\Delta pVO_{2\text{-}perkg}$ o $\Delta pVO_{2\text{-}perkg/\,año}$) era la variable dependiente, para ver la asociación entre el nivel de actividad física durante el periodo de tiempo entre las pruebas de esfuerzo o el cambio de actividad física entre dos visitas, y las variables dependientes estudiadas. Se realizó un análisis multivariante, para comprobar si las asociaciones observadas eran independientes de potenciales factores de confusión como: edad, género, tipo de cardiopatía congénita, tiempo entre pruebas, $pVO_{2\text{-}perkg}$ (u otras variables de la prueba de esfuerzo) basal, talla o peso basales (o IMC), cambio de peso entre estudios, uso de tabaco, uso de marcapasos, presencia de disfunción ventricular sistémica diagnosticada por ecocardiografía (ninguna, ligera, moderada/severa), frecuencia cardiaca de base y uso de medicamentos cardiacos específicos (digoxina, beta-bloqueantes, IECA/EIA, diuréticos).

También se valoró la proporción de pacientes de cada grupo de actividad física que cambiaron de debajo a encima de la mediana basal (o al revés) durante el tiempo entre pruebas y aquellos que demostraron un incremento o descenso del $pVO_{2\text{-}\%pred}$ >1SD con respecto a la diferencia de medias.

IV. RESULTADOS

4.1 Artículo 1. Exercise testing and training in patients with congenital heart disease

Aportación del doctorando: búsqueda y revisión bibliográfica, redacción y edición del texto.

Existen diversas pruebas para determinar la capacidad de ejercicio en esta población, pero la precisión del método es fundamental, ya que como ya se ha mencionado previamente está directamente relacionada con su morbimortalidad.

1) *Prueba de la marcha de 6 minutos*. Consiste en medir la cantidad de metros que recorre un individuo en 6 minutos. Es una prueba muy utilizada y popular, sobre todo en pacientes con hipertensión pulmonar. Es fácil de realizar y muy bien tolerada. Se puede registrar la frecuencia cardiaca (FC), la saturación de oxígeno y la presión arterial. Entre las limitaciones de esta prueba cabe destacar la influencia de factores no cardiopulmonares en los resultados como la amplitud de la zancada y el esfuerzo del paciente.

2) *Pruebas de esfuerzo.* Permiten determinar de forma más objetiva la tolerancia al ejercicio. En niños menores de 6 años, en general, no suelen realizarse por falta de colaboración.
   Existen dos tipos de pruebas de esfuerzo:

   a. *Sin análisis de gases*: se realizan en una cinta rodante con el paciente monitorizado. El protocolo de Bruce[62, 63] es el más utilizado, con un incremento de la velocidad y la inclinación de la cinta cada 3 minutos. La capacidad de ejercicio se deduce a partir de la duración de la prueba y se compara con unas tablas de normalidad.[62] Pueden registrarse alteraciones de la respuesta de la presión arterial, la saturación de oxígeno y el ritmo cardíaco, o cambios del segmento ST en el ECG. En esta prueba también

encontramos la limitación de poder determinar si es una prueba de esfuerzo máximo o no, lo que afectará a la interpretación de los datos que obtengamos.

b. *Con análisis de gases o metabólica*: la prueba de esfuerzo se completa con análisis del gas espirado. Se puede realizar en cinta rodante con un protocolo similar al que se ha explicado previamente, o en cicloergómetro con aumento progresivo de la carga. El paciente respira aire ambiente pero lleva una máscara que analiza las concentraciones de oxígeno que consume y dióxido de carbono que genera, además de los volúmenes de aire movilizados. La información que aporta este tipo de prueba es particularmente detallada y objetiva e ilustra la interacción entre los sistemas cardiovascular, pulmonar y musculoesquelético. Con estos datos se pueden calcular diversos parámetros clínicos imprescindibles en el estudio de las respuestas fisiopatológicas del paciente con cardiopatía congénita.
   Los parámetros obtenidos en las pruebas de esfuerzo y su significado, se describen a continuación:

   i. El consumo máximo de oxígeno o consumo de oxígeno pico (pVO_2), se trata de un indicador de la capacidad de ejercicio. El pVO_2 representa la capacidad del organismo de proporcionar oxígeno, como sustrato energético, a la musculatura. En la gran mayoría de los individuos este consumo está limitado por el aparato cardiopulmonar, más concretamente de la capacidad del sistema circulatorio de aumentar el gasto cardiaco durante el ejercicio. Con lo cual es un indicador excelente de la capacidad del sistema cardiovascular del paciente.

      Sin embargo el cálculo de los valores normales de pVO_2 no es tan fácil, depende de ciertas características del individuo tales como el peso, la talla, la composición corporal, género y edad, existiendo distintas ecuaciones para su cálculo. Las más utilizadas son las de Wasserman [64] en adultos y en la población infantil son las de Cooper[29] salvo para pacientes con una talla inferior a 130 cm en cuyo caso se presupone

42 ml/kg en chicos y 38 ml/kg también descrito por Cooper et al.[29]

Se ha demostrado la importancia clínica de esta variable a través del poder predictivo de muerte y/o hospitalización que se ha visto en pacientes con Tetralogía de Fallot[65], en aquellos intervenidos de switch atrial en transposición de las grandes arterias[66], en pacientes con hipertensión pulmonar[67, 68] y pacientes intervenidos de Fontan.[27]

ii. La frecuencia cardiaca máxima (FCmax), o número de latidos por minuto. Durante el ejercicio la relación entre la FC y el pVO_2 es lineal hasta intensidades muy altas. Se puede calcular con la fórmula FC=220-edad en años. No es infrecuente, en pacientes con cardiopatías complejas o con múltiples cirugías, la presencia de una alteración cronotrópica, que rompe esta relación lineal.[69] Aquellos pacientes que no son capaces de incrementar su volumen sistólico intentan compensarlo con incremento excesivo de la frecuencia cardiaca con el esfuerzo. La incompetencia cronotrópica es relativamente frecuente tras la cirugía de cardiopatías congénita[17, 69, 70] y se ha relacionado con un peor pronóstico.[69]

iii. El pulso de oxígeno (PO_2) se ha relacionado con el volumen sistólico efectivo, y por lo tanto es una de las variables más útiles para el clínico. La relación entre el PO_2 y el volumen sistólico se entiende al dividir los dos lados de la ecuación de Fick por la frecuencia cardiaca (FC):

$VO_2/FC = PO_2$= (gasto cardiaco)/(FC)x(extracción de O_2)

La extracción de O_2 es equivalente al contenido arterial de O_2 menos el contenido venoso. Estas variables a su vez dependen de la concentración de hemoglobina y la saturación de oxígeno. En pacientes con cardiopatía congénita reparada las saturaciones y las

concentraciones de hemoglobina son normales. Además con el ejercicio pico se maximiza la extracción de O_2, por lo tanto en la mayoría de cardiopatía congénita la concentración venosa es parecida, por lo que la extracción de O_2 en la mayoría de los casos es homogénea y por lo tanto el PO_2 es equivalente al volumen sistólico efectivo. Los valores normales van a depender por supuesto del tamaño, sexo y edad del paciente. Los valores normales se pueden calcular dividiendo el pVO_2 predicho entre la FC predicha.

Sin embargo hay que tener en cuenta las limitaciones del concepto del PO_2 al interpretar las pruebas, aquellos pacientes con un contenido arterial de oxígeno por debajo de lo normal (Ej. pacientes con una anemia severa) tendrán una extracción de oxígeno por debajo de lo normal y el PO_2 subestimaría el volumen sistólico efectivo. Por lo contrario, en aquellas situaciones que aumentan el contenido arterial de oxigeno como la policitemia lo sobrestimarían. Por la ley de Starling una bradicardia relativa con el ejercicio máximo se debería de compensar con un aumento del volumen sistólico efectivo, en consecuencia la falta de aumento del PO_2 en pacientes con una alteración cronotrópica con el ejercicio es anormal.

Los pacientes que son incapaces de aumentar el volumen sistólico efectivo tales como aquellos con disfunción ventricular[71], lesiones valvulares severas tanto insuficientes como estenóticas[62, 72] y pacientes con enfermedades vasculares sistémicas o pulmonares[24, 67, 68] tendrán un PO_2 bajo.

En patologías con circulación univentricular (como el Fontan) frecuentemente encontramos un PO_2 bajo a pesar de una integridad de la función ventricular y valvular, esto se puede deber a la falta de una “bomba” pulmonar y la capacidad limitada de aumentar el flujo

pulmonar al ser pasiva la circulación. En estos pacientes existe una correlación muy alta entre el PO_2 y el pVO_2[70] , lo mismo se aplica a otras alteraciones cardiacas con disfunción ventricular.[70, 71]

iv. El coeficiente respiratorio (CR) es la relación de VCO_2/VO_2, su valor depende del tipo de sustrato que utiliza el organismo para generar energía, a nivel de actividad basal oscila entre 0.7-0.8. Durante una prueba de esfuerzo al sobrepasar el umbral anaeróbico el CO_2 generado excede al O_2 consumido. Un CR ≥1.09 se considera con un esfuerzo máximo y aceptable.[64, 73]

Si un paciente no realiza una prueba máxima los datos obtenidos probablemente no reflejen la capacidad cardiopulmonar verdadera del paciente. Una interpretación óptima de la prueba requiere información válida acerca del esfuerzo del paciente. La medición del coeficiente respiratorio nos aportará este dato.

v. El umbral anaeróbico (UA) es el momento durante el ejercicio, en el que el metabolismo aeróbico no es suficiente para mantener los niveles energéticos requeridos para dicho esfuerzo y empieza a complementarlo el metabolismo anaeróbico. En este momento aumenta desproporcionadamente la producción de CO_2 respecto al consumo de O_2.

Existen ecuaciones de predicción basados en la edad, el tamaño y el sexo del paciente.[29] Se suele expresar como porcentaje del consumo pico de O_2 predicho. En ausencia de una enfermedad cardiovascular el UA no suele caer por debajo del 40% del pVO_2 predicho. En pacientes con condiciones que limitan el aumento del gasto cardiaco o el transporte de O_2 con el ejercicio, el UA estará disminuido.[64, 70, 73]

vi. La pendiente VE/VCO_2 representa la relación lineal existente entre la ventilación y la eliminación de CO_2 durante el ejercicio. Corresponde

al número de litros de aire que hay que movilizar para eliminar 1 litro de CO_2 y se considera un índice de eficiencia del intercambio gaseoso. En patologías como la transposición de grandes arterias corregida con switch atrial, la insuficiencia cardiaca, o la Tetralogía de Fallot se ha relacionado un incremento en la pendiente, con un aumento del riesgo de muerte.[65, 66, 74-76]

vii. Alteraciones características por cardiopatía congénita

Cada tipo de cardiopatía congénita va a dar lugar a alteraciones específicas de las variables descritas en la prueba de esfuerzo metabólica como se especifican a continuación en la Tabla 3.

Defecto	***↓VO_2 pico***	***↓FCmax***	***↓PO_2***	***↑VE/VCO_2***	***↓UA***
TOF reparado/Truncus	+++	++	+++	+++	++
Fontan	++++	+++	++++	++++	+++
EVPO	++++	+	++++	++++	++++
Ebstein	+++	++	+++	++	++
Post switch arterial	+++	++	+++	++	++
Valvulopatía aórtica	++	+	++	+	++
Coartación	++	+	++	+	+++
Miocardiopatía dilatada	++++	+	++++	++	++++
Miocardiopatía hipertrófica	++	+	++	+	++
IP aislada	+	+	+	+	+

TOF: Tetralogia de Fallot, EVPO: Enfermedad vascular pulmonar obstructiva, IP: Insuficiencia pulmonar, VO_2 pico: consumo de oxígeno pico, FCmax: Frecuencia cardiaca máxima, PO_2: Pulso de oxígeno, VE/VCO_2: porción lineal de la pendiente de ventilación y CO_2 producido, UA: Umbral anaeróbico, + raramente presente, ++ presente a veces, +++ frecuentemente presente, ++++ generalmente presente. Esta tabla asume que el paciente recibe tratamiento de antiarritmicos ni betabloqueantes que puedan afectar la respuesta cronotrópica al ejercicio.

Tabla 3. Alteraciones de la prueba de esfuerzo específicas por cardiopatía.[12]

4.2 Artículo 2: Paediatric cardiac rehabilitation in congenital heart disease: a systematic review

Aportación del doctorando: planteamiento del trabajo científico y la hipótesis, búsqueda bibliográfica, clasificación de la evidencia, redacción y edición del artículo.

Se encontraron un total de 193 artículos con las palabras clave, de los cuales solamente 24 cumplían con los criterios de inclusión. De estos, 21 tenían un programa estructurado y únicamente 18 tenían un componente de reentrenamiento al esfuerzo.

La revisión se realiza en estos últimos 18 artículos, si bien 2 por ser casos clínicos no se incluyeron en el análisis final. No se registraron efectos adversos. En la Tabla 1_{anexo} se recoge la descripción de la población y el programa rehabilitador, el paciente más joven incluido tenía 4 años. El número de pacientes incluidos en los estudios variaba de 1 a 103 y la duración de los programas de 2 semanas a 10 meses. En las Tabla 2_{anexo} se recogen las características principales de cada estudio, lo más frecuente fueron series de casos, el tipo de entrenamiento y las medidas de ejercicio eran heterogéneas, y el seguimiento se hacía a corto plazo.

El nivel de evidencia de estos estudios se clasifico según el sistema de Oxford y se presenta en la Tabla 4. No se realizaron estudios randomizados con grupo control y los estudios más rigurosos recibieron una puntuación de 3.

El nivel de evidencia que apoya la eficacia de la rehabilitación cardiaca en niños con cardiopatía se puede definir como sugestiva pero no definitiva: Clasificación de nivel B del Oxford Center for Evidence-Based Medicine.

Autor	*Nivel de evidencia*
Mc Bride 2007[77]	4
Rhodes 2006[78]	2B
Moalla 2006[79]	2B
Brassard 2006[80]	2B
Opocher 2005[81]	4
Rhodes 2005[82]	3B
Minamisawa 2001[83]	4
Fredriksen 2000[84]	2B
Sklansky 1994[85]	4
Balfour 1991[86]	4
Calzolari 1990[87]	2B
Longmuir 1990[88]	2B
Longmuir 1985[89]	2B
Bradley 1985[90]	4
Ruttenberg 1983[91]	2B
Goldberg 1981[92]	4

Tabla 4. Clasificación por autores según los niveles de evidencia de Oxford.[93]

4.3 Artículo 3: Physical Activity is Associated with Improving Aerobic Exercise Capacity over Time in Adults with Congenital Heart Disease.

Aportación del doctorando: planteamiento de la hipótesis, recogida de datos, análisis de datos, redacción y edición del texto.

Características de los pacientes

La actividad física se clasificó a partir de la historia clínica de los pacientes en n=147 (72.4%) de los 203 pacientes que cumplían los criterios de inclusión. Tras analizar la distribución por porcentaje de cambio en el $pVO_{2\text{-abs}}$, se excluyó a un outlier cuyo $pVO_{2\text{-abs}}$ había aumentado un 70.4% entre pruebas (en el resto de los sujetos el $\Delta pVO_{2\text{-abs}}$ era de -24.2% + 35.5%). De los 146 sujetos que se incluyeron en el análisis, en 145 se pudo clasificar la actividad física en la primera prueba. Se recogieron datos demográficos, clínicos y de las pruebas de esfuerzo de todos los pacientes (Tabla 5). No se hallaron diferencias significativas entre aquellos excluidos (n=57) y aquellos incluidos en el análisis (Ej. edad 32.8 vs. 33.5 años, p=0.65; el tiempo entre estudios era de 13.3 vs. 13.6 meses, p=0.63; $\Delta pVO_{2\text{-abs}}$ inicial 1.48 vs. 1.61 l/min, p=0.15; $\Delta pVO_{2\text{-\%pred}}$ +2.4 vs. +3.0%, p=0.76).

	Physical activity frequency				
	Overall	Low	Occasional	Frequent	P
N	145	61	47	37	
Age (y)	33.5 ± 10.2	34.1 ± 11.4	35.2 ± 9.9	30.3 ± 7.8	0.09
Male (%)	49.6	50.8	55.3	40.5	0.39
Height (cm)	167.8 ± 9.9	166.9 ± .9.9	167.6 ± 7.7	169.5 ± 12.2	0.53
Weight (kg)	73.9 ± 17.8	77.1 ± 20.1	72.4 ± 13.5	70.7 ± 18.1	0.21
BMI, baseline (kg/m^2)	26.1 ± 4.9	27.5 ± 5.8	26 ± 4.0	24 ± 4.0	0.01
Peak $VO_{2\text{-perkg}}$, baseline (ml/min/kg)	21.9 ± 6.7	19.0 ± 5.0	21.4 ± 6.1	27.4 ± 6.7	<0.01
O_2 pulse, baseline (mL/beat)	10.6 ± 3.6	9.7 ± 3.0	10.4 ± 3.6	12.0 ± 4.0	<0.01
Diabetes mellitus (%)	1.5	3.3	0	0	0.27
Tobacco (%)	9.9	15.8	6.7	3.3	0.15
Systolic BP (mmHg)	122 ± 15	125 ± 16	119 ± 14	119 ± 13	0.04
Diagnosis (%)					0.49
Tetralogy of Fallot	35.8	34.4	29.8	46.0	
Fontan	10.3	14.8	6.4	8.1	
Systemic right ventricle	22.8	16.4	29.8	24.3	
Other	31.0	34.4	34.0	21.6	
Ventricular dysfunction (%)					0.42
Moderate/severe	13.1	18.0	12.8	5.4	
Mild	23.5	18.0	25.5	29.7	
Normal	61.4	60.6	61.7	62.1	
Unknown	2.1	3.2	0	2.7	
Arrhythmia with exercise (%)					0.62
None	92.4	90.2	93.6	94.6	
Atrial fibrillation/flutter/SVT	2.1	3.3	2.1	0	
Ventricular tachycardia	0.7	0	2.1	0	
Frequent APBs or VPBs	4.8	6.6	2.1	5.4	
Pacemaker (%)	19.3	19.7	23.4	13.5	0.51
Medication (%)					
ACEI	33.8	37.7	34.0	27.0	0.58
Beta blocker	33.8	36.0	46.8	13.5	<0.01
Digoxin	10.3	8.2	8.5	16.2	0.44
Diuretic	17.2	23.0	17.0	8.11	0.17

Tabla 5. Descripción basal de la población estudiada.[94]

Datos iniciales

De los 145 pacientes clasificables en la primera prueba de esfuerzo 61 (42%) eran sedentarios, 47 (32.4%) realizaban actividad física de forma ocasional y 37 (25.5%) frecuentemente. El IMC y la presión sistólica tendían a ser más altos en el grupo sedentario mientras que el $pVO_{2\text{-perkg}}$ así como el PO_2 eran significativamente más altos ($p<0.01$) en el grupo de pacientes que hacia ejercicio frecuentemente. Los datos obtenidos en la segunda prueba de esfuerzo eran parecidos.

Se halló una diferencia significativa a nivel del $pVO_{2\text{-}\%pred}$ basal entre los distintos tipos de cardiopatías congénitas (Fig.4_a). La mediana del $pVO_{2\text{-}\%pred}$ estaba muy por debajo de lo normal en todos los grupos diagnósticos y más de un 75% de los pacientes de todos los grupos están por debajo del valor predicho.

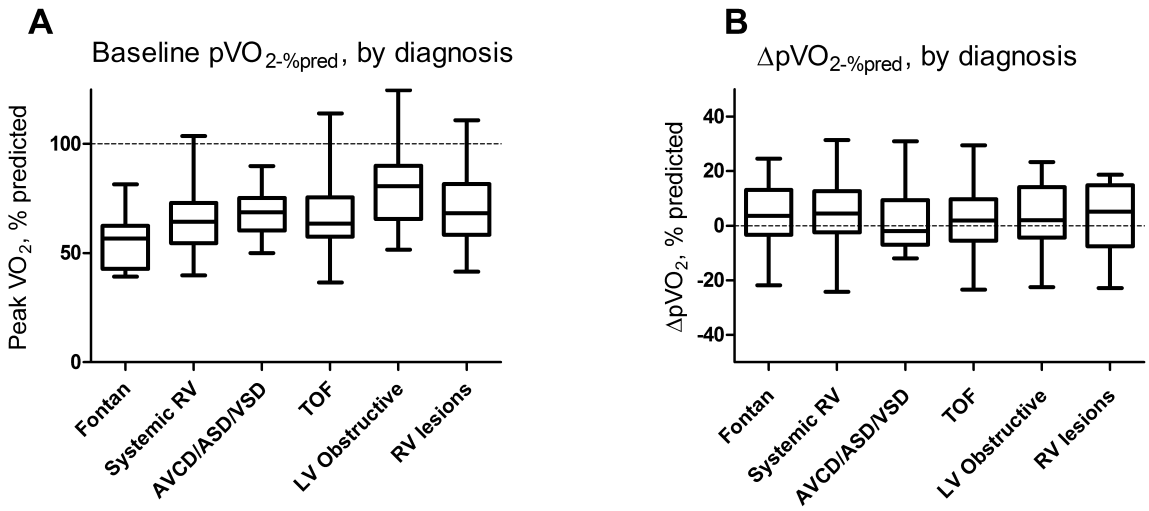

Fig 4. Capacidad de ejercicio en cada tipo de cardiopatía de la población de estudio. Systemic RV: ventrículo derecho sistémico, AVCD: defecto de canal, ASD: comunicación interauricular, VSD: comunicación interventricular, TOF: Tetralogía de Fallot, LV obstructive: lesión obstructiva de ventrículo izquierdo, RV lesions: lesiones de ventrículo derecho. [94]

Por otra parte, no hubo diferencias en cuanto a $\Delta pVO_{2\text{-}\%pred}$ entre los distintos grupos diagnósticos a lo largo del estudio (Fig.4_b).

Predictores de cambio en el VO_2 pico

El predictor más significativo de % de cambio de $pVO_{2\text{-}abs}$ era el IMC (Tabla 6). Los pacientes con un IMC más alto inicialmente tendían a tener un $pVO_{2\text{-}abs}$ más bajo en la segunda prueba (por cada 5 Kg/m^2 de más en la primera prueba, el $pVO_{2\text{-}abs}$ en la segunda prueba era un 3% más bajo, p=0.001, r^2=0.07). La altura no se asociaba al $\Delta pVO_{2\text{-}abs}$ (p=0.26) mientras que si lo hacia el peso inicial (por cada 10 kg de más el $pVO_{2\text{-}abs}$ disminuía un 1.6% entre pruebas, p=0.002, r^2 = 0.06). Aquellos que tenían un $pVO_{2\text{-}abs}$ más alto solían tener un $pVO_{2\text{-}abs}$ más bajo en la segunda prueba. Por cada $pVO_{2\text{-}abs}$ inicial un 10% más bajo, aumentaba un 1.4% (p=0.01, r^2 = 0.04) El $\Delta pVO_{2\text{-}abs}$ no se relacionó con otras variables clínicas o demográficas basales. No se halló una relación entre el uso crónico de medicación cardiaca o la introducción de una nueva medicación durante el periodo de estudio con un $\Delta pVO_{2\text{-}abs}$ (beta bloqueantes n=10 p=0.27, IECAs/ARB n=5 p=0.21, digoxina n=2 p=0.82, diuréticos n=7 p=0.22). Los pacientes que empezaban a tomar un beta bloqueante tendían a tener una frecuencia cardiaca más

baja ($\Delta = -13.5$ lpm, $p< 0.001$) en el segundo estudio pero un pulso de O_2 mayor ($\Delta =$ +14 ml/latido, $p<0.001$). No se hallaron asociaciones entre el resto de los medicamentos y cambios de frecuencia cardiaca máxima ni pulso de oxígeno.

	r^2	β	P
Edad (años)	0.012	-0.12	0.19
Sexo (hombres)	< 0.001	0.51	0.79
IMC (kg/m^2)	0.07	-0.62	0.001
Altura (cm)	0.009	-0.11	0.26
Peso (kg)	0.063	-0.16	0.002
Tabaco	< 0.001	-0.35	0.92
Diabetes mellitus	< 0.001	-0.76	0.93
Marcapasos	< 0.001	-0.21	0.93
Disfunción ventricular severa	0.017	4.46	0.12
pVO_2 basal	0.045	-4.41	0.01
PAM (mmHg)	0.002	0.05	0.6

Tabla 6. Regresión lineal univariable de predictores del cambio del porcentaje de cambio de pVO_2. IMC: índice de masa corporal, PAM: presión arterial media, pVO_2: consumo de oxígeno pico.[94]

Otras medidas de ΔpVO_2 (Ej. $\Delta pVO_{2\%pred}$, $\Delta pVO_{2\text{-por kg}}$) tenían una asociación con las variables predictivas parecida a las observadas con el ΔpVO_{2abs}.

Efecto de la época del año en los resultados de la prueba de esfuerzo

No se observaron diferencias significativas en el $\Delta pVO_{2\%pred}$ en la prueba de esfuerzo en relación al mes ($p=0.34$) o a la época del año (Octubre-Marzo vs. Abril-Septiembre,

p=0.74). La época del año de la prueba de esfuerzo inicial no afectaba al cambio del $pVO2_{\%pred}$. Aquellos que hicieron la segunda prueba de esfuerzo en la misma época que la prueba inicial (n = 82, $\Delta pVO_{2\text{-}\%pred}$ = +1.8 ± 1.1), aquellos que realizaron la primera prueba en invierno y la segunda en verano (n = 35, $\Delta pVO_{2\text{-}\%pred}$ = +2.0 ± 1.8) y los que lo realizaron en sentido opuesto (n = 29, $\Delta pVO_{2\text{-}\%pred}$ = +2.2 ± 1.6) tuvieron el mismo cambio en $pVO_{2\text{-}\%pred}$ (p = 0.98).

El impacto de la actividad física en los parámetros de ejercicio

No se hallaron diferencias demográficas ni clínicas significativas entre los grupos de pacientes clasificados por su nivel de actividad física en la segunda prueba de esfuerzo (representa el nivel de actividad física entre pruebas). Se encontraron diferencias estadísticamente significativas en el IMC (p = 0.02) que era más bajo y el VO_2 pico (p = 0.01) que era más alto en los pacientes más activos, y el número de fumadores que era más alto en aquellos pacientes que realizaban ejercicio de forma moderada (p<0.01). Hubo menos paciente clasificados como sedentarios en la segunda visita comparada con la primera (n = 42 vs. 61).

		Physical activity frequency			
	Overall	Low	Occasional	Frequent	P
N	146	42	49	55	
Time between tests (mos.)	13.6 ± 4.7	14.3 ± 4.5	13.7 ± 5.2	13.0 ± 4.5	0.58
BMI, baseline (kg/m^2)	26.1 ± 4.9	27.7 ± 5.6	26.1 ± 4.8	24.9 ± 4.0	0.03
Weight (kg)					
Baseline	74.0 ± 17.7	78.0 ± 19.9	74.1 ± 16.3	70.8 ± 16.9	0.14
Δ	−0.2 ± 3.7	0.5 ± 3.0	0.2 ± 3.9	−1.2 ± 3.7	0.008
Rest MAP (mmHg)					
Baseline	91.0 ± 9.4	92.9 ± 11.3	90.3 ± 9.0	90.2 ± 7.9	0.43
Δ	0.0 ± 9.0	−0.6 ± 9.7	2.1 ± 8.9	−1.3 ± 8.5	0.19
Rest HR (bpm)					
Baseline	77.3 ± 13.9	81.6 ± 12.9	76.8 ± 13.5	74.6 ± 14.4	0.05
Δ	−0.6 ± 12.0	0.3 ± 13.2	−2.0 ± 9.3	0.1 ± 13.1	0.81
Peak HR (bpm)					
Baseline	153.2 ± 24.7	153.6 ± 29.8	152.2 ± 24.0	153.8 ± 21.3	0.95
Δ	0.7 ± 12.4	−0.8 ± 13.5	−0.5 ± 11.9	3.0 ± 11.8	0.34
Peak Work (W)					
Baseline	148.6 ± 56.6	134.9 ± 46.9	148.6 ± 60.3	159.0 ± 58.6	0.14
Δ	3.3 ± 16.5	−0.7 ± 18.0	3.0 ± 16.9	6.7 ± 14.3	0.21
$pVO_{2\text{-perkg}}$ (ml/kg/min)					
Baseline	22.0 ± 6.7	19.3 ± 5.7	22.0 ± 6.1	24.0 ± 7.3	0.005
Δ	0.6 ± 2.7	0.07 ± 2.1	0.0 ± 3.0	1.6 ± 2.7	0.004
Δ (ml/min/kg/year)	0.7 ± 2.9	0.06 ± 2.0	−0.07 ± 2.77	1.8 ± 3.2	0.002
$pVO_{2\text{-\%pred}}$ (%)					
Baseline	67.3 ± 16.7	61.2 ± 13.1	67.3 ± 12.8	71.9 ± 20.6	0.02
Δ	1.9 ± 9.9	0.5 ± 8.6	0.2 ± 9.7	4.6 ± 10.5	0.04
Δ (%pred/year)	1.9 ± 9.9	0.3 ± 8.0	−0.5 ± 9.0	5.2 ± 11.2	0.01
$pVO_{2\text{-abs}}$ (L/min)					
Baseline	1.6 ± 0.6	1.49 ± 0.53	1.64 ± 0.62	1.68 ± 0.60	0.29
Δ	0.03 ± 0.18	0.01 ± 0.17	0.00 ± 0.19	0.08 ± 0.19	0.07
Δ (%/year)	2.3 ± 14.4	1.6 ± 10.1	0.2 ± 12.2	6.6 ± 13.3	0.04
O_2 pulse (ml/beat)					
Baseline	10.6 ± 3.6	9.7 ± 2.9	10.9 ± 4.0	10.9 ± 3.6	0.19
Δ	0.1 ± 1.3	0.1 ± 1.4	0.0 ± 1.4	0.2 ± 1.2	0.62
Δ (%/year)	2.3 ± 14.4	2.0 ± 13.6	0.8 ± 12.8	3.8 ± 16.3	0.56
VE/VCO_2 Slope					
Baseline	28.2 ± 4.6	29.5 ± 4.4	27.9 ± 4.2	27.5 ± 5.0	0.02
Δ	−0.01 ± 4.16	−0.1 ± 5.4	´−0.4 ± 3.0	0.3 ± 4.0	0.37

CPX data at baseline and change in CPX data between both tests, based on PA classification at follow-up.

Tabla 7. Datos de la prueba de esfuerzo clasificado por nivel de actividad física en la 2ª prueba N: número de pacientes, mos: meses, BMI: Índice de masa corporal, MAP: presión arterial media, HR: frecuencia cardiaca, peak W: capacidad de trabajo máximo, pVO_2: consumo de oxígeno pico, VE/VCO_2slope: pendiente VE/VCO_2, O_2 pulse: pulso de oxígeno.[94]

Los datos de la prueba de esfuerzo inicial y el cambio entre pruebas según la clasificación por nivel de actividad física están representados en la Tabla 7. Una actividad física frecuente se asociaba a una mejoría tanto de $pVO_{2\text{-perkg}}$ y $pVO_{2\%\text{-pred}}$ (es decir, el $\Delta pVO_{2\text{-perkg}}$ y el $\Delta pVO_{2\%\text{-pred}}$ eran positivos con p = 0.003 y 0.04 respectivamente). Se observaba una tendencia positiva en el $pVO_{2\text{-abs}}$ (p = 0.07) y una mejora significativa del $pVO_{2\text{-abs}}$ si se ajustaban por año (p=0.04). Estas relaciones se ilustran gráficamente en la Fig.5, en la que se comparan los clasificados en los dos grupos de menor actividad física con los que realizaban ejercicio físico de forma frecuente.

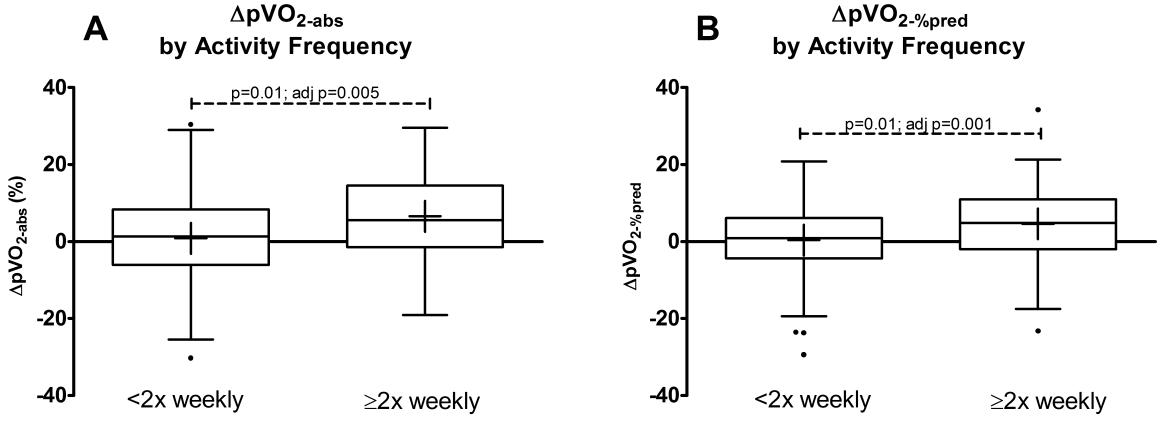

Fig.5. Cambio en pVO_2tanto de forma absoluta como en porcentaje predicho, comparando pacientes que realizaban ejercicio físico menos de 2 veces por semana comparado con los que realizaban 2 o más.[94]

La asociación entre la frecuencia de ejercicio y el $\Delta pVO_{2\text{-}\%pred}$ se mantenía a pesar del ajuste multivariable que incluía edad, sexo, $pVO_{2\text{-}\%pred}$ (p = 0.02) y otros factores tales como el IMC, tiempo entre pruebas, cambios de peso, diabetes, uso de tabaco y necesidad de marcapasos (p = 0.03). Esta misma asociación existía entre frecuencia de ejercicio y el $\Delta pVO_{2\text{-per/kg}}$ tras ajustar por características clínicas y demográficas (p = 0.002 y 0.02 respectivamente).

Para entender mejor si las diferencias entre grupos de $\Delta pVO_{2\text{-abs}}$ eran clínicamente significativas, analizamos la proporción de pacientes que habían incrementado o disminuido su $pVO_{2\text{-abs}}$ al menos una desviación estándar (cambio medio de +3 ± 11%, con +1SD definido como un incremento de 14% y -1SD como -8%; Fig.6). Los pacientes con poca o nula actividad física durante el tiempo de intervalo entre pruebas eran más susceptibles de sufrir una caída de su pVO_2 de al menos 1 SD (19.8%) en vez de un aumento (11.0%). Contrariamente, aquellos que realizaban ejercicio físico frecuentemente tendían a aumentar su $pVO_{2\text{-abs}}$ al menos 1SD (27.3%), mientras solamente un 12.7% de aquellos que hacían ejercicio de forma frecuente disminuían su $pVO_{2\text{-abs}}$ más de 1 SD (p=0.03). Este hallazgo era independiente de la edad, IMC y $pVO_{2\text{-abs}}$ basal del paciente (regresión logística multivariable OR = 7.4, 95%CI, 1.5–35.7, para +1SD en $pVO_{2\text{-abs}}$ para los que realizaban frecuentemente actividades físicas).

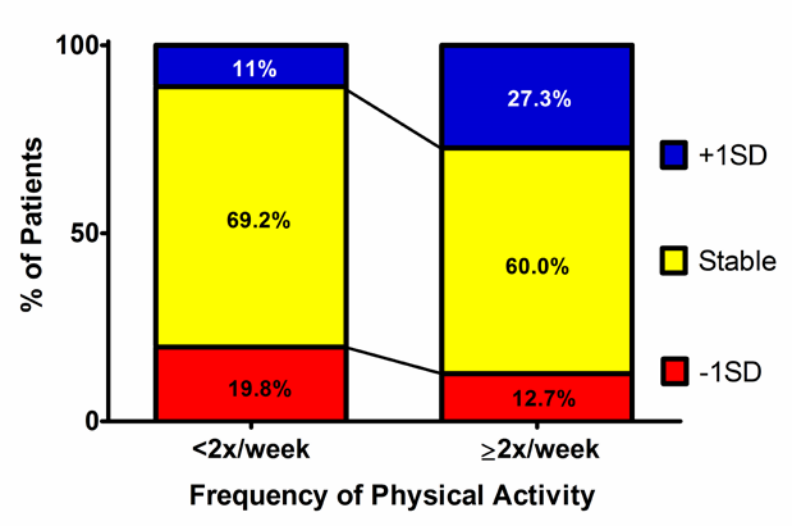

Fig.6. Proporción de pacientes que varían su capacidad de ejercicio al menos 1DS (11%) según su nivel de actividad física, lo cual se consideraría clínicamente relevante.[94]

Cambio en la frecuencia de la actividad física y pVO2

La mayoría de los pacientes (61.4%) mantenían el mismo nivel de actividad física durante el tiempo de estudio; un 29.7% lo aumento y un 9% disminuyó su frecuencia. Se demostró una relación estadísticamente significativa entre el cambio de actividad física entre pruebas y el $\Delta pVO_{2\text{-abs}}$ (l/min), y $\Delta pVO_{2\text{-\%pred}}$ (Fig. 7). La disminución de la actividad física se asociaba con una disminución de $pVO_{2\text{-perkg}}$ (−1.9 ± 3.3 ml/min/kg), mientras que el mantenimiento de la actividad física se asociaba con una estabilidad del $pVO_{2\text{-perkg}}$ (+0.5 ± 2.7 ml/min/kg) y el aumento de la actividad física se asoció con una mejoría de $pVO_{2\text{-perkg}}$ (+1.6 ± 2.1 ml/min/kg).

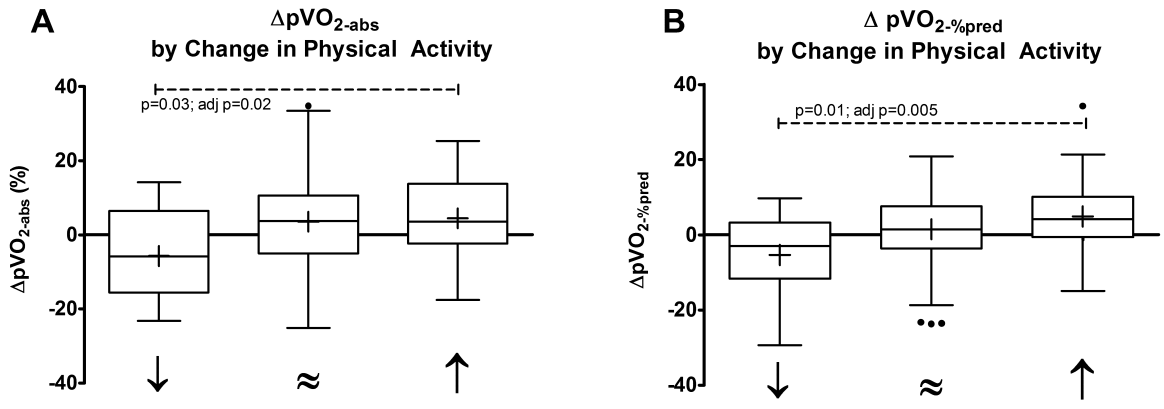

Fig.7. Cambio en pVO_2 debido al cambio de la actividad física (disminución="↓", mantenida="≈", aumento="↑") entre las 2 pruebas.[94]

V. DISCUSIÓN

El número de pacientes supervivientes con cardiopatía congénita aumenta progresivamente, sin embargo su vida no va a estar exenta de complicaciones. Las intervenciones destinadas a disminuir el impacto de la posible discapacidad de los pacientes con cardiopatía congénita pueden ser desarrolladas y estudiadas con mayor profundidad.

5.1 Artículo 1: Exercise testing and training in patients with congenital heart disease

La capacidad del ejercicio en el paciente con cardiopatía congénita es de máxima relevancia como ya hemos expuesto con anterioridad, por la relación demostrada con el riesgo de hospitalización y mortalidad, porque puede ser una de las primeras variables que se alteran con el deterioro de la función cardiaca y porque algunas de las alteraciones fisiológicas vistas en estos pacientes solo se detecta al someter al aparato cardiopulmonar y musculoesquelético a estrés. El propósito de esta revisión era discutir las ventajas e inconvenientes de cada prueba de esfuerzo, resaltar las variables fisiológicas, las alteraciones asociadas a las distintas cardiopatías y explicar su significado.

En la población infantil es fundamental ser mínimamente invasivo y esta prueba aporta mucha información sin necesidad de sedación ni agresiones mayores, lo único que requiere es la colaboración por parte del paciente.

Existen una variedad de pruebas de esfuerzo que ya se habían aplicado previamente a distintas patologías en adultos[95] tales como la insuficiencia cardiaca[96, 97], la hipertensión pulmonar, la enfermedad pulmonar obstructiva crónica (EPOC)[98] o enfermedades pulmonares intersticiales.[99, 100] Las variables halladas con estas pruebas han demostrado, tanto en enfermedades cardiacas como pulmonares, tener un valor pronostico mayor que aquellas variables pronosticas halladas en reposo.

En algunas de estas patologías como la insuficiencia cardiaca o EPOC se recurre a pruebas más simples tales como la prueba de los 6 minutos marcha, ya que han demostrado su validez para representar la intolerancia al ejercicio relacionada con las actividades de la vida diaria.[101-103]

Sin embargo la prueba de esfuerzo con análisis metabólico con gases sigue proporcionando más información y más detallada en todas esas patologías, especialmente en las cardiacas.

El consumo de oxigeno se considera el gold estándar en cuanto a la cuantificación de la capacidad de ejercicio y su valor pronóstico es fundamental, sobre todo en la insuficiencia cardiaca. Permite una clasificación pronostica[104] y ayuda a la decisión del transplante cardiaco.[71, 97]

Previo a este artículo poca discusión había habido acerca de la importancia de la medición de capacidad de ejercicio, las variables importantes a analizar y las razones de su alteración así como los efectos del programa de rehabilitación cardiaca. Sin embargo en la población adulta con cardiopatía adquirida y patología pulmonar si que había sido discutida la utilidad e indicación de este tipo de pruebas[105, 106], no siendo tan utilizada la prueba metabólica con análisis de gases.

Harkel y Takken[107] publicaron el mismo año una revisión de las pruebas de esfuerzo, la capacidad de ejercicio y el reentrenamiento al esfuerzo en los pacientes con cardiopatías congénitas. Al igual que nosotros resaltaron la relevancia de este tipo de prueba y la capacidad de ejercicio en esta población.

La parte técnica de la prueba de esfuerzo viene muy bien detallada por parte de Paridon en el 2006.[63]

Las intervenciones como la rehabilitación cardiaca que se lleva a cabo en adultos con cardiopatía adquirida, que han demostrado disminuir la morbimortalidad y los gastos sanitarios así como aumentar la calidad de vida y la capacidad de ejercicio no son habituales en pacientes con cardiopatías congénitas.[57, 108] Según nuestra revisión preliminar parecen mejorar la capacidad de ejercicio y ser intervenciones de bajo riesgo.

5.2 Artículo 2: Paediatric cardiac rehabilitation in congenital heart disease: a systematic review

El objetivo de esta revisión era la de cuantificar y describir los datos existentes con relación a los programas de rehabilitación en niños con cardiopatías congénitas. Algunos estudios han aportado datos que demuestran el beneficio a corto plazo de la rehabilitación cardiaca en este tipo de población.[78, 79, 81-86, 109] No se observaron efectos adversos en ninguno de los estudios. Un pequeño número de revisiones previas[110, 111] han evaluado esta intervención y en general las conclusiones son similares a las nuestras.

Sin embargo nuestra revisión pone en evidencia algunos puntos que no se habían tratado previamente. Los efectos beneficiosos no se observaron y no se usó una randomización adecuada en todos los casos. Los diferentes tipos de cardiopatías dan lugar a distintas alteraciones fisiológicas y secuelas residuales muy distintas y que pueden responder de forma diferente a los programas de rehabilitación. Lo ideal sería estudiar cada tipo de cardiopatía por separado y esto se llevó acabo solo en siete de los estudios clínicos.[80, 81, 83, 85, 87, 112, 113]

La estructura de los programas de rehabilitación cardiaca variaba en cuanto a intensidad, frecuencia y duración del ejercicio. Los estudios más antiguos se limitaban al ejercicio aeróbico[81-83, 85-87, 91, 92], observándose un aumento de la combinación de aeróbico y resistencia en estudios más recientes.[77, 79, 80, 84, 88-90, 112, 113] Dada la fuerte correlación entre la fuerza muscular y la tolerancia de ejercicio[80, 112] los resultados subóptimos de algunos de los programas se pueden deber a esto.

Los programas estudiados no tienen en cuenta la posible asociación de la cardiopatía congénita con otras anomalías congénitas o adquiridas que ya se comentaron en la introducción[5, 6, 33, 38, 41, 43, 114-116] y que se podrían trabajar en un programa de rehabilitación.

Otros elementos típicos de los programas de adultos con cardiopatía adquirida[57] que no se incluyeron en los de cardiopatía congénita fueron la educación, consejo nutricional, manejo de los factores de riesgo cardiovascular, atención psicológica y

recomendaciones acerca del ejercicio físico. La parte educativa tan importante en los adultos sólo se incluyó en cuatro de los estudios.[86, 90, 112, 117] Dado que no son infrecuentes los problemas psicológicos y de comportamiento en estos niños y sus cuidadores, no incluir este tipo de servicios puede afectarles negativamente e influir en las probabilidades de éxito del programa.

Solo se proporcionaron datos de medio y largo plazo en dos de los estudios[78, 88] , donde se observaron mejorías significativas que duraban más allá del período post-programa inmediato. Aunque es difícil de llegar a una conclusión sólida con estos dos pequeños estudios. Para obtener cambios en el estilo de vida a largo plazo, una necesidad en pacientes con enfermedades crónicas y uno de los objetivos de la rehabilitación, se debe llevar a cabo una intervención multinivel que se centre en los pacientes, sus estilos de vida y sus cuidadores. Para mantener los beneficios inmediatos de la rehabilitación se debería tratar de crear programas de continuación, este tipo de planteamiento se ha llevado a cabo con éxito en programas de niños con obesidad.[118, 119] Los resultados de estos programas de obesidad con intervención multinivel demuestran mejores resultados que otros con menos recursos.

Los medios para valorar el impacto de la rehabilitación cardiaca también variaba mucho entre estudios, la prueba de esfuerzo con análisis metabólico- una de las herramientas más valiosas para cuantificar la capacidad de ejercicio y valorar el impacto del programa de rehabilitación- se utilizó en escasos estudios. El coeficiente respiratorio no se proporcionó complicando la interpretación de los resultados en algunos casos.

Aparte del consumo de oxígeno, no hay un consenso con respecto a qué tipo de medidas a emplear para valorar los efectos de un programa de rehabilitación cardiaca. Algunas posibilidades serían la fuerza muscular, composición corporal, calidad de vida, etc. Para poder valorar eficazmente los efectos y beneficios de un programa de rehabilitación cardiaca hay que identificar variables que midan las distintas áreas que se puedan ver afectadas por dicha intervención.

A partir de los artículos revisados para este estudio y la bibliografía existente acerca de programas para pacientes obesos y con enfermedades crónicas tales como la fibrosis quística[120, 121] y el transplante renal[121, 122] parece haber cierto consenso acerca de una

duración mínima de los programas de 12 semanas y una frecuencia de 2-3 veces por semana con sesiones que duren por lo menos 40 minutos. Creemos que los programas deberían de incluir ejercicios aeróbicos, de resistencia, de flexibilidad así como educación e intervención psicológica. La intensidad del entrenamiento debería de establecerse alrededor del umbral anaeróbico. Este punto es importante en pacientes con cardiopatía congénita ya que suelen presentar alteraciones cronotrópicas.

Una observación, producto final de este análisis, es que los programas de rehabilitación para pacientes con cardiopatía congénita están infrautilizados y su valor no es apreciado. Hay una serie de factores que pueden explicar esta situación tales como limitación de personal y recintos especializados, falta de recursos económicos, de cobertura por parte del seguro médico, falta de conocimiento por parte del médico o problemas relacionados con los padres: logísticos, coste económico o ansiedad de los padres. Para poder solucionar estos inconvenientes habría que hacer cambios a nivel de la política, protocolos y educar a los médicos y cuidadores.

5.3 Artículo 3. Physical Activity is Associated with Improving Aerobic Exercise Capacity over Time in Adults with Congenital Heart Disease

Se ha encontrado que la actividad física frecuente de intensidad al menos moderada se asocia con un mayor mantenimiento de la capacidad de ejercicio en adultos con cardiopatías congénitas.

Los pacientes que eran más activos tenían tendencia a mantener o mejorar su pVO_2 y perder peso entre pruebas, por el contrario pacientes que realizaban ejercicio de forma menos frecuente solían incrementar de peso y disminuir su pVO_2. Es más, no solo la mayor actividad física a nivel basal sino que también aquellos pacientes que incrementaban su actividad física mejoraban significativamente el pVO_2 comparados con los que lo disminuían. El cambio de pVO_2 no se podía atribuir a la pérdida de peso, ya que al ajustar por cambio de peso en los distintos modelos de regresión multivariable no se veía afectada la relación entre la actividad física y el cambio de pVO_2.

Nuestros datos apoyan el concepto de que la capacidad aeróbica de los adultos con cardiopatías congénitas no está limitada únicamente por el defecto cardiaco, sino que el declive que se observa con el tiempo en estos pacientes que se había observado en estudios previos es modificable. Para muchos adultos con cardiopatías congénitas el ejercicio físico habitual tiene el potencial de atenuar o revertir esa caída.

El ejercicio realizado de forma regular tiene una variedad de efectos que pueden explicar estos resultados. Incluyen factores periféricos (Ej. Un aumento en el número de mitocondrias, aumento de las enzimas aeróbicas, el tamaño muscular y la densidad capilar[123], una mejora de la capacidad de bombeo muscular[82] y una serie de cambios beneficiosos en los lechos vasculares) que pueden mejorar la extracción de oxígeno y/o el gasto cardiaco[124] con el ejercicio; así como factores centrales(Ej. Incremento de la masa miocárdica y mejora de la función sistólica y diastólica)[125] que también pueden mejorar la reserva miocárdica y mejorar el gasto cardiaco con el ejercicio.

El sedentarismo es común en adultos con cardiopatías congénitas y >70% de estos pacientes refieren ansiedad moderada-extrema con el ejercicio.[126] Esta aprehensión parece originarse en consejos inapropiados o sobreprotección durante la niñez y el periodo adulto. Históricamente se restringía la actividad física en pacientes con cardiopatías congénitas[127] o no se podía dar consejos específicos al no haber guías. Un estudio reciente de pacientes con estenosis aórtica sugirió que la restricción de ejercicio no prevenía eventos adversos y que los efectos negativos de la restricción de ejercicio en factores de riesgo cardiovascular, capacidad de ejercicio y bienestar mental se subestimaban.[128]

Nuestras observaciones son consistentes con la experiencia en otras poblaciones. En la población general la actividad física se relaciona con una disminución de la mortalidad y de eventos cardiovasculares primarios[47, 129] y secundarios[130] así como una mejora de la calidad de vida. Intervenciones para aumentar la actividad física parecen ser beneficiosos en pacientes con insuficiencia cardiaca[50], obesidad[52] y diabetes.[51]

El impacto observado de la actividad física sobre la capacidad de ejercicio de pacientes con cardiopatías congénitas es mayor que otros procedimientos quirúrgicos y/o cateterismos.[131, 132] En los pocos estudios que se han hecho sobre la rehabilitación

cardiaca en adultos con cardiopatías congénitas se han obtenido resultados prometedores en cuanto a capacidad de ejercicio y calidad de vida.[133-135] La rehabilitación cardiaca se ha estudiado en profundidad en adultos con cardiopatía adquirida y se ha demostrado que aumenta la capacidad de ejercicio, reduce la morbimortalidad y los costes médicos[57]. El número de adultos con cardiopatía congénita está aumentando y los gastos sanitarios que generan incluso más.[136, 137] El impacto de intervenciones de bajo coste económico como prescripciones de ejercicio o rehabilitación cardiaca podría mejorar su "historia natural" y calidad de vida a la par que disminuye los gastos sanitarios.

El hallazgo de que el IMC y el peso eran predictores significativos de cambio de pVO_2 sugiere que añadir un componente educacional, nutricional y/o de modificación del comportamiento podría tener un efecto beneficioso independiente del ejercicio.

Nuestros datos apoyan la necesidad de ensayos clínicos prospectivos para evaluar el impacto de distintas estrategias para aumentar la actividad física y mejorar la capacidad aeróbica en esta población. Sigue sin estar claro si la mejora de $pVO_{2\%pred}$ tendría un beneficio a nivel de calidad de vida, eventos cardiovasculares y mortalidad.

VI. CONCLUSIONES

- La prueba de esfuerzo con análisis metabólico es la forma más objetiva y detallada de medir la capacidad de ejercicio en la cardiopatía congénita.
- Las variables más importantes a valorar son el consumo pico de oxígeno, el pulso de oxígeno, la frecuencia cardiaca, el umbral anaeróbico y el coeficiente respiratorio.
- Los pacientes con cardiopatía congénita se podrían beneficiar de un programa de rehabilitación cardiaca.
- La evidencia científica de la eficacia de los programas de rehabilitación cardiaca en cardiopatías congénitas infantiles es limitada.
- La composición idónea de este tipo de programa en cardiopatía congénita está aún por definir.
- Se deben de realizar estudios clínicos para determinar el beneficio y la composición idónea de dichos programas.
- La disminución de capacidad de ejercicio en las cardiopatías congénitas, no se debe sólo a la patología de base, sino a un estilo de vida sedentario. Hemos objetivado reversibilidad de esta intolerancia al esfuerzo.

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VIII. ANEXOS

Table 1. Description of patient population and rehabilitation programme.

References	Location	Patient population	Ages	n	Patients treated	Type of excercise	Duration	Frequency	Intensity	Sessions
McBride[42]	Hospital	Heterogeneous	10–16	20	20	Aerobic, resistance	2–10 months	3/week	HR at AT, 60% of maximal voluntary contraction	30–60 min
Rhodes[30]	Hospital	Heterogeneous	8–18	33	15	Aerobic, resistance	3 months	2/week	HR at AT, light resistance	60 min
Moalla[28]	Home	Heterogeneous	12–15	18	10	Aerobic	12 weeks	3/week	HR at AT	45 min
Brassard[39]	Home (2), hospital (3)	Fontan	11–26	5	5	Aerobic, resistance	2 months	3/week	50–80% peak VO_2	20–30 min
Opocher[31]	Hospital + home	Fontan	7–12	10	10	Aerobic	8 months	2/week	50–70% peak VO_2	30–45 min
Rhodes[27]	Hospital	Heterogeneous	8–17	16	16	Aerobic, resistance	3 months	2/week	HR at AT, light resistance	60 min
Minamisawa[29]	Home	Fontan	11–25	11	11	Aerobic	2–3 months	2–3/week	60–80% peak HR	40 min
Fredriksen[32]	Hospital or supervised gym	Heterogeneous	10–16	93	55	Aerobic, resistance, flexibility, education	2 weeks or 5 months	Daily or 2/week	65–80% peak HR	Not specified
Sklansky[33]	Hospital	TOF	6–16	11	11	Aerobic	2 months	3/week	60–70% peak HR	30 min
Balfour[34]	Hospital	Heterogeneous	13.5–19.8	6	6	Aerobic, education	3 months	3/week	>70% peak HR	30–40 min
Calzolari[38]	Hospital	TOF	6–16.5	18	9	Aerobic, respiratory	3 months	3/week	60–70% peak HR	60 min
Longmuir[43]	Home	Heterogeneous	4.7–14.3	40	17	Aerobic, resistance, flexibility, coordination	6 weeks	2/week	Capability of talking during exercise	Not specified
Longmuir[44]	Home	Heterogeneous	4.7–14.3	60	30	Aerobic, resistance, flexibility, coordination	6 weeks	2/week	Capability of talking during exercise	Not specified
Bradley[45]	Hospital	TOF/TGA	4–13	9	9	Aerobic, resistance, flexibility, coordination	12 weeks	2/week	60–80% peak HR	60 min
Ruttenberg[40]	Hospital	Heterogeneous	7–18	21	21	Aerobic	9 weeks	3/week	65–75% peak HR	30 min
Goldberg[41]	Home	TOF/VSD	7–18	26	26	Aerobic	6 weeks	3–4/week	50–70% peak VO_2	45 min

AT = anaerobic threshold; HR = heart rate; TGA = transposition of the great arteries; TOF = tetralogy of Fallot; VSD = ventricular septal defect; VO_2 = oxygen consumption

Table 2. Study description.

References	Type of study	Follow-up period	Outcome variables	Results	Comments
McBride[42]	Case series	Immediately post programme	Safety	No major complications.	No CPX data
Rhodes[30]	NRCT*	5 years post programme	• Serial cardiopulmonary exercise testing • Activity, self-esteem and emotional state questionnaires	Significant increase ($p < 0.01$) in: • peak work rate (7.8%) • peak VO_2 (21.8%) Non-significant decline in these parameters in control group	• Well-controlled study • RER reported • Examined midterm effects of the intervention and quality of life
Moalla[28]	NRCT*	Immediately post programme	• Serial cardiopulmonary exercise testing • Respiratory muscle oxygenation (near-infrared spectroscopy)	Significant increase in: • peak VO_2 (21%; $p < 0.05$) • peak respiratory muscle oxygenation (22%; $p < 0.01$) Significant correlation between tissue oxygenation and peak VO_2 at AT ($p < 0.01$) Non-significant improvement in pulmonary function was observed in the training group	• Home exercised regime • Compliance not assessed • RER not reported • Suggests that respiratory physiotherapy in the programme might be helpful
Brassard[39]	Case series	Immediately post programme	• Serial cardiopulmonary exercise testing • Muscle strength (Dynamometer) • Blood pressure • Ergoreflex	Non-significant increase in: • peak VO_2 ($p = 0.47$) • muscle strength ($p = 0.57$) Significative ergoreflex contribution to systolic blood pressure ($p = 0.02$)	• Short duration and variable programme structure might account for lack of improvement
Opocher[31]	Case series	Immediately post programme	• Serial cardiopulmonary exercise testing	Significant increase in: • estimated workload (11.3%; $p = 0.03$) • O_2 pulse (19%; $p = 0.004$) Non-significant increase: • peak VO_2 (11%; $p = 0.07$)	• RER not reported

Table 2. *Continued*

References	Type of study	Follow-up period	Outcome variables	Results	Comments
Rhodes[27]	Case series	Immediately post programme	• Serial cardiopulmonary exercise testing	Significant increase ($p < 0.01$) in: • peak work rate (14%; $p < 0.001$) • peak VO_2 (16.3%; p 0.005) %predicted? • predicted O_2 pulse (27.6%; $p = 0.01$) • FEV1 (7%; $p < 0.001$)	• No control group • RER reported
Minamisawa[29]	Case series	Immediately post programme	• Serial cardiopulmonary exercise testing	Significant increase in: • 7% workload ($p = 0.04$) • 7% peak VO_2 ($p = 0.03$) Significant decrease in: • HR with sub-maximal effort ($p < 0.05$)	• Home programmes might be a more economical option but compliance is more difficult to assess • RER not reported
Fredriksen[32]	NRCT*	Immediately post programme	• Serial cardiopulmonary exercise testing • Activity monitor (accelerometer) • Psychosocial function (youth self-report and child behaviour checklist)	Significant increase in: • peak VO_2 (1.67 ± 0.57 versus $1.82 \pm 0.661 \times min^{-1}$; $p < 0.001$) • exercise time (614 ± 138 versus 655 ± 155 s; $p = 0.005$) • activity (p 0.028) and psychosocial ($p < 0.001$) levels	• Large study population • Varied activities might have enhanced patient compliance • One of the few to incorporate education • RER reported
Sklansky[33]	Case series	Immediately post programme	• Serial cardiopulmonary exercise testing • Ventricular function (echocardiography)	Significant increase in: • endurance time (1.7 min; $p < 0.0004$) Significant decrease in: • sub-maximal heart rate ($p < 0.001$) No increase in: • ectopy with exercise • arrhythmias • deterioration of ventricular function	• Retrospective study • RER not reported

Table 2. *Continued*

References	Type of study	Follow-up period	Outcome variables	Results	Comments
Balfour[34]	Case series	Immediately post programme	• Serial cardiopulmonary exercise testing	Significant increase in: • peak VO_2 (20%; $p < 0.005$) • endurance time (21%; $p < 0.03$) Significant decrease in: • systolic blood pressure (7%; $p < 0.03$)	• Includes stress management and nutrition counselling • RER not reported • High drop-out rate
Calzolari[38]	NRCT*	Immediately post programme	• Serial cardiopulmonary exercise testing	Non-significant increase in: • maximal • sub-maximal exercise capacity	• No CPX data • Respiratory therapy included
Longmuir[43,44]	NRCT*	5 years post programme and immediately post programme	• Exercise test (Canada fitness awards test: cardiovascular endurance, strength, flexibility, and coordination)	Significant increase ($p < 0.01$) in: • different scores at 6 months and 5 years post programme	• Large patient population • Control group • No CPX testing • Long-term follow-up
Bradley[45]	Case series	Immediately post programme	• Anthropometric measurements • Serial cardiopulmonary exercise testing	Significant increase in: • peak systolic pressure (17%; $p < 0.001$) • peak VO_2 (20%; $p < 0.01$) • endurance time (18%; $p < 0.01$)	• Youngest study population • One of the most complete programmes • RER not reported
Ruttenberg[40]	NRCT*	Immediately post programme	• Basic exercise test	Significant increase: • endurance time ($p < .01$) • non-significant increase in peak VO_2 ($p = 0.1$)	• RER not reported • Sub-optimal control group
Goldberg[41]	Case series	Immediately post programme	• Exercise capacity (cyclergometer) • Body composition	Significant increase: • maximal work capacity ($p < 0.001$) Non-significant increase: • peak VO_2 • peak HR Improvement of body composition	• Short programme duration

AT = anaerobic threshold; CPX = cardiopulmonary testing; FEV1 = forced expiratory volume in the first second; HR = heart rate; NRCT = non-randomized controlled tria; RER = respiratory exchange ratio; VO_2 = oxygen consumption
*NRCT – equivalent to a cohort study in the modified CONSORT definition[56]

Exercise Testing and Training in Children With Congenital Heart Disease

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Exercise Testing and Training in Children With Congenital Heart Disease

Jonathan Rhodes, MD; Ana Ubeda Tikkanen, MD; and Kathy J. Jenkins, MD, MPH

The primary function of the cardiopulmonary system is to provide blood flow (and oxygen) in quantities sufficient to support the metabolic needs of the body. The capacity of the cardiopulmonary system to fulfill this function is maximally stressed when an individual's metabolic rate is increased, a condition that occurs most commonly during physical activity/exercise. A number of physiological changes accompany and facilitate the accommodation of the circulatory system to the hemodynamic demands of exercise (Figure 1). In normal individuals, these changes (which during upright exercise include a tripling of the resting heart rate, a >60% reduction in systemic and pulmonary vascular resistance, and a >50% increase in stroke volume) can ultimately produce a >5-fold increase in cardiac output. The increase in cardiac output is accompanied by enhanced ventricular preload (as the ventricles move up their Starling curves to accommodate the increased workload), a doubling of systolic and mean pulmonary artery pressures (most of the increase in pulmonary artery pressures is due to the concomitant rise in left-sided filling pressures; the increase in transpulmonary pressure gradient is relatively small), and a more modest increase in systemic arterial pressures.[1–4]

Congenital heart disease (CHD) may, in a variety of ways and to a variable extent, adversely affect these hemodynamic adaptations. For instance, patients with a Fontan procedure lack a pulmonary ventricle. They therefore cannot increase their pulmonary blood flow and pressures normally (and consequently cannot maintain their ventricular preload and systemic blood flow) during exercise.[5] Patients with tetralogy of Fallot and other CHDs often have congenital and/or acquired abnormalities of their pulmonary vasculature and therefore may be unable to reduce their pulmonary vascular resistance normally. Patients with complex CHD often have sinus node dysfunction and may be incapable of developing a normal heart rate (HR) response to exercise.[6] Ventricular dysfunction, residual shunts, valvular disorders, and associated pulmonary and skeletal muscle disorders may also impair the cardiopulmonary response to exercise.

An evaluation of a CHD patient's ability to exercise can therefore impart important information on the health of a child's cardiopulmonary system and provide valuable insights into the factors that might be limiting a child's ability to perform physical activities. The assessment of a child's or adolescent's exercise function, however, poses unique challenges related to the patient's size and maturity. In addition, the dramatic changes that occur in the cardiopulmonary and musculoskeletal systems during the pediatric years complicate the interpretation of data acquired during these assessments. These considerations must be taken into account when children with CHD are evaluated.

Most of the clinical tests employed by the pediatric cardiologist assess the cardiopulmonary system when the patient is at rest. Although valuable, these tests do not necessarily predict the manner in which the cardiopulmonary system will respond to the demands of exercise, nor do they reliably inform the clinician about a patient's true capacity to perform physical activities. To acquire this information, assessments of exercise function must be undertaken. A number of tools are available to the clinician seeking to address this issue. The strengths and limitations of these tools will now be reviewed.

History

Assessments of a CHD patient's cardiopulmonary status should certainly include questions about the patient's exercise tolerance. It is important to recognize, however, that data derived from the responses to these questions must be interpreted cautiously.[7] In a study of adolescents and young adults with CHD, Diller et al[8] found that that self-reporting of exercise capacity is unreliable and that New York Heart Association class (a classification system based on the patients' self-reported symptoms) underestimated the true degree of exercise limitation. Indeed, "asymptomatic" CHD patients (New York Heart Association class I) had exercise capacities comparable to those of older adult subjects with congestive heart failure secondary to acquired heart disease. This discrepancy is probably to a large extent due to the fact that patients with CHD have never known what it feels like to have a normal cardiopulmonary system and therefore have an unrealistic concept of the normal "asymptomatic" state.

More complex instruments (such as the Child Health Questionnaire–Parental Form 50 and the Short Form-36 and other quality of life questionnaires) have encountered similar difficulties. For instance, in a study of 564 patients aged >14 years, with a variety of CHDs, Gratz et al[9] found that self-reported physical functioning was a poor predictor of

From the Department of Cardiology, Children's Hospital, Boston, Mass (J.R., K.J.J.) and the Departments of Rehabilitation and Pediatric Cardiology, Hospital Gregorio Marañón, Madrid, Spain (A.U.T.).

Correspondence to Jonathan Rhodes, MD, Department of Cardiology, Children's Hospital, Boston, MA 02115. E-mail jonathan.rhodes@cardio.chboston.org

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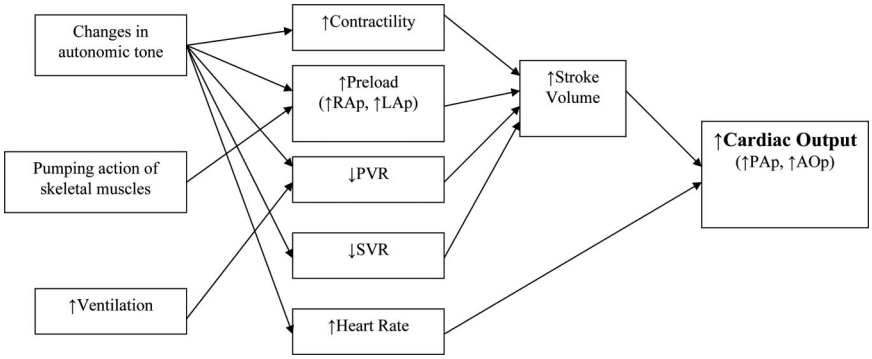

Figure 1. Some of the physiological changes that accompany and facilitate the accommodation of the circulatory system to the hemodynamic demands of exercise. RAp indicates right atrial pressure; LAp, left atrial pressure; PVR, pulmonary vascular resistance; SVR, systemic vascular resistance; PAp, pulmonary artery pressure; and AOp, aortic pressure.

exercise capacity and that most patients with CHD severely overestimated their level of physical functioning.

The difficulties associated with deriving reliable data from patient self-reports are further compounded when the patient is a child or when the reports must be obtained from the parents of the patient.[7] For instance, in the multicenter Pediatric Heart Network Fontan Study, the Child Health Questionnaire Physical Functioning Summary Score correlated poorly with results from formal exercise testing.[10] In addition, there was a significant discrepancy between the patient's perception of his/her level of physical functioning compared with the parents' perception (parents perceived that their children were more impaired).

The 6-Minute Walk Test

The 6-Minute Walk Test (6MWT) requires a patient to walk as far as he/she can in 6 minutes. The course is a straight path 30 m (or 100 ft) in length; the patient must turn each time he/she reaches the end of the course. The patient is encouraged to cover as much ground as possible during the 6 minutes, but his/her pace should not be directly influenced by the examiner.[11] Portable pulse oximetry may be incorporated into the test, but the patient's heart rhythm and ECG are not monitored.

The advantages of the 6MWT are that it is easy to perform, does not require sophisticated equipment, and mimics activities of daily living.[11] It has therefore commonly been used in drug trials for adults with congestive heart failure or pulmonary hypertension. However, in all but the most limited patients, it is a submaximal test. Consequently, although it correlates fairly well with peak oxygen consumption in highly symptomatic patients, its utility and validity in patients with "only" mild or moderate impairments is dubious.[12] Indeed, the reliability and meaning of the 6MWT for patients who can walk >400 m has been questioned.[13] In addition, the test is strongly influenced by patient motivation and other factors (such as leg length, body weight, orthopedic issues, and the ability to turn quickly at the ends of the course) unrelated to the cardiopulmonary system. It is difficult to control for or to quantify the influence of these variables on the outcome (distance walked) of the 6MWT. Hence, for any individual patient the test has a rather small "signal to noise ratio." Although these issues are mitigated somewhat in drug trials that include large numbers of patients, they make the interpretation of an individual's test (or serial studies in 1 individual) ambiguous and difficult. On account of these considerations, the utility of the 6MWT in children with CHD is limited.

Finally, although the incidence of serious adverse events during a 6MWT is extremely low, having highly symptomatic patients exercise to (near) the limit of their capabilities, with limited monitoring, in a public corridor, appears imprudent.

Exercise Testing With ECG Monitoring

Exercise testing may be undertaken in conjunction with 12-lead ECG monitoring. The Bruce treadmill protocol is commonly employed for this purpose [14,15]; endurance time is used as an index of exercise capacity. Nomograms are available for calculating the predicted, normal endurance time.[14] For pediatric subjects, the normal range may be quite broad, however, and the clinical utility of this index is therefore somewhat limited. Endurance time is also heavily influenced by factors unrelated to the cardiopulmonary system (eg, obesity, orthopedic issues) and therefore often does not provide reliable information on a patient's cardiopulmonary status. This issue is further complicated by factors particularly relevant to pediatric exercise testing. Specifically, with this testing modality, it is often difficult to confidently ascertain whether a child has expended an optimal effort. A child's self-reported symptoms are subjective and potentially unreliable indicators of effort expenditure. Depending on the peak HR as an index of patient effort is also unreliable because many patients with postoperative CHD have sinus node dysfunction and/or are on medications that may impair the chronotropic response to exercise. Hence, the ability of exercise testing with ECG monitoring to provide objective quantitative information on a patient's exercise capacity is suboptimal. This testing modality also provides little information on the factors that may be responsible for a CHD patient's exercise intolerance.

Exercise testing with ECG monitoring is useful for detecting abnormal blood pressure responses, exercise-induced rhythm disturbances, ST changes, and arterial oxygen desaturation (when pulse oximetry is employed). In conjunction with myocardial perfusion imaging or stress echocardiography, it can also detect evidence of myocardial ischemia during exercise.[15] For pediatric subjects with CHD, the presence or absence of exercise-induced ST-T abnormalities is not helpful with regard to the question of myocardial ischemia because of the presence of intraventricular conduction delays, baseline abnormalities, and ventricular

hypertrophy (especially in single ventricles) and the absence of normative data.

The treadmill speeds used for the higher levels of the Bruce protocol may be too fast for small children. Under these circumstances, alternative protocols or modifications of the Bruce protocol may be employed (although interpretation of endurance time then becomes even more problematic). Bicycle protocols may also be used.[15] For these protocols, the peak work rate, rather than the endurance time, is used as an index of exercise capacity. Equations are available for calculating the predicted, normal peak work rate on the basis of a patient's age, gender, and size. The limitations associated with peak work rate as an index of cardiopulmonary function are similar to those described for the endurance time.

Cardiopulmonary Exercise Testing

In cardiopulmonary exercise testing, ECG monitoring is supplemented with expiratory gas analysis. For this analysis, a patient breathes room air through a mouthpiece (or face mask). The air passing through the mouthpiece is continually sampled, and the instantaneous concentrations of O_2 and CO_2 are ascertained. The volume of air passing through the mouthpiece is also measured. From these measurements, breath-by-breath estimates of oxygen consumption ($\dot{V}O_2$), carbon dioxide production ($\dot{V}CO_2$), minute ventilation ($\dot{V}E$), end-tidal PO_2, and end-tidal PCO_2 can be generated. These estimates can then be used to calculate clinically useful parameters that are particularly relevant to the assessment of patients with CHD. A number of these parameters will now be enumerated and discussed.

Peak $\dot{V}O_2$

For most normal individuals (and especially for individuals with cardiovascular disease), peak $\dot{V}O_2$ is limited by the amount of O_2 that the cardiopulmonary system can deliver to the exercising muscles. This in turn is limited by the ability of the circulatory system to increase cardiac output during exercise. Hence, peak $\dot{V}O_2$ (ie, the highest rate of $\dot{V}O_2$ detected during a progressive exercise test) is an excellent indicator of the capabilities of a patient's cardiovascular system.

Unfortunately, determining normal values for peak $\dot{V}O_2$ (in mL O_2 per minute) is not straightforward. Peak $\dot{V}O_2$ varies with age; it tends to increase and reach a maximum during adolescence/early adulthood and to decline progressively thereafter. It also differs significantly between males and females, especially after puberty. Normal values for peak $\dot{V}O_2$ are also dependent on body size; larger individuals can consume more oxygen than smaller individuals. The relationship between body mass and peak $\dot{V}O_2$ is, however, quite complicated. During exercise, adipose tissue consumes virtually no O_2 compared with skeletal muscle. Hence, merely normalizing peak $\dot{V}O_2$ for body mass ignores this important biological fact and can be misleading. The relationship between peak $\dot{V}O_2$ and body surface area or other anthropomorphic measurements is also complex. Normalizing peak $\dot{V}O_2$ for lean body mass or skeletal muscle mass is theoretically appealing, but accurate estimation of these parameters is difficult and impractical outside of the research setting.

Hence, normal values for peak $\dot{V}O_2$ are usually calculated from prediction equations, based on age, gender, height, and/or weight, that have been generated from a group of normal subjects. Ideally, the equation selected for an individual patient should have been generated with the use of a similar exercise protocol and from a population whose age and demographic background are similar to the patient's. For pediatric subjects, few studies have generated these kinds of data. The most widely used prediction equations are drawn from the study of Cooper and Weiler-Ravell.[16] These investigators studied a group of 107 healthy children and adolescents aged 6 to 17 years and generated prediction equations based on gender and height (by relying on height rather than weight, the potential confounding effects of adiposity/obesity on the predictions are theoretically mitigated). The limitations of these prediction equations must, however, be recognized. They tend to generate unrealistically low values for small children. Hence, for subjects $<$130 cm tall, we calculate the predicted peak $\dot{V}O_2$, using the patient's ideal weight for height, on the basis of data from the study of Cooper and Weiler-Ravell that found that the peak $\dot{V}O_2$ of an average prepubescent boy was 42 mL/kg per minute and for an average prepubescent girl was 38 mL/kg per minute. For subjects aged $\geq$18 years, the equation of Jones et al,[17] which generates predictions on the basis of age, height, body mass, and gender (height is weighted much more heavily than body mass), is theoretically appealing and has gained wide acceptance.[18] The Wasserman equation, based on ideal body weight, is also widely used[18] (albeit somewhat more cumbersome) and may have superior predictive power.[19] Whichever equations are chosen by a laboratory, the validity of the predictions for the population served by the laboratory should be established by testing a number of normal subjects and confirming that the predicted values agree well with the results of these tests.[18]

Measurements of peak $\dot{V}O_2$ have been found to possess important clinical implications for patients with CHD. Peak $\dot{V}O_2$ has been found to be an independent predictor of death and/or hospitalization for patients with repaired tetralogy of Fallot,[20] patients who have undergone atrial switch procedures for transposition of the great arteries,[21] patients with pulmonary hypertension,[22,23] and patients with Fontan surgery.[24]

HR During Exercise

During a progressive exercise test, HR increases linearly in proportion with $\dot{V}O_2$, from baseline levels to peak HR. The normal peak HR, for treadmill exercise, may be estimated from the following equation: peak HR=220−age (years).[25] Peak HR during bicycle exercise tends to be 5% to 10% lower,[26] and therefore it is reasonable to multiply the predicted peak HR derived from this equation by 0.925 if a bicycle exercise protocol is used.

Patients with sinus node dysfunction cannot increase their HRs to normal levels at peak exercise. In addition, the HR versus $\dot{V}O_2$ relationship tends to be depressed below the expected normal curve. In contrast, patients who cannot increase forward stroke volume normally during exercise tend to compensate by increasing their HRs more rapidly than normal during exercise, and the HR versus $\dot{V}O_2$ relationship is

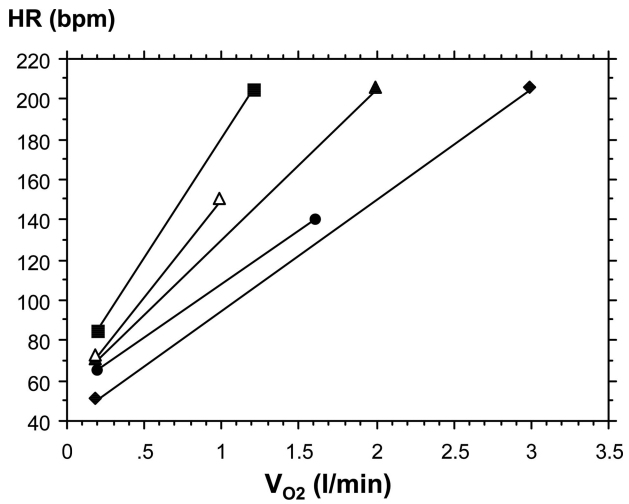

Figure 2. Influence of various clinical conditions on the relationship between HR and $\dot{V}O_2$ during exercise. Variation of HR with respect to $\dot{V}O_2$ during a progressive exercise test for a hypothetical 50-kg, 15-year-old normal subject (solid triangle), athlete (diamond), patient with a depressed chronotropic response (circle), patient with a depressed stroke volume response (square), and patient with both a depressed chronotropic and stroke volume response (open triangles) is shown. Note that the athlete's peak O_2P (peak oxygen consumption divided by peak HR) is above normal. The patient with a depressed stroke volume response has a below-normal peak O_2P and partially compensates for this condition by increasing HR more rapidly than normal, causing the slope of the HR-$\dot{V}O_2$ curve to be abnormally steep. In contrast, the patient with a depressed chronotropic response has an abnormally flattened curve and cannot achieve a normal peak HR, although a partial compensation for the chronotropic deficiency is achieved by increasing the peak O_2P (ie, stroke volume) to above-normal levels. (This pattern is also encountered in patients with structurally normal hearts who are receiving β-blocker therapy.) The patient with the depressed chronotropic and stroke volume response still has a steeper-than-normal slope but cannot achieve a normal peak HR and cannot compensate for this chronotropic deficiency by increasing stroke volume. This individual's peak $\dot{V}O_2$ is therefore more depressed than that of any of the other subjects. Reprinted with permission of the publisher from Rhodes.[27] Copyright © 2006, Elsevier.

elevated. Patients with impairment of both the chronotropic and stroke volume response to exercise may have "pseudonormalization" of the HR versus $\dot{V}O_2$ relationship but would be unable to achieve a normal peak HR. Athletes, on the other hand, tend to have a larger-than-normal increase in stroke volume during exercise. Their HR versus $\dot{V}O_2$ relationship therefore appears depressed below the expected curve, but their peak HR is normal (Figure 2).[27]

Recent adult studies have focused on the HR reserve (peak HR−resting HR) and the chronotropic index [100×(HR reserve)/(predicted peak HR−resting HR)]. These new indices have not been studied widely in pediatric patients, and their relevance to this population remains uncertain.[28,29]

Chronotropic incompetence (ie, an inability to increase HR to >80% of predicted at peak exercise) is common after surgery for CHD[6,28,30,31] and has been associated with a poor prognosis.[30]

Oxygen Pulse

The oxygen pulse (O_2P) at peak exercise is related to the forward stroke volume at peak exercise and is therefore, for the clinician, one of the most useful indices available from the exercise physiology laboratory. The relationship between the O_2P and stroke volume is best understood by dividing both sides of the Fick equation by HR, as follows:

$$\dot{V}O_2/HR = O_2P = (\text{cardiac output})/(HR) \times (O_2 \text{ extraction})$$

O_2 extraction is equal to arterial O_2 content minus mixed venous O_2 content. These variables are in turn determined by the hemoglobin concentration and the corresponding O_2 saturations. Most patients with repaired CHDs have normal arterial O_2 saturations and normal hemoglobin concentrations. Furthermore, at peak exercise, O_2 extraction is maximized, and it has been found that the mixed venous O_2 saturation at peak exercise varies little across a wide spectrum of cardiovascular function. Hence, under most circumstances, O_2 extraction at peak exercise will vary little from patient to patient, and the O_2P will be proportional to forward stroke volume.[32] Normal values for O_2P at peak exercise will, of course, be dependent on patient size, age, and gender. Normal values may be calculated by dividing the predicted peak $\dot{V}O_2$ by the predicted peak HR.[18]

The limitations associated with the O_2P concept must be borne in mind when these data are interpreted. In patients with depressed arterial O_2 content at peak exercise (eg, patients with anemia or patients with significant arterial desaturation), O_2 extraction at peak exercise would be less than normal and the O_2P would therefore underestimate stroke volume. In contrast, polycythemia increases arterial O_2 content and would therefore cause the O_2P to overestimate the stroke volume. Solely on the basis of Starling factors, relative bradycardia at peak exercise should engender a compensatory increase in the stroke volume and hence the O_2P at peak exercise. Consequently, in patients with low peak-exercise HRs, the absence of a compensatory increase in O_2P, above normal predicted values, is in fact abnormal.

The O_2P tends to be depressed in patients with conditions that impair their ability to increase forward stroke volume to appropriate levels at peak exercise. Patients with depressed ventricular function,[33] severe obstructive lesions, severe valvular regurgitation,[34,35] and pulmonary or systemic vascular disease[22,23,36] often have a low peak-exercise O_2P.

The O_2P is often depressed in patients who have undergone a Fontan procedure, even in the absence of ventricular or valvular dysfunction.[28] In these patients, the low O_2P probably reflects the absence of a pulmonary ventricle and the limited ability of the passively perfused pulmonary vascular bed to accommodate the high rate of blood flow normally present at peak exercise (a physiological function that greatly influences the exercise capacity of Fontan patients). Indeed, the O_2P is one of the strongest correlates of peak work rate in patients with Fontan circulations.[28]

Skeletal muscle abnormalities that impair oxygen extraction, such as glycogen storage diseases, mitochondrial and other metabolic defects, or severe deconditioning, will also cause the O_2P to be depressed.

Young patients with chronic aortic regurgitation usually have well-preserved exercise function and peak-exercise O_2P.[34,37] In these patients, the fall in systemic vascular resistance that normally accompanies exercise tends to lessen the severity of the regurgitation during exercise. In addition, the left ventricular

dilation typically present in chronic aortic regurgitation helps to maintain forward stroke volume and usually compensates effectively for the hemodynamic burden imposed by the leaky valve. (In the subset of patients with poor exercise function, however, a low O_2P is almost always present.) Similar factors may also help to preserve the exercise function of patients with other valvular insufficiency lesions.[38]

Respiratory Exchange Ratio

If a patient does not expend a maximal or near maximal effort on an exercise test, the peak exercise data may not accurately reflect the true status of his/her cardiopulmonary system. Optimal interpretation of peak exercise data therefore requires information on the effort expended by the patient. Measurements of the respiratory exchange ratio (RER) during exercise often help to provide this important information.

The RER is the ratio of $\dot{V}CO_2$ over $\dot{V}O_2$. At rest, the RER is usually determined primarily by the stoichiometry of the chemical equations describing the aerobic metabolism of the fuels that the body uses to support its metabolic activities. For the aerobic metabolism of carbohydrates, 1 mol of CO_2 is produced for every mole of O_2 that is consumed; for fats, 1 mol of CO_2 is produced for every 1.5 mol of O_2 consumed. Hence, at rest, the RER is usually $\approx$0.85 (ie, somewhere between 0.67 and 1.00). During a progressive exercise test, as the anaerobic threshold is passed and an increasing fraction of the energy required by the exercising muscles is derived from anaerobic metabolism, $\dot{V}CO_2$ rises out of proportion to $\dot{V}O_2$, and the RER rises progressively. An RER $\geq$1.09 is considered to be compatible with a good effort. (Some investigators believe that the anaerobic metabolic pathways are less developed in children and therefore believe that, for young subjects, an RER $\geq$1.05 is a more appropriate threshold.) If a patient's RER at peak exercise is $<$1.09, it is likely that exercise was not terminated on account of insufficient O_2 delivery to the exercising muscles.[39,40]

Ventilatory Anaerobic Threshold

During a progressive exercise test, the anaerobic threshold occurs when aerobic metabolism, limited as it is by the amount of O_2 delivered by the cardiovascular system, is insufficient to meet the energy requirements of the exercising muscles. The anaerobic threshold is a physiological phenomenon that is not affected by patient effort or motivation and may be determined on a submaximal exercise test. Consequently, it is an excellent index of the capacity of the cardiovascular system to support the hemodynamic demands of exercise. Because anaerobic metabolism produces CO_2 (through the buffering of lactic acid by bicarbonate) but does not consume O_2, during a progressive exercise test the ventilatory anaerobic threshold (VAT) is marked by an increase in $\dot{V}CO_2$ out of proportion to the associated increase in $\dot{V}O_2$.

Prediction equations exist for the calculation of normal values for the VAT on the basis of age, size, and gender.[16] VAT is also commonly expressed as a percentage of predicted peak $\dot{V}O_2$. In the absence of cardiovascular disease, VAT rarely falls below 40% of predicted peak $\dot{V}O_2$. However, VAT is often depressed below this value in patients with conditions that significantly impair the ability to increase cardiac output or oxygen delivery appropriately during exercise.[41,42] In children with CHD, the VAT is often depressed in a manner similar to, although milder than, the peak $\dot{V}O_2$.[28] Therefore, when peak $\dot{V}O_2$ data are available, VAT data do not often provide significant additional information. The HR at the VAT has been recommended as the target HR for rehabilitation training.

$\dot{V}E/\dot{V}CO_2$ Slope

Empirically, it has been observed that $\dot{V}E$ rises linearly in proportion with $\dot{V}CO_2$ during a progressive exercise test until a point above the VAT, when the accumulating lactic acidosis engenders a compensatory increase in $\dot{V}E$ out of proportion to the increase in $\dot{V}CO_2$. The $\dot{V}E/\dot{V}CO_2$ slope is the slope of the linear portion of this curve. It may be thought of as an index of gas exchange efficiency during exercise, equivalent to the number of liters of air that must be breathed out to eliminate 1 L of CO_2.[43] In pediatric patients, the $\dot{V}E/\dot{V}CO_2$ slope should be $<$28.

The $\dot{V}E/\dot{V}CO_2$ slope is often elevated in patients with tetralogy of Fallot,[20] congestive heart failure,[44–46] atrial switch procedures,[21] and pulmonary hypertension.[22,23] In these patients, $\dot{V}E/\dot{V}CO_2$ slope elevation has been associated with an increased risk of mortality. Although multiple factors may influence the $\dot{V}E/\dot{V}CO_2$ slope, pulmonary blood flow maldistribution and consequent ventilation/perfusion (V/Q) mismatch are probably the most important pathophysiological processes that underlie these observations and associations.[47,48]

Efficient gas exchange across the alveolar/capillary membrane requires optimal V/Q matching. Patients who have undergone repair of tetralogy of Fallot often have residual pulmonary artery stenoses that cause pulmonary blood flow maldistribution, which in turn has been linked to $\dot{V}E/\dot{V}CO_2$ slope elevation and depressed peak $\dot{V}O_2$.[48–50] These stenoses can have a particularly deleterious effect on the physiology of the postoperative tetralogy of Fallot patient and a strong, negative impact on a patient's prognosis. Effective relief of these stenoses has been associated with improvements in peak $\dot{V}O_2$ and the $\dot{V}E/\dot{V}CO_2$ slope (Figure 3).[48]

Patients with CHF have pulmonary blood flow maldistribution as a consequence of the elevated pulmonary capillary wedge pressure that accompanies CHF.[47,51] As ventricular function deteriorates and the wedge pressure rises, the pulmonary blood flow maldistribution (and consequent V/Q mismatch) worsens, and the $\dot{V}E/\dot{V}CO_2$ slope progressively rises. This strong link between pulmonary capillary wedge pressure and the $\dot{V}E/\dot{V}CO_2$ slope probably accounts for the prognostic power of the $\dot{V}E/\dot{V}CO_2$ slope in this patient population. In a similar manner, for patients who have had an atrial switch procedure for transposition of the great arteries, elevation of the $\dot{V}E/\dot{V}CO_2$ slope probably reflects the progressive systemic ventricular dysfunction that often develops in these patients as they age.

In patients with pulmonary hypertension, pulmonary blood flow maldistribution results from pulmonary vascular obstructive disease. As the vascular obstruction progresses, the pulmonary blood flow maldistribution worsens, gas exchange within the lungs becomes more and more inefficient, and the $\dot{V}E/\dot{V}CO_2$ slope rises. Hence, for patients with this condition, the $\dot{V}E/\dot{V}CO_2$ slope reflects the extent of disease within the

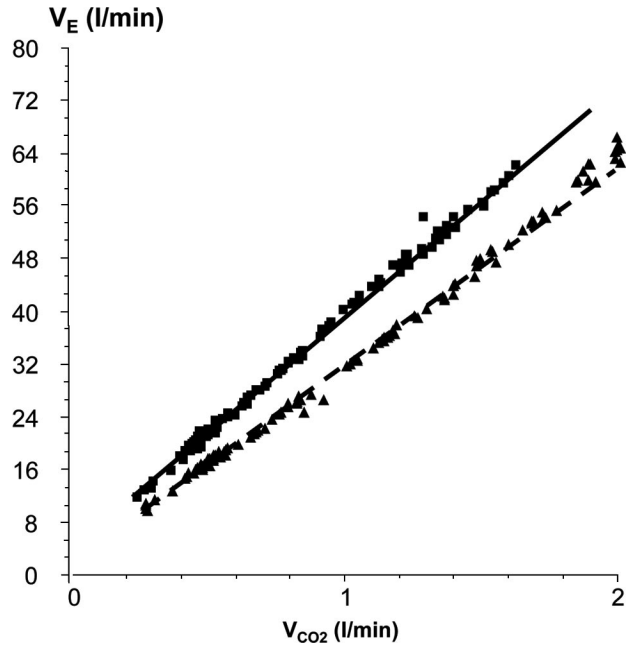

Figure 3. Relationship between $\dot{V}_E$ and $\dot{V}_{CO_2}$ in a patient with tetralogy of Fallot before and after successful pulmonary artery balloon angioplasty that increased left pulmonary artery blood flow from 13% to 35% of the total pulmonary blood flow. Square symbols are data points before angioplasty; triangular symbols are data points after angioplasty. The solid line represents the linear portion of the $\dot{V}_E/\dot{V}_{CO_2}$ relationship before angioplasty (the slope of the line is the $\dot{V}_E/\dot{V}_{CO_2}$ slope). The dashed line is the relationship after angioplasty. Note that, after the angioplasty, the patient's $\dot{V}_E$ was lower for any given $\dot{V}_{CO_2}$. The $\dot{V}_E/\dot{V}_{CO_2}$ slope fell from 35 to 29 and was associated with an increase in the peak $\dot{V}_{O_2}$ from 18.8 to 23.7 mL/kg per minute and a rise in the end-tidal P_{CO_2} at the anaerobic threshold from 32 to 36 mm Hg.

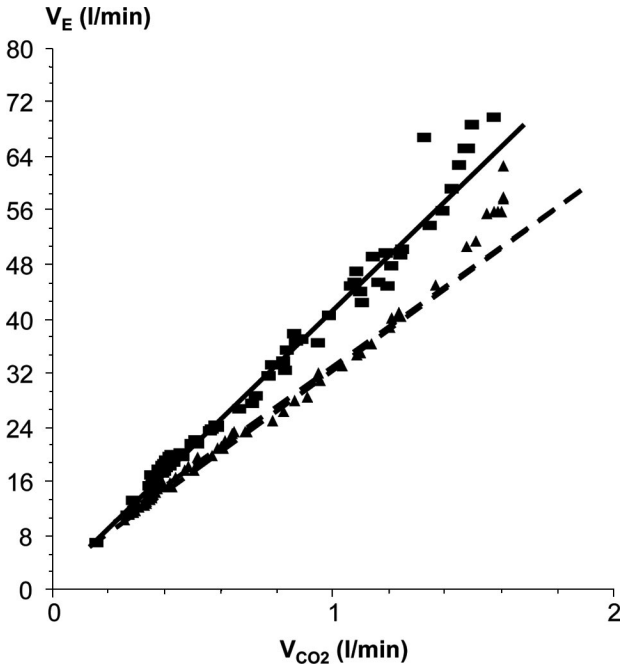

Figure 4. Relationship between $\dot{V}_E$ and $\dot{V}_{CO_2}$ in a patient with fenestrated Fontan before and after successful fenestration closure. Square symbols are data points before fenestration closure; triangular symbols are data points after closure. The solid line represents the linear portion of the $\dot{V}_E/\dot{V}_{CO_2}$ relationship before closure (the slope of the line is the $\dot{V}_E/\dot{V}_{CO_2}$ slope). The dashed line is the relationship after closure. Note that, after the fenestration closure, the patient's $\dot{V}_E$ was lower for any given $\dot{V}_{CO_2}$. The $\dot{V}_E/\dot{V}_{CO_2}$ slope fell from 41 to 30 and was associated with an increase in the end-tidal P_{CO_2} at the anaerobic threshold from 26 to 34 mm Hg. Peak $\dot{V}_{O_2}$ fell from 34.5 to 34.4 mL/kg per minute.

pulmonary vasculature.[22,23] (This physiology may also be relevant to patients with transposition of the great arteries who develop pulmonary vascular obstructive disease after an atrial switch procedure.)

The $\dot{V}_E/\dot{V}_{CO_2}$ slope is also almost always elevated in patients with Fontan procedures.[52,53] Once again, this observation is probably due, to a large extent, to pulmonary blood flow maldistribution (and associated V/Q mismatch) secondary to the absence of a pulmonary ventricle.[54] In Fontan patients, however, the degree of $\dot{V}_E/\dot{V}_{CO_2}$ slope elevation is not strongly associated with increased mortality because, in contrast to the aforementioned conditions, the elevated slope is intrinsic to the patients' single ventricle physiology and not closely related to the progression/severity of the underlying cardiovascular disease process.[24]

Right to left intracardiac or intrapulmonary shunting will also cause the $\dot{V}_E/\dot{V}_{CO_2}$ slope to be elevated. The shunting allows CO_2-rich systemic venous blood to enter the systemic arterial circulation. The consequent increase in arterial P_{CO_2} is sensed by chemoreceptors, inducing central nervous system respiratory centers to increase the patient's respiratory drive (and $\dot{V}_E$) and causing the $\dot{V}_E/\dot{V}_{CO_2}$ slope to rise. The resulting alveolar hyperventilation reduces the P_{CO_2} of the blood returning from the lungs and helps to normalize the patient's arterial P_{CO_2}. Eliminating right to left shunting (eg, by closing a Fontan patient's fenestration; Figure 4) almost always produces a reduction in the $\dot{V}_E/\dot{V}_{CO_2}$ slope.[55]

Assessments of Pulmonary Function

The exercise capacity of normal individuals is usually limited by cardiovascular, rather than respiratory, factors. By this, we mean that the $\dot{V}_E$ at peak exercise is usually less than the maximum voluntary ventilation (the maximum amount of air that a subject can breathe in and out in 1 minute). The maximum voluntary ventilation is usually estimated by measuring the maximum amount of air a subject can breathe during 12 seconds of maximal hyperventilation and multiplying this quantity by 5. This maneuver requires a degree of patient cooperation that is often beyond the capacity of young subjects. Alternatively, the maximum voluntary ventilation may be estimated by multiplying the FEV_1 (from baseline spirometry) by 40.[56] (Some recommend multiplying the FEV_1 by 35.) The breathing reserve is the percentage of a subject's maximum voluntary ventilation that is not used at peak exercise and normally measures ≈30%.[18] Patients with isolated cardiovascular disease typically have high breathing reserves because they have a greater cardiovascular limitation. Many patients with CHD, however, also have coexistent pulmonary problems. Measurement of the breathing reserve (as well as baseline spirometry) often helps to elucidate the factors contributing to a patient's exercise intolerance.

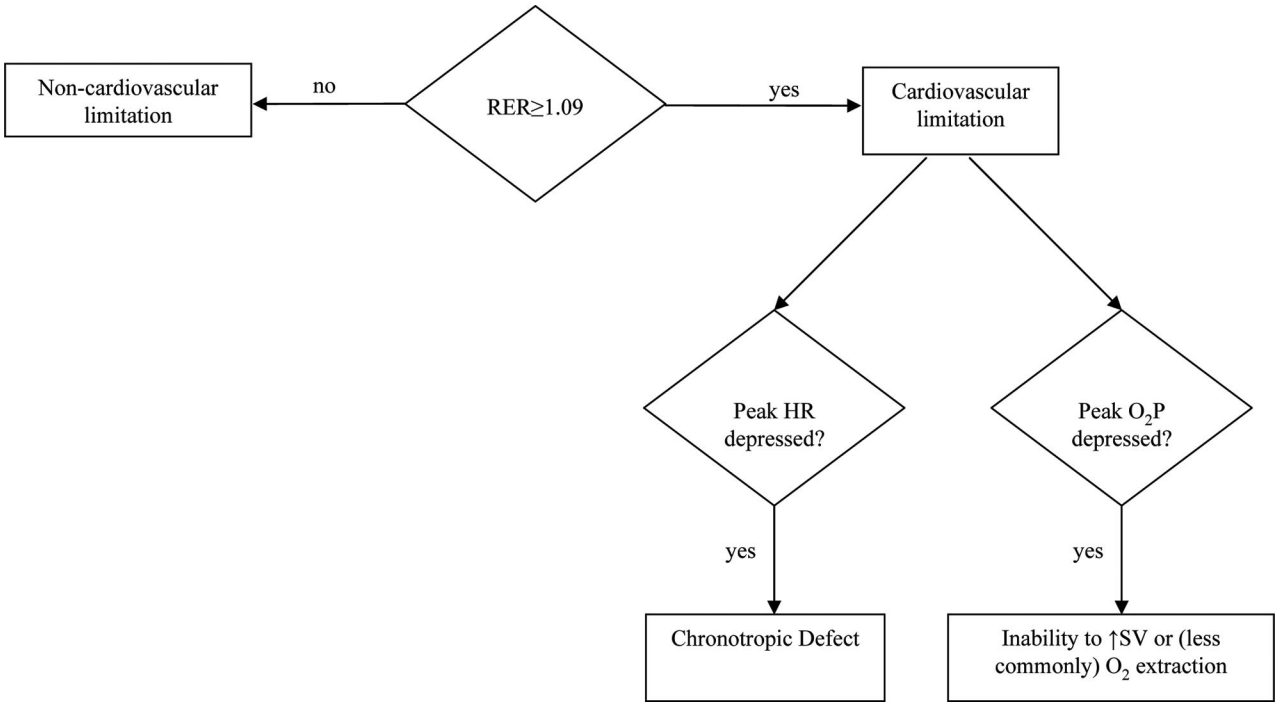

Figure 5. Algorithm for initial categorization of patients with low peak $\dot{V}O_2$. SV indicates stroke volume.

Interpretation of data from exercise tests in patients with CHD is also often enhanced by measurements of end-tidal P_{CO_2}. In healthy individuals, end-tidal P_{CO_2} approximates arterial P_{CO_2}. Consequently, at rest and at low exercise intensities, end-tidal P_{CO_2} measures ≈40 mm Hg. However, when exercise continues at intensities above the anaerobic threshold, arterial P_{CO_2} should fall as a compensatory respiratory alkalosis develops in response to the accumulating lactic acidosis. This fall should be accompanied by an almost parallel decline in the end-tidal P_{CO_2}.[57] Certain conditions sometimes encountered in patients with CHD, such as airway obstruction or hypoventilation secondary to obesity, will impede (and may even reverse) this normal decline. End-tidal P_{CO_2} measurements can help to identify this pathophysiology. In contrast, patients with CHD associated with V/Q mismatch often have low end-tidal P_{CO_2}.[49,50,55] In these subjects, air from alveoli with high V/Q ratios (and hence low P_{CO_2}) dilutes air from other alveoli and causes end-tidal P_{CO_2} to fall to levels below the arterial P_{CO_2}. Right to left shunting is also associated with low end-tidal P_{CO_2} measurements because the patient must reduce the P_{CO_2} of the blood returning from the alveoli to compensate for the hypercapnic blood that shunts from right to left (during exercise, the P_{CO_2} of systemic venous blood may approach 60 mm Hg).[55]

Other Measurements

For some patients with CHD, data from other technologies can fruitfully complement and supplement data from standard cardiopulmonary exercise testing. Stress echocardiography can be used to assess the effect of exercise on right ventricular and pulmonary artery pressures, gradients across obstructions, valvular regurgitation, and ventricular function.[58,59] Exercise flow-volume loops can provide additional insights into the pulmonary function during exercise.[60] Near-infrared spectroscopy technology may provide interesting data on tissue oxygenation during exercise.[61,62] Blood sampling and/or invasive hemodynamic measurements can provide important physiological data.[1,5,63] Although these technologies may be invaluable in research settings, as well as in some special clinical circumstances, their role in routine clinical testing is yet to be established.

Patients with low peak $\dot{V}O_2$ may be categorized, on the basis of the RER, HR, and O_2P at peak exercise, according to the algorithm illustrated in Figure 5. Additional data from cardiopulmonary exercise testing and other modalities can then be used to more specifically pinpoint the factor(s) most likely to be responsible for the patient's poor exercise performance and to help to identify potential therapeutic strategies most likely to effectively alleviate the exercise intolerance. In addition, comparing a CHD patient's cardiopulmonary exercise testing data with data from normal subjects or with data from patients with similar types of CHD could help to guide decisions about the timing of interventions. Serial studies in the same patient can also be extremely valuable in this regard and can also be used to objectively assess the effectiveness of any interventions that are undertaken. The cardiopulmonary exercise testing abnormalities typically encountered among patients with various forms of CHD are presented in Table 1.

Safety of Exercise and Exercise Testing

Cardiopulmonary exercise testing for children with CHD is an extremely low-risk testing modality. Since 2002, almost 15 000 exercise tests have been undertaken at our institution without encountering a serious testing-related complication. Nevertheless, the value of any information that might be derived from cardiopulmonary exercise testing should always be weighed carefully against the theoretical risks associated with the test. Patients with certain conditions (such as acute myocardial or pericardial inflammatory disease, severe out-

Table 1. Cardiopulmonary Exercise Testing Abnormalities Encountered in Pediatric Patients With Various CHDs

Defect	↓ Peak $\dot{V}o_2$	↓ Peak HR	↓ O_2 Pulse	↑ $\dot{V}_E/\dot{V}co_2$	↓ VAT
Repaired TOF/truncus arteriosus	+++	++	+++	+++	++
Fontan	++++	+++	++++	++++	+++
PVOD	++++	+	++++	++++	++++
Ebstein anomaly	+++	++	+++	++	++
Status post atrial switch	+++	++	+++	++	++
Aortic valve disease	++	+	++	+	++
Coarctation	++	+	++	+	+++
Dilated cardiomyopathy	++++	+	++++	++	++++
Hypertrophic cardiomyopathy	++	+	++	+	++
Isolated PR	+	+	+	+	+

TOF indicates tetralogy of Fallot; PVOD, pulmonary vascular obstructive disease; PR, pulmonary regurgitation, post valvuloplasty; peak $\dot{V}o_2$, oxygen consumption at peak exercise; peak HR, heart rate at peak exercise; O_2 pulse, oxygen pulse at peak exercise; $\dot{V}_E/\dot{V}co_2$, slope of the linear portion of minute ventilation vs carbon dioxide production curve; VAT, ventilatory anaerobic threshold; +, rarely present; ++, sometimes present; +++, often present; and ++++, usually present. This table assumes that the patient is not receiving β-blocker or other antiarrhythmic therapy that might impair the chronotropic response to exercise.

flow tract obstruction for which surgical intervention is clearly indicated, severe aortic dilation) should, in general, not be tested.[15]

Regular exercise is associated with many physical, psychological, and social benefits and is a key factor in prevention of acquired cardiovascular diseases. These benefits should not be denied to most children with CHD. Historically, "guidance" documents have tended toward conservative restrictions on exercise participation despite an absence of clear-cut data. Fortunately, these conservative recommendations are changing. Indeed, the 36th Bethesda Conference[64] recommended that, with rare exceptions, patients with mild CHD such as mild semilunar valve stenoses (congenital or residual), small shunt lesions, or mild aortic coarctations be permitted to participate competitively in all sports. Even patients with successful arterial switch procedures or excellent tetralogy of Fallot repairs may participate in competitive sports without restriction provided that they have normal exercise tests, no evidence of ventricular dysfunction, normal or near-normal right heart pressures and chamber sizes, no significant residual shunts, and no tachyarrhythmias on ambulatory ECG or exercise testing. Although patients with more serious congenital or residual heart anomalies are advised to avoid high-intensity competitive sports, these recommendations do not necessarily preclude participation in these activities in a less competitive, recreational environment. For these patients, the numerous benefits of regular exercise should be weighed carefully against the potential risks of these activities. Exercise testing, as well as other testing modalities, can help to inform this assessment. We believe that, in most cases, the risk/benefit ratio for regular exercise will be judged to be favorable, and we strongly encourage clinical research in this important area.

Cardiac Rehabilitation for Children With CHD

When subjected to formal cardiopulmonary exercise testing, it has been found that children with "repaired" CHD often have reduced exercise capacity.[28,37,65–70] Residual hemodynamic lesions certainly account for some of this phenomenon. However, it has been observed that children with CHD often lead relatively sedentary lifestyles, perhaps on account of restrictions imposed on them by physicians, parents, teachers, coaches, or the children themselves.[71,72] Any disability related to their CHD may therefore be compounded by deconditioning. This component of their disability should respond to exercise training.

Although theoretically appealing, proof of this concept has, until recently, been hard to come by. Goldberg et al[73] studied 26 patients with repaired tetralogy of Fallot or ventricular septal defects and found that a 6-week home exercise program with the use of stationary bicycles improved peak work capacity but had no effect on peak $\dot{V}o_2$. Ruttenberg et al[74] studied 12 patients with a variety of CHDs and reported that a 9-week program based on a jogging and walking regimen improved treadmill endurance time but did not improve peak $\dot{V}o_2$. Fredriksen et al[75] found that 55 patients with a variety of CHDs, who participated in a training program that introduced them to several sports and other physical activities, achieved a small (<5%) improvement in endurance time and no improvement in peak $\dot{V}o_2$ normalized for body weight. Minamisawa et al[76] studied 11 children and young adults with Fontan procedures and reported that a 2- to 3-month home exercise program produced only small (≈7%) improvements in peak $\dot{V}o_2$ and peak work rate.

In contrast, Bradley et al[77] found, in a study of 9 patients with tetralogy of Fallot or transposition of the great arteries, that a 12-week rehabilitation program improved endurance time and achieved a 21% increase in peak $\dot{V}o_2$. However, their data suggested that their findings may have been due to increased effort rather than an objective improvement in exercise function. Balfour et al[78] reported data from 6 patients with CHD who completed a 3-month rehabilitation program. They found a 20% increase in peak $\dot{V}o_2$ after rehabilitation. However, their study was quite small, was plagued by a high

Table 2. Cardiac Rehabilitation Studies in Patients With CHD

Study	n	Diagnosis	Program Duration, wk	Sessions per Week	Time per Session, min	Type	Control	Impact on Peak $\dot{V}O_2$ (mL/kg per Minute), %	Comment
Goldberg[73]	26	16 TOF, 10 VSD	6	3	<45	Home-based	No	Unchanged	Other parameters improved
Ruttenberg[74]	12	3 TOF, 3 TGA, 1 AVC, 5 AS	9	3	45	Facility-based	No	Unchanged	Large (50%) dropout rate; other parameters improved
Bradley[77]	9	5 TGA, 9 TOF	12	2	60	Facility-based	No	↑ 20	Internally inconsistent data; RER not measured; improvements may be effort related
Balfour[78]	6	1 Fontan, 5 other	12	3	60	Facility-based	No	↑ 20	Large (>50%) dropout rate
Fredriksen[75]	55	12 TGA, 8 ASD/VSD, 11 LVOTO, 3 RVOTO, 10 TOF, 4 Fontan, 7 other	20	2	NA	Facility-based and home-based	Yes	Unchanged	Large program variability; other parameters improved
Minamisawa[76]	11	Fontan	8–12	2–3	30	Home-based	No	↑ 7	
Opocher[79]	10	Fontan	32	2	30–45	Facility-based and home-based	No	↑ 11	
Rhodes[80,81]	16	12 Fontan, 4 other	12	2	60	Facility-based	Yes	↑ 16	Rehabilitation patients' improvement was sustained 7 mo after the program and was significantly superior to that of control subjects

TOF indicates tetralogy of Fallot; VSD, ventricular septal defect; TGA, transposition of the great arteries; AVC, atrioventricular canal; AS, aortic stenosis; LVOTO, left ventricular outflow tract obstruction; and RVOTO, right ventricular outflow tract obstruction.

dropout rate, and could not exclude the possibility that the improvement was due solely to increased effort. In a study of 10 children with Fontan procedures, Opocher et al[79] detected an 11% improvement in peak $\dot{V}O_2$ after an 8-month, primarily home-based exercise program. None of these studies was well controlled, however, nor did they provide insights into the mechanisms responsible for the observed improvements.

More recently, Rhodes et al[80] reported that, in a study of 16 children with serious CHD, a 12-week rehabilitation program was associated with a 17% increase in peak $\dot{V}O_2$. Improvements in the $\dot{V}O_2$ at the VAT were even more substantial. Most of the improvement appeared to be due to an increase in the O_2P at peak exercise. Peak HR and peak RER were similar in the prerehabilitation and postrehabilitation studies, indicating that the observed improvements could not be ascribed to a better effort in the postrehabilitation study. The improvements were sustained 6 to 9 months after the termination of the rehabilitation program (1 year after the prerehabilitation study) and were associated with improvements in lifestyle, perceived exercise function, self-esteem, and emotional state. Improvements in exercise function and other areas were not observed in a control group comprised of 18 children with similar diagnoses observed over the same time period.[81]

The mechanisms responsible for the rehabilitation patients' improved peak $\dot{V}O_2$ and O_2P were not elucidated. The magnitude of the improvements appears to be too great to be explained solely by increased O_2 extraction. A rehabilitation-related increase in forward stroke volume at peak exercise therefore seems likely, although whether the increase is related to vascular, muscular, or cardiological factors remains uncertain.

The favorable results achieved in the study of Rhodes et al were ascribed to the low patient/staff ratio and the age-appropriate environment/activities that were incorporated into the rehabilitation program.[80] However, data on the optimal design of pediatric cardiac rehabilitation programs do not exist, and further investigations are needed to elucidate the most effective rehabilitation strategies for children with CHD. Furthermore, reliance on a facility-based rehabilitation program is, for many patients, impractical, and the costs of these programs are not covered reliably by most third-party payers. Home-based programs, possibly supported by Internet and/or social networking technologies, may represent a practical and attractive alternative to facility-based programs. It is, in any event, unfortunate that restrictive medical insurance policies and/or unfavorable institutional priorities cause the benefits of cardiac rehabilitation to be unavailable to most children with CHD.

Conclusion

The acquisition and interpretation of exercise test data from children and adolescents with CHD present clinicians with some unique challenges. The information gained from these studies can, however, be quite valuable and often provides unique insights into a patient's clinical status and prognosis. Cardiac rehabilitation programs also have the potential to benefit many patients with CHD. Unfortunately, the limited experience with (Table 2) and availability of these programs has caused the benefits of cardiac rehabilitation to be unavailable to most children with CHD.

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Disclosures

None.

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KEY WORDS: exercise test ■ excercise ■ heart defects, congenital

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Review Article

Paediatric cardiac rehabilitation in congenital heart disease: a systematic review

Ana Ubeda Tikkanen,[1] Ainhoa Rodriguez Oyaga,[2] Olga Arroyo Riaño,[2] Enrique Maroto Álvaro,[3] Jonathan Rhodes[1]

[1]*Department of Cardiology, Childrens Hospital of Boston, 300 Longwood Avenue, Boston, Massachusetts 02115, United States of America;* [2]*Department of Physical Medicine and Rehabilitation, Hospital Gregorio Marañón, C/Dr Esquerdo 46, 28007;* [3]*Department of Paediatric Cardiology, Hospital Materno-Infantil Gregorio Marañón, C/ O'Donnell 48-50, 28009 Madrid, Spain*

Abstract *Background:* Advances in medical and surgical care have contributed to an important increase in the survival rates of children with congenital heart disease. However, survivors often have decreased exercise capacity and health-related issues that affect their quality of life. Cardiac Rehabilitation Programmes have been extensively studied in adults with acquired heart disease. In contrast, studies of children with congenital heart disease have been few and of limited scope. We therefore undertook a systematic review of the literature on cardiac rehabilitation in children with congenital heart disease to systematically assess the current evidence regarding the use, efficacy, benefits, and risks associated with this therapy and to identify the components of a successful programme. *Methods:* We included studies that incorporated a cardiac rehabilitation programme with an exercise training component published between January, 1981 and November, 2010 in patients under 18 years of age. *Results:* A total of 16 clinical studies were found and were the focus of this review. Heterogeneous methodology and variable quality was observed. Aerobic and resistance training was the core component of most studies. Diverse variables were used to quantify outcomes. No adverse events were reported. *Conclusions:* Cardiac Rehabilitation Programmes in the paediatric population are greatly underutilised, and clinical research on this promising form of therapy has been limited. Questions remain regarding the optimal structure and efficacy of the programmes. The complex needs of this unique population also mandate that additional outcome measures, beyond serial cardiopulmonary exercise testing, be identified and studied.

Keywords: Exercise; quality of life; children

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The incidence of congenital heart disease is 4 to 8 per 1000 live births.[1] Although advances in medical knowledge and technology have, over the past few decades, dramatically improved the survival of children with congenital heart defects, for many lesions life expectancy of patients remains short and quality of life low.[2–4] Residual cardiovascular defects are responsible for some of these hardships. Survivors of congenital heart disease are also often afflicted with pulmonary, neurological, neurodevelopmental, orthopaedic, and other comorbidities that impair their ability to function.[5–8] Superimposed upon these physical impairments, patients with congenital heart disease are often subject to overprotection on the part of parents, educators, and healthcare providers predisposing them to physical inactivity and exercise intolerance.[9,10]

These factors can have serious implications for congenital heart disease survivors' long-term health and quality of life. In adults, physical inactivity has been found to be an independent risk factor for atherosclerosis, cardiovascular disease, and diabetes.[11] Indeed, sedentary living is estimated to be responsible

Correspondence to: Dr A. Ubeda Tikkanen, Childrens Hospital of Boston, 300 Longwood Avenue, Boston, Massachusetts 02115, United States of America. Tel: +1 617 817 4941; Fax: +1 617 734 9930; E-mail: Ana.UbedaTikkanen@cardio.chboston.org

for approximately one-third of deaths due to coronary heart disease and type II diabetes, and low cardiopulmonary fitness is a strong independent predictor of all-cause mortality. Among adults, the relative risk for cardiovascular death that is associated with being unfit exceeds that associated with smoking, elevated systolic blood pressure, hypercholesterolaemia, or obesity.[11–13] Among patients with congenital heart disease, diminished exercise capacity has been found to be an independent predictor of death/and or hospitalisation for individuals with repaired Tetralogy of Fallot, Transposition of the Great Arteries, Pulmonary Hypertension, and Fontan Physiology.[13–17] To optimally manage patients with complex congenital heart disease, the role of ancillary therapies that may not cure but may potentially improve cardiac function and quality of life – such as cardiac rehabilitation – should be explored.[12]

Cardiac rehabilitation programmes have been widely studied in adults with acquired heart disease. Programmes for acute – post-MI or post-surgery – and chronic patients differ with regard to the intensity of endurance training, the level of monitoring employed, and the number/training of the personnel required for supervision; other aspects of the programmes are similar. In addition to improving oxygen consumption and exercise capacity, they have been found to reduce morbidity, mortality, and economic costs, as well as improve quality of life.[18–21] They also have a salutary effect upon standard cardiovascular risk factors such as lipid profiles, adiposity, and hypertension. The effects of exercise on these conventional cardiovascular risk factors are, however, substantially less compared with those achieved by pharmacological therapies alone, and the mortality benefits associated with exercise and fitness cannot be explained solely by the impact of these dynamics upon the conventional risk factors.[11,22–24]

Unfortunately, only 10% of all potential adult candidates for exercise training/cardiac rehabilitation actually receive this therapy. Among children this percentage is much lower.

One would expect that the benefits associated with exercise training in adults with cardiovascular disease would also be recognised among children with congenital heart disease. However, there have been relatively few clinical studies of paediatric cardiac rehabilitation. These studies vary greatly in design, inclusion criteria, assessment of risk factors, duration of follow-up, attrition, and particularly in outcome measures. Thus, a systematic review of the existing literature is needed to summarise and evaluate the existing data regarding the benefits of cardiac rehabilitation in children, to determine the proper outcome measurements, and to identify the attributes of a successful programme.

Methods

Search strategy: The bibliographical search was performed using the following strategy: heart, cardiac, rehabilitation, exercise, lung, human, infant, child, adolescent.

The databases searched during the study were: MEDLINE/PubMed, EMBASE, Cardiosource Clinical Trials Database, and Cochrane Library. Additional studies were obtained from the bibliography of the studies obtained.

Inclusion criteria: Studies were included if they contained a structured cardiac rehabilitation programme with an exercise training component in cardiac patients up to 18 years of age or if they reviewed these types of studies. Only complete articles published from January, 1981 until November, 2010 were included.

Exclusion criteria: Languages other than English, Spanish, French, or Italian or studies with a rehabilitation component but without an exercise training component were not included.

Classification of the evidence: Two independent authors reviewed each paper. Each reviewer classified each study according to the OXFORD classification for evidence-based medicine[25] – a classification system based on the type of study (Table 3). When the authors' classifications differed, the case was discussed and a consensus classification was determined. The quality of the evidence supporting the use of cardiac rehabilitation in children with congenital heart disease was then graded, based upon the entirety of the studies reviewed, as described by the Oxford Center for Evidence-Based Medicine (Table 4).

Results

A total of 193 articles were found; however, only 24 met our inclusion criteria. Of these, 21 had a structured rehabilitation programme, but only 18 had an exercise training component. These papers are the focus of this review. Of these articles, two were case reports and were not included in our final analysis.[12,26] The youngest patients included were 4 years old. The number of patients included per study ranged from 1 to 103, and the duration of the programme ranged from 2 weeks to 10 months. No adverse events were reported. The essential features of each study are summarised in Tables 1 and 2.

The level of evidence of these studies was scored according to the OXFORD classification system and is presented in Table 3. There were no randomised control trials, and the best studies receive a score of only 3. Overall, the level of evidence supporting the efficacy of cardiac rehabilitation in children with

Table 1. Description of patient population and rehabilitation programme.

References	Location	Patient population	Ages	n	Patients treated	Type of excercise	Duration	Frequency	Intensity	Sessions
McBride[42]	Hospital	Heterogeneous	10–16	20	20	Aerobic, resistance	2–10 months	3/week	HR at AT, 60% of maximal voluntary contraction	30–60 min
Rhodes[30]	Hospital	Heterogeneous	8–18	33	15	Aerobic, resistance	3 months	2/week	HR at AT, light resistance	60 min
Moalla[28]	Home	Heterogeneous	12–15	18	10	Aerobic	12 weeks	3/week	HR at AT	45 min
Brassard[39]	Home (2), hospital (3)	Fontan	11–26	5	5	Aerobic, resistance	2 months	3/week	50–80% peak VO_2	20–30 min
Opocher[31]	Hospital + home	Fontan	7–12	10	10	Aerobic	8 months	2/week	50–70% peak VO_2	30–45 min
Rhodes[27]	Hospital	Heterogeneous	8–17	16	16	Aerobic, resistance	3 months	2/week	HR at AT, light resistance	60 min
Minamisawa[29]	Home	Fontan	11–25	11	11	Aerobic	2–3 months	2–3/week	60–80% peak HR	40 min
Fredriksen[32]	Hospital or supervised gym	Heterogeneous	10–16	93	55	Aerobic, resistance, flexibility, education	2 weeks or 5 months	Daily or 2/week	65–80% peak HR	Not specified
Sklansky[33]	Hospital	TOF	6–16	11	11	Aerobic	2 months	3/week	60–70% peak HR	30 min
Balfour[34]	Hospital	Heterogeneous	13.5–19.8	6	6	Aerobic, education	3 months	3/week	>70% peak HR	30–40 min
Calzolari[38]	Hospital	TOF	6–16.5	18	9	Aerobic, respiratory	3 months	3/week	60–70% peak HR	60 min
Longmuir[43]	Home	Heterogeneous	4.7–14.3	40	17	Aerobic, resistance, flexibility, coordination	6 weeks	2/week	Capability of talking during exercise	Not specified
Longmuir[44]	Home	Heterogeneous	4.7–14.3	60	30	Aerobic, resistance, flexibility, coordination	6 weeks	2/week	Capability of talking during exercise	Not specified
Bradley[45]	Hospital	TOF/TGA	4–13	9	9	Aerobic, resistance, flexibility, coordination	12 weeks	2/week	60–80% peak HR	60 min
Ruttenberg[40]	Hospital	Heterogeneous	7–18	21	21	Aerobic	9 weeks	3/week	65–75% peak HR	30 min
Goldberg[41]	Home	TOF/VSD	7–18	26	26	Aerobic	6 weeks	3–4/week	50–70% peak VO_2	45 min

AT = anaerobic threshold; HR = heart rate; TGA = transposition of the great arteries; TOF = tetralogy of Fallot; VSD = ventricular septal defect; VO_2 = oxygen consumption

Table 2. Study description.

References	Type of study	Follow-up period	Outcome variables	Results	Comments
McBride[42]	Case series	Immediately post programme	Safety	No major complications.	No CPX data
Rhodes[30]	NRCT*	5 years post programme	• Serial cardiopulmonary exercise testing • Activity, self-esteem and emotional state questionnaires	Significant increase ($p < 0.01$) in: • peak work rate (7.8%) • peak VO_2 (21.8%) Non-significant decline in these parameters in control group	• Well-controlled study • RER reported • Examined midterm effects of the intervention and quality of life
Moalla[28]	NRCT*	Immediately post programme	• Serial cardiopulmonary exercise testing • Respiratory muscle oxygenation (near-infrared spectroscopy)	Significant increase in: • peak VO_2 (21%; $p < 0.05$) • peak respiratory muscle oxygenation (22%; $p < 0.01$) Significant correlation between tissue oxygenation and peak VO_2 at AT ($p < 0.01$) Non-significant improvement in pulmonary function was observed in the training group	• Home exercised regime • Compliance not assessed • RER not reported • Suggests that respiratory physiotherapy in the programme might be helpful
Brassard[39]	Case series	Immediately post programme	• Serial cardiopulmonary exercise testing • Muscle strength (Dynamometer) • Blood pressure • Ergoreflex	Non-significant increase in: • peak VO_2 ($p = 0.47$) • muscle strength ($p = 0.57$) Significative ergoreflex contribution to systolic blood pressure ($p = 0.02$)	• Short duration and variable programme structure might account for lack of improvement
Opocher[31]	Case series	Immediately post programme	• Serial cardiopulmonary exercise testing	Significant increase in: • estimated workload (11.3%; $p = 0.03$) • O_2 pulse (19%; $p = 0.004$) Non-significant increase: • peak VO_2 (11%; $p = 0.07$)	• RER not reported

Table 2. *Continued*

References	Type of study	Follow-up period	Outcome variables	Results	Comments
Rhodes[27]	Case series	Immediately post programme	• Serial cardiopulmonary exercise testing	Significant increase ($p < 0.01$) in: • peak work rate (14%; $p < 0.001$) • peak VO_2 (16.3%; p 0.005) %predicted? • predicted O_2 pulse (27.6%; $p = 0.01$) • FEV1 (7%; $p < 0.001$)	• No control group • RER reported
Minamisawa[29]	Case series	Immediately post programme	• Serial cardiopulmonary exercise testing	Significant increase in: • 7% workload ($p = 0.04$) • 7% peak VO_2 ($p = 0.03$) Significant decrease in: • HR with sub-maximal effort ($p < 0.05$)	• Home programmes might be a more economical option but compliance is more difficult to assess • RER not reported
Fredriksen[32]	NRCT*	Immediately post programme	• Serial cardiopulmonary exercise testing • Activity monitor (accelerometer) • Psychosocial function (youth self-report and child behaviour checklist)	Significant increase in: • peak VO_2 (1.67 ± 0.57 versus $1.82 \pm 0.661 \times min^{-1}$; $p < 0.001$) • exercise time (614 ± 138 versus 655 ± 155 s; $p = 0.005$) • activity (p 0.028) and psychosocial ($p < 0.001$) levels	• Large study population • Varied activities might have enhanced patient compliance • One of the few to incorporate education • RER reported
Sklansky[33]	Case series	Immediately post programme	• Serial cardiopulmonary exercise testing • Ventricular function (echocardiography)	Significant increase in: • endurance time (1.7 min; $p < 0.0004$) Significant decrease in: • sub-maximal heart rate ($p < 0.001$) No increase in: • ectopy with exercise • arrhythmias • deterioration of ventricular function	• Retrospective study • RER not reported

Table 2. *Continued*

References	Type of study	Follow-up period	Outcome variables	Results	Comments
Balfour[34]	Case series	Immediately post programme	• Serial cardiopulmonary exercise testing	Significant increase in: • peak VO_2 (20%; $p < 0.005$) • endurance time (21%; $p < 0.03$) Significant decrease in: • systolic blood pressure (7%; $p < 0.03$)	• Includes stress management and nutrition counselling • RER not reported • High drop-out rate
Calzolari[38]	NRCT*	Immediately post programme	• Serial cardiopulmonary exercise testing	Non-significant increase in: • maximal • sub-maximal exercise capacity	• No CPX data • Respiratory therapy included
Longmuir[43,44]	NRCT*	5 years post programme and immediately post programme	• Exercise test (Canada fitness awards test: cardiovascular endurance, strength, flexibility, and coordination)	Significant increase ($p < 0.01$) in: • different scores at 6 months and 5 years post programme	• Large patient population • Control group • No CPX testing • Long-term follow-up
Bradley[45]	Case series	Immediately post programme	• Anthropometric measurements • Serial cardiopulmonary exercise testing	Significant increase in: • peak systolic pressure (17%; $p < 0.001$) • peak VO_2 (20%; $p < 0.01$) • endurance time (18%; $p < 0.01$)	• Youngest study population • One of the most complete programmes • RER not reported
Ruttenberg[40]	NRCT*	Immediately post programme	• Basic exercise test	Significant increase: • endurance time ($p < .01$) • non-significant increase in peak VO_2 ($p = 0.1$)	• RER not reported • Sub-optimal control group
Goldberg[41]	Case series	Immediately post programme	• Exercise capacity (cyclergometer) • Body composition	Significant increase: • maximal work capacity ($p < 0.001$) Non-significant increase: • peak VO_2 • peak HR Improvement of body composition	• Short programme duration

AT = anaerobic threshold; CPX = cardiopulmonary testing; FEV1 = forced expiratory volume in the first second; HR = heart rate; NRCT = non-randomized controlled tria; RER = respiratory exchange ratio; VO_2 = oxygen consumption

*NRCT – equivalent to a cohort study in the modified CONSORT definition[56]

Table 3. Levels of evidence.

References	Level of evidence
McBride[43]	4
Rhodes[30]	2B
Moalla[28]	2B
Brassard[39]	2B
Opocher[31]	4
Rhodes[27]	3B
Minamisawa[29]	4
Fredriksen[32]	2B
Sklansky[33]	4
Balfour[34]	4
Calzolari[38]	2B
Longmuir[43]	2B
Longmuir[44]	2B
Bradley[45]	4
Ruttenberg[40]	2B
Goldberg[41]	4

Table 4. Classification of level of evidence.

Level of evidence	Type of study
1	Systematic review of randomized trials
2	Individual randomized control trial or observational study with dramatic effect
3	Non-randomized controlled cohort/follow-up study
4	Case series, case-control studies or historically controlled studies
5	Mechanism-based reasoning

congenital heart disease may be characterised as suggestive but not as definitive (Oxford Center for Evidence-Based Medicine Classification B; Table 4).

Discussion

The main goal of this review was to describe and quantify existing data regarding rehabilitation programmes for children with congenital heart disease. Several studies have found evidence supporting the acute benefits of cardiac rehabilitation in these patients.[27–35] Serious adverse events have not been encountered. A limited number of previous reviews have evaluated this subject[36,37] and have, in general, concurred with these findings.

However, our review raises a number of important issues that have not been previously addressed. Beneficial results were not uniformly observed and adequate randomisation was not often employed. It must also be acknowledged that the physiologic alterations and residual impairments associated with different congenital heart defects vary greatly, and the response to rehabilitation may differ depending upon the defects present. Ideally, each pathologic variant should be studied individually. However, only seven of the clinical trials studied a homogenous population.[12,26,29,31,33,38,39]

The structure of the rehabilitation programmes also varied considerably with regard to the intensity, frequency, and duration of exercise. Most early studies also limited their training programmes to aerobic exercises.[27,29,31,33,34,38,40,41] In contrast, most current rehabilitation programmes employ a combination of aerobic and resistance training.[12,26,28,32,39,42–45] Owing to the fact that a strong relationship exists between muscle strength and exercise tolerance,[12,36] suboptimal training regimen may account for the ambiguous results that emerged from some of the paediatric rehabilitation programmes.

However, even the current rehabilitation programmes do not take into account the fact that congenital heart disease may also be associated with congenital or acquired abnormalities in other organ systems, which may be appropriately addressed in rehabilitation therapy. These organ systems include:

Pulmonary: Coexisting pulmonary pathology is common among patients with congenital heart disease including restrictive lung disease, obstructive lung disease, diaphragmatic paralysis, recurrent pulmonary infections, etc. Although pulmonary dysfunction is usually not the main factor limiting exercise capacity,[46] it could contribute to exercise limitation during a maintained submaximal effort. Respiratory physiotherapy may therefore improve the congenital heart disease patient's cardiorespiratory response to exercise, just as it does in patients with chronic heart failure.[5,28,46–48]

Neurologic: The neurologic deficits encountered among patients with congenital heart disease may range from major syndromes such as hemiparesis, cerebral palsy, or epilepsy to more subtle symptoms such as neurodevelopmental delays, learning disabilities, or attention deficit disorders.[6–8] These disabilities may be appropriate targets for rehabilitation therapy and/or may influence the structure of an individual's rehabilitation programme.

Musculoskeletal: Musculoskeletal abnormalities are among the most common extracardiac anomalies associated with congenital heart disease. These patients may have scoliosis and other thoracic deformities, connective tissue disorders, hypotonia, etc.[49,50] all of which may be relevant to one or more aspects of a patient's rehabilitation programme.

Few of the paediatric cardiac rehabilitation programmes reviewed here incorporated features designed to address these issues and most did not include recommended components of adult rehabilitation programmes,[20] such as nutritional counselling, aggressive risk factor management,

psychosocial and vocational counselling, physical activity counselling, education, and psychological intervention. Indeed, educational intervention, one of the main pillars in adult cardiac rehabilitation, was employed in only four of the trials.[12,32,34,45] Similarly, psychological assessment/counselling was never included. Owing to the fact that behavioural issues are not uncommon among children with congenital heart disease and their caretakers[6–8], these omissions may have significant negative consequences and decrease the success rate of a cardiac rehabilitation intervention.

Mid/long-term follow-up data have been provided by only two studies (Longmuir[43] and Rhodes[30]). Significant improvements, persisting beyond the immediate post-programme period, were observed. These studies suggest that rehabilitation programmes can have persistent beneficial effects in children with congenital heart disease. However, it is difficult to draw firm conclusions from these two, small studies. Certainly, to reliably achieve long-standing lifestyle changes – a necessity for these patients with a chronic disease, and one of the major goals of cardiac rehabilitation – a multi-level intervention that targets the children, their lifestyles, and their caretakers seems desirable. To sustain acute improvements, reinforcement with long-term follow-up programmes should be pursued. These approaches have been productively incorporated into exercise programmes for children with obesity.[51,52] The outcomes of obesity programmes that incorporate these multidimensional features have been found to be superior to those of programmes with more limited resources.[51] Better results may also accrue to children with congenital heart disease if their rehabilitation programmes were to be enhanced with these capabilities.

The technology used to assess the impact of cardiac rehabilitation also varied considerably from study to study. Serial cardiopulmonary exercise testing – one of the most valuable tools for objectively and quantitatively assessing the impact of cardiac rehabilitation – was used in a fraction of the studies. The respiratory exchange ratio – probably the best objective measure of effort expenditure in this population – often was not reported or used to establish that the observed changes were due to the effects of the rehabilitation programme rather than the variations in effort expenditure. It is therefore difficult to reliably interpret the peak exercise data of these studies.

Apart from the peak oxygen consumption, there is no consensus regarding the other outcome measures that should be used to assess the effects of cardiac rehabilitation. Potential candidates include muscle strength,[12] body composition, quality of life questionnaires, etc. In order to fully assess the effects and benefits of a cardiac rehabilitation programme, variables that reliably measure the impact of the programme upon the different areas affected by congenital heart disease must be identified and studied.

From the articles reviewed for this study, and the literature regarding exercise programmes for patients with obesity and other chronic paediatric diseases, such as cystic fibrosis[53] and renal transplantation,[54,55] there appears to be a consensus that rehabilitation programmes should have a duration of at least 12 weeks and a frequency of two to three times a week, with sessions lasting at least 40 minutes. We believe that the programmes should include aerobic, resistance, and flexibility training, as well as education and psychological intervention. The intensity of aerobic exercise should be at a heart rate approximately equivalent to that associated with the anaerobic threshold. This consideration is particularly relevant to children with congenital heart disease, as chronotropic impairment is commonly encountered in this population.

A final point that emerges from this analysis is that rehabilitation programmes for children with congenital heart disease are underutilised and their potential value underappreciated. A number of factors may account for this state of affairs, including systematic deficiencies, for example, a limited number of specialised facilities/personnel; economic limitations, for example, a lack of insurance coverage for the programmes; provider unawareness, for example, healthcare providers underestimate the value and/or availability of rehabilitation programmes; and patient-related factors, for example, logistic problems, expense, parental anxiety. Resolution of these issues will require changes at various levels of healthcare policies, protocols and increasing awareness of these programmes among healthcare dispensers and families.

Conclusion

We are now confronted with a growing patient population of survivors of congenital heart disease. These individuals continue to suffer from disabilities that affect their present and future quality of life. Multidisciplinary interventions, such as cardiac rehabilitation, which could greatly benefit many of these patients, are underappreciated and almost invariably overlooked as a first-line approach to secondary intervention.

Benefits have been observed in many studies of cardiac rehabilitation in children with congenital heart disease, and no adverse events have been reported. Although challenging at various levels,

randomised controlled studies on larger homogeneous population are needed to prove the efficacy of these interventions, stratify risk in these patients, and develop optimal protocols. Long-term effects and outcomes should be determined.

The chosen outcome variables have also been incomplete. Ideally, they should assess the effects of the programme on multiple areas including impairment of body structures or functions, limitation of activities, and restriction of participation. Serial cardiopulmonary exercise testing is best suited for measuring exercise capacity and prescribing exercise intensity. Other modalities should be developed to quantitatively assess other areas of impairment.

The optimal structure of a paediatric cardiac rehabilitation programme also remains unclear. A combination of aerobic and resistance exercise is probably ideal. Including complementary therapies such as respiratory physiotherapy, education and psychological interventions might improve the outcome of these programmes; however, this issue has not been thoroughly studied. Comorbidities and environmental impediments that often confront patients with congenital heart disease have, historically, not been addressed by rehabilitation programmes. The role of parents in the rehabilitation programmes has also been overlooked. These are areas that deserve greater attention. We believe that a cardiac rehabilitation programme should be based on multidisciplinary interventions that apply a holistic approach to the patient and treat the ensemble of problems that they confront.

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Physical activity is associated with improved aerobic exercise capacity over time in adults with congenital heart disease ☆

Ana Ubeda Tikkanen [a,*,1,2], Alexander R. Opotowsky [a,b,1,2], Ami B. Bhatt [c,1], Michael J. Landzberg [a,b,1], Jonathan Rhodes [a,1]

[a] Department of Cardiology, Boston Children's Hospital, Boston, MA, United States
[b] Department of Medicine, Brigham and Women's Hospital, Boston, MA, United States
[c] Heart Center, Massachusetts General Hospital, Boston, MA, United States

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ABSTRACT

Background: Impaired exercise capacity is common in adults with congenital heart disease (ACHD). This impairment is progressive and is associated with increased morbidity and mortality. We studied the influence of the frequency of at least moderately strenuous physical activity (PhysAct) on changes in exercise capacity of ACHD patients over time.
Methods: We studied ACHD patients ≥21 years old who had repeated maximal (RER ≥ 1.09) cardiopulmonary exercise tests within 6 to 24 months. On the basis of data extracted from each patient's clinical records, PhysAct frequency was classified as (1) Low: minimal PhysAct, (2) Occasional: moderate PhysAct <2 times/week, or (3) Frequent: moderate PhysAct ≥2 times/week.
Results: PhysAct frequency could be classified for 146 patients. Those who participated in frequent exercise tended to have improved pVO_2 ($\Delta pVO_2 = +1.63 \pm 2.67$ ml/kg/min) compared to those who had low or occasional activity frequency ($\Delta pVO_2 = +0.06 \pm 2.13$ ml/kg/min, $p = 0.003$) over a median follow-up of 13.2 months. This difference was independent of baseline clinical characteristics, time between tests, medication changes, or weight change. Those who engaged in frequent PhysAct were more likely to have an increase of pVO_2 of ≥1SD between tests as compared with sedentary patients (multivariable OR = 7.4, 95%CI 1.5–35.7). Aerobic exercise capacity also increased for patients who increased activity frequency from baseline to follow-up; 27.3% of those who increased their frequency of moderately strenuous physical activity had a clinically significant (at least +1SD) increase in pVO_2 compared to only 11% of those who maintained or decreased activity frequency.
Conclusions: ACHD patients who engage in frequent physical activity tend to have improved exercise capacity over time.

1. Introduction

As a consequence of improvements in medical and surgical care, adults with congenital heart disease (ACHD) now outnumber children with congenital heart disease in developed nations [1]. Survival is not, however, synonymous with optimal functional capacity and quality of life [2]. The importance of these less easily quantifiable outcomes is becoming increasingly appreciated [3,4].

ACHD patients have lower peak oxygen consumption (pVO_2), a measure of exercise capacity, than seen in the general population. Low pVO_2 in ACHD has strong independent prognostic value; it is associated with increased risk of morbidity and mortality and with worse quality of life [5,6]. An accelerated age-related decline has also been described. Several factors may account for these observations. Residual hemodynamic and electrophysiological defects are often present following surgical "repair." Congenital heart disease (and its treatments) may also cause, or be associated with, impairment of other organs including the pulmonary and systemic vascular beds, lung and airways, central nervous system, and neuroendocrine system [7–9], that can affect exercise capacity.

The adverse physiological consequences of residual hemodynamic inefficiency and other medical problems are compounded by deconditioning related to a sedentary lifestyle [10]. The majority of ACHD patients do not engage in physical activity (PhysAct) as frequently as recommended by published guidelines for the general population [11,12].

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* Corresponding author at: Boston Children's Hospital, 300 Longwood Ave, Boston, MA 02115. Tel.: +1 617 355 6508; fax: +1 617 734 9930.
E-mail address: anaubedatikkanen@yahoo.es (A. Ubeda Tikkanen).
[1] This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.
[2] Drs. Ubeda Tikkanen and Opotowsky contributed equally to this work and share first authorship.

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While PhysAct frequency does seem to be associated with higher aerobic capacity in ACHD at a single point in time [13], it is unclear whether increasing frequency of PhysAct results in maintenance of aerobic capacity over time.

To better characterize the impact of frequent PhysAct upon exercise capacity in ACHD patients, we undertook a retrospective study of the relationship between the frequency of at least moderately strenuous PhysAct and changes in objective measures of exercise capacity.

2. Methods

2.1. Subjects

We identified ACHD patients ≥ 21 years old that underwent cycle ergometry exercise testing at Boston Children's Hospital between January 2006 and July 2011. Patients with 2 maximal (RER ≥ 1.09) tests during the period of study, separated by 6–24 months (median = 13.2 mos, IQR 10.8–16.8), were included. Exclusion criteria included pregnancy at or between tests, intervening cardiac percutaneous or surgical interventions with the potential to impact exercise capacity, or acute illness at the time of exercise testing. The first 2 exercise tests fulfilling these requirements were used for this analysis.

2.2. Cardiopulmonary testing

Cardiopulmonary exercise testing (CPX) involved symptom-limited cycle-ergometry using a standard ramp protocol with electrocardiographic monitoring and breath-by-breath expiratory gas analysis (CardiO$_2$ exercise testing system, Medical Graphics, Minneapolis, Minnesota). Calculations and predicted values were obtained as described by Wasserman et al. [14].

2.3. Physical activity frequency assessment

PhysAct frequency was assessed from patients' clinical notes based upon the following guidelines (with representative clinical descriptions):

(1) *Low*: minimal PhysAct, e.g., "He has a recumbent bike at home but has not been using this."
(2) *Occasional*: light activity, or moderately strenuous activity (activity that makes the patient sweat or breathe hard) <2 times weekly and/or <40 min per session, e.g., "He has been exercising regularly, spending 10–20 min on the treadmill about 3 times a week."
(3) *Frequent*: at least moderately strenuous activity ≥2 times weekly for ≥40 min, i.e. "He is now going to the gym two hours a day Monday, Wednesday, and Friday."
(4) *Undetermined:* inadequate documentation to assign a level.

Changes in PhysAct frequency as defined above (low, occasional, frequent), between the clinic note at the time of the first CPX and at the time of the second CPX, were assessed. Changes were classified as: stable, increased or decreased.

Two investigators (AUT, JR) independently classified PhysAct frequency and change in PhysAct frequency for 50 subjects to assess inter-observer variability. The weighted kappa for PhysAct frequency was 0.79; the value for change in PhysAct between visits was lower (0.66), but still acceptable.

The baseline median percent predicted pVO_2 ($pVO_{2\text{-}\%pred}$) for univentricular (56.5%) and biventricular (66.7%) physiology was determined, and patients with $pVO_{2\text{-}\%pred}$ above this value were classified as having "above average" exercise capacity for their underlying physiology; those with $pVO2_{\text{-}\%pred}$ below this value were classified as having "below average" exercise capacity. The proportion of patients with values above/below the median $pVO_{2\text{-}\%pred}$ baseline value at the second CPX was assessed.

2.4. Statistical analysis

Change in pVO_2 over time, including the change in absolute pVO_2 ($pVO2_{\text{-}abs}$ expressed in l/min), weight normalized pVO_2 ($pVO_{2\text{-}perkg}$, expressed in ml/min/kg) and percent predicted pVO_2 ($pVO_{2\text{-}\%pred}$), was the primary outcome of interest. Secondary outcomes of interest were changes in the peak heart rate (pHR), peak O_2pulse, and VE/VCO_2 slope.

Continuous variables are presented as mean ± SD and categorical variables as counts and percentages. Because characteristics of the low and occasional PhysAct frequency groups were similar, these were combined into a single comparison group for most analyses. The relationships between PhysAct frequency categories and individual CPX variables were analyzed using ANOVA or the Kruskal–Wallis test. Paired t tests were used to compare the initial and final values for each normally distributed CPX variable (Wilcoxon rank sum test for non-normal distributions). Given varying time between studies for each patient, we also analyzed relationships between predictors of interest and change in exercise test variables per year (e.g. $\Delta pVO_{2\text{-}perkg/year}$). We performed linear regression analysis, with change in an exercise parameter of interest (e.g. $\Delta pVO_{2\text{-}perkg}$ or $\Delta pVO_{2\text{-}perkg/year}$) as the dependent variable, to assess the association between the level of PA during the interval between the visits, or the change in level of PhysAct reported at the two visits, and the dependent variables under analysis. Multivariable models were used to assess whether the observed associations were independent of potential confounders including age, sex, CHD diagnosis, time between tests, baseline $pVO_{2\text{-}perkg}$ (or other CPX variable), baseline height and weight (or BMI), weight change between studies, tobacco use, presence of a pacemaker, presence of systemic ventricular dysfunction by echocardiography (none, mild, moderate/severe), baseline heart rate, and use of specific cardiac medications (digoxin, beta-blocker, ACEI/ARB, diuretics). We also assessed the proportion of patients in each PhysAct group who changed from below to above median baseline $pVO_{2\text{-}\%pred}$ categories (or vice versa) during the interval between exercise tests, and those who had an increase or decrease of $pVO_{2\text{-}\%pred}$ by >1SD around the mean difference.

3. Results

3.1. Patient characteristics

PhysAct was classifiable from clinical records at the time of the second test for 72.4%(n = 147) of 203 patients who met study criteria. After examining distributions for percent change in $pVO_{2\text{-}abs}$ we excluded 1 outlier whose $pVO_{2\text{-}abs}$ increased 70.4% between the exercise tests (among the remaining subjects, $\Delta pVO_{2\text{-}abs}$ ranged from −24.2% to +35.5%). Of the 146 subjects included, 145 had PhysAct classifiable at the time of the first test. Demographic, clinical and CPX data were collected on all patients. There were no important differences between those excluded (n = 57) and those included in the analysis (e.g. age 32.8 vs. 33.5 y, p = 0.65; time between studies 13.3 vs. 13.6 mos, p = 0.63; baseline $pVO_{2\text{-}abs}$ 1.48 vs. 1.61 l/min, p = 0.15; $\Delta pVO_{2\text{-}\%pred}$ +2.4 vs. +3.0%, p = 0.76).

3.2. Baseline data

Of the 145 patients classifiable at the time of the first test, 42%(n = 61) had low PhysAct, 32.4%(n = 47) participated in occasional PhysAct and 25.5%(n = 37) engaged in frequent PhysAct. BMI and systolic BP tended to be higher in the lowest PhysAct group while $pVO_{2\text{-}perkg}$ and O_2 pulse were significantly higher ($p < 0.01$) in patients who exercised more frequently (Table 1). Data for the 146 patients with classifiable data at follow-up were similar.

There were significant differences in baseline $pVO_{2\text{-}\%pred}$ between CHD diagnoses (Fig. 1a). Median $pVO_{2\text{-}\%pred}$ was well below normal for all diagnoses, and more than $3/4^{ths}$ of patients in all diagnostic groups fell below the predicted value. On the other hand, there was no difference between diagnostic groups with regard to $\Delta pVO_{2\text{-}\%pred}$ over the study (Fig. 1b).

3.3. Predictors of change in peak VO_2

The strongest predictor of % change in $\Delta pVO_{2\text{-}abs}$ was BMI (Table 2). Patients with higher baseline BMI tended to have lower $pVO_{2\text{-}abs}$ at the second test (for +5 kg/m^2 BMI, $pVO_{2\text{-}abs}$ on repeat testing was 3.0% lower, p = 0.001, $r^2 = 0.07$). Height was not associated with $\Delta pVO_{2\text{-}abs}$ (p = 0.26) while baseline weight was (for +10 kg, $pVO_{2\text{-}abs}$ decreased by 1.6% between tests, p = 0.002, $r^2 = 0.06$). Those with higher baseline $pVO_{2\text{-}abs}$ tended to have slightly lower follow-up $VO_{2\text{-}abs}$. For every 10% lower baseline $pVO_{2\text{-}abs}$, $pVO_{2\text{-}abs}$ increased by 1.4% (p = 0.01, $r^2 = 0.04$). No other baseline clinical or demographic variable was associated with $\Delta pVO_{2\text{-}abs}$ (Table 2). There was no relationship between chronic cardiac medication use of any class or initiation of a new cardiac medication during the study interval and ΔpVO_{2abs} (beta-blockers n = 10 p = 0.27, ACEi/ARB n = 5 p = 0.21, digoxin n = 2 p = 0.82, diuretics n = 7 p = 0.22) were associated with $\Delta pVO_{2\text{-}abs}$. Patients who started a beta-blocker tended to have lower peak heart rate ($\Delta = -13.5$ bpm, $p < 0.001$) on follow-up study but higher O_2 pulse ($\Delta = +14$ ml/beat, $p < 0.001$). None of the other medications were associated with changes in either peak heart rate or O_2 pulse.

Predictors of other measures of ΔpVO_2 (i.e. $\Delta pVO_{2\text{-}\%pred}$, $\Delta pVO_{2\text{-}perkg}$) were equivalent with similar magnitudes of association to that seen with $\Delta pVO_{2\text{-}abs}$.

Table 1
Baseline demographic and clinical description based on physical activity frequency classification at the 1st CPX.

	Physical activity frequency				
	Overall	Low	Occasional	Frequent	P
N	145	61	47	37	
Age (y)	33.5 ± 10.2	34.1 ± 11.4	35.2 ± 9.9	30.3 ± 7.8	0.09
Male (%)	49.6	50.8	55.3	40.5	0.39
Height (cm)	167.8 ± 9.9	166.9 ± .9.9	167.6 ± 7.7	169.5 ± 12.2	0.53
Weight (kg)	73.9 ± 17.8	77.1 ± 20.1	72.4 ± 13.5	70.7 ± 18.1	0.21
BMI, baseline (kg/m^2)	26.1 ± 4.9	27.5 ± 5.8	26 ± 4.0	24 ± 4.0	0.01
Peak $VO_{2\text{-perkg}}$, baseline (ml/min/kg)	21.9 ± 6.7	19.0 ± 5.0	21.4 ± 6.1	27.4 ± 6.7	<0.01
O_2 pulse, baseline (mL/beat)	10.6 ± 3.6	9.7 ± 3.0	10.4 ± 3.6	12.0 ± 4.0	<0.01
Diabetes mellitus (%)	1.5	3.3	0	0	0.27
Tobacco (%)	9.9	15.8	6.7	3.3	0.15
Systolic BP (mmHg)	122 ± 15	125 ± 16	119 ± 14	119 ± 13	0.04
Diagnosis (%)					0.49
Tetralogy of Fallot	35.8	34.4	29.8	46.0	
Fontan	10.3	14.8	6.4	8.1	
Systemic right ventricle	22.8	16.4	29.8	24.3	
Other	31.0	34.4	34.0	21.6	
Ventricular dysfunction (%)					0.42
Moderate/severe	13.1	18.0	12.8	5.4	
Mild	23.5	18.0	25.5	29.7	
Normal	61.4	60.6	61.7	62.1	
Unknown	2.1	3.2	0	2.7	
Arrhythmia with exercise (%)					0.62
None	92.4	90.2	93.6	94.6	
Atrial fibrillation/flutter/SVT	2.1	3.3	2.1	0	
Ventricular tachycardia	0.7	0	2.1	0	
Frequent APBs or VPBs	4.8	6.6	2.1	5.4	
Pacemaker (%)	19.3	19.7	23.4	13.5	0.51
Medication (%)					
ACEI	33.8	37.7	34.0	27.0	0.58
Beta blocker	33.8	36.0	46.8	13.5	<0.01
Digoxin	10.3	8.2	8.5	16.2	0.44
Diuretic	17.2	23.0	17.0	8.11	0.17

Descriptive statistics (mean ± SD or %) based on physical activity frequency classification at the time of the first CPX, using ANOVA or Kruskal–Wallis and Fisher's exact or chi-squared tests for continuous and categorical variables respectively.

3.4. Effect of season on exercise testing results

There was no significant difference in $pVO_{2\text{-}\%pred}$ achieved on baseline exercise test by month ($p = 0.34$) or season (October-March versus April-September, $p = 0.74$) of testing. Season of baseline versus follow-up testing did not affect change in $pVO_{2\text{-}\%pred}$. Those who were re-tested in the same season as the baseline test ($n = 82$, $\Delta pVO_{2\text{-}\%pred} = +1.8 \pm 1.1$), those who had baseline testing in the winter and repeat in the summer ($n = 35$, $\Delta pVO_{2\text{-}\%pred} = +2.0 \pm 1.8$) and those who had the converse ($n = 29$, $\Delta pVO_{2\text{-}\%pred} = +2.2 \pm 1.6$) had the same mean change in $pVO_{2\text{-}\%pred}$ ($p = 0.98$).

3.5. Impact of physical activity on exercise parameters

No significant demographic and clinical differences were found between groups patients categorized according to their PhysAct levels reported at the time of the second CPX test (i.e., the activity level that they sustained during the interval between the exercise tests) except for BMI ($p = 0.02$), peak VO_2 ($p < 0.01$) that were better in those who were more active and tobacco users that were more frequent in the moderate physical activity group ($p < 0.01$). Fewer patients were classified as having low PhysAct at the follow-up visit, as compared with the baseline visit ($n = 42$ vs. 61).

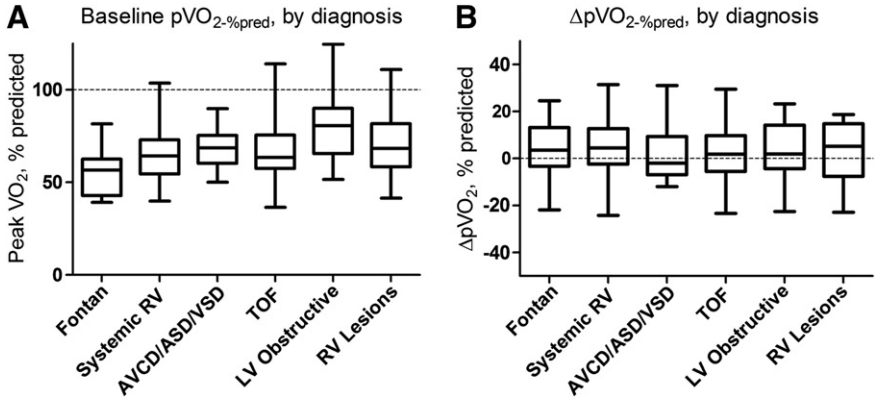

Fig. 1. Baseline % predicted peak VO_2 (A) and change in % predicted peak VO_2 between baseline and follow-up cardiopulmonary exercise tests (B) by congenital heart disease diagnostic category. While baseline $pVO_{2\text{-}\%pred}$ differed by diagnosis (Kruskal–Wallis, $p = 0.006$), there was no such difference in $\Delta pVO_{2\text{-}\%pred}$ between diagnoses (Kruskal–Wallis, $p = 0.96$). RV = right ventricular lesion, LV = left ventricular lesion, AVCD = atrioventricular canal defect, ASD/VSD = atrial/ventricular septal defect, TOF = tetralogy of Fallot.

Table 2
Predictors of % change in absolute peak VO_2.

	r^2	β	P
Age (/y)	0.012	−0.12	0.19
Sex (male)	<0.001	0.51	0.79
BMI (/kg/m^2)	0.07	−0.62	0.001
Height (/cm)	0.009	−0.11	0.26
Weight (/kg)	0.063	−0.16	0.002
Tobacco	<0.001	−0.35	0.92
Diabetes mellitus	<0.001	−0.76	0.93
Pacemaker	<0.001	−0.21	0.93
Severe systemic ventricular dysfunction	0.017	4.46	0.12
Baseline $pVO_{2\text{-perkg}}$ (mL/kg/min)	0.045	−4.41	0.01
MAP (mmHg)	0.002	0.05	0.6

Univariate linear regression of various predictors of % change in absolute peak VO_2.

CPX data from the baseline test and change between tests, classified by PhysAct level sustained between tests, are presented in Table 3. Frequent PhysAct was associated with an improvement in both $pVO_{2\text{-perkg}}$ and $pVO_{2\%\text{-pred}}$ (i.e., $\Delta pVO_{2\text{-perkg}}$ and $\Delta pVO_{2\%\text{-pred}}$ were positive, $p = 0.003$ and 0.04 respectively). There was a trend towards improved $pVO_{2\text{-abs}}$ ($p = 0.07$), and a significant improvement in $pVO_{2\text{-abs}}$ when expressed on a per year basis ($p = 0.04$). These relationships are shown graphically in Fig. 2, comparing the lower 2 PhysAct frequency levels to those who engaged in frequent PhysAct.

The association between exercise frequency and $\Delta pVO_{2\text{-}\%\text{pred}}$ was maintained despite multivariable adjustment for age, sex, and baseline $pVO_{2\text{-}\%\text{pred}}$ ($p = 0.02$) and additional factors including BMI, time between tests, weight change, diabetes, tobacco use, and presence of a pacemaker ($p = 0.03$). The relationship between PhysAct frequency and $\Delta pVO_{2\text{-perkg}}$ likewise persisted after equivalent adjustment for demographic and clinical data ($p = 0.002$ and 0.02 respectively).

In order to better understand whether inter-group differences in $\Delta pVO_{2\text{-abs}}$ were clinically significant, we assessed the proportion of patients who had either an increase or decrease in $pVO_{2\text{-abs}}$ of at least 1SD (mean change +3 ± 11%, with +1SD defined as increase of 14% and −1SD as −8%; Fig. 3). Patients with little or no PhysAct during the time interval between tests were more likely to sustain a decrease of at least 1SD in pVO_2 (19.8%) than an increase (11.0%). Conversely, those who participated in frequent PhysAct during that time interval were more likely to improve $pVO_{2\text{-abs}}$ by at least 1 SD (27.3%), while in only 12.7% of those engaging in frequent PhysAct did $pVO_{2\text{-abs}}$ drop by >1SD ($p = 0.03$). This finding was independent of age, BMI and baseline $VO_{2\text{-abs}}$ (multivariable logistic regression OR = 7.4, 95%CI 1.5–35.7, for +1SD in $pVO_{2\text{-abs}}$ for frequent PhysAct).

3.6. Change in physical activity frequency and pVO_2

Most patients (61.4%) maintained the same level of PhysAct over the study period; 29.7% increased and 9.0% decreased PhysAct frequency. A statistically significant relationship existed between the Δ PhysAct between tests, the concomitant $\Delta pVO_{2\text{-abs}}$ (l/min), and $\Delta pVO_{2\text{-}\%\text{pred}}$ (Fig. 4). Decreasing PhysAct frequency was associated with a decrease in $pVO_{2\text{-perkg}}$ (−1.9 ± 3.3 ml/min/kg), while stable PhysAct frequency was associated with stable $pVO_{2\text{-perkg}}$ (+0.5 ± 2.7 ml/min/kg) and

Table 3
Exercise data by physical activity frequency at the 2nd CPX.

		Physical activity frequency			
	Overall	Low	Occasional	Frequent	P
N	146	42	49	55	
Time between tests (mos.)	13.6 ± 4.7	14.3 ± 4.5	13.7 ± 5.2	13.0 ± 4.5	0.58
BMI, baseline (kg/m^2)	26.1 ± 4.9	27.7 ± 5.6	26.1 ± 4.8	24.9 ± 4.0	0.03
Weight (kg)					
Baseline	74.0 ± 17.7	78.0 ± 19.9	74.1 ± 16.3	70.8 ± 16.9	0.14
Δ	−0.2 ± 3.7	0.5 ± 3.0	0.2 ± 3.9	−1.2 ± 3.7	0.008
Rest MAP (mmHg)					
Baseline	91.0 ± 9.4	92.9 ± 11.3	90.3 ± 9.0	90.2 ± 7.9	0.43
Δ	0.0 ± 9.0	−0.6 ± 9.7	2.1 ± 8.9	−1.3 ± 8.5	0.19
Rest HR (bpm)					
Baseline	77.3 ± 13.9	81.6 ± 12.9	76.8 ± 13.5	74.6 ± 14.4	0.05
Δ	−0.6 ± 12.0	0.3 ± 13.2	−2.0 ± 9.3	0.1 ± 13.1	0.81
Peak HR (bpm)					
Baseline	153.2 ± 24.7	153.6 ± 29.8	152.2 ± 24.0	153.8 ± 21.3	0.95
Δ	0.7 ± 12.4	−0.8 ± 13.5	−0.5 ± 11.9	3.0 ± 11.8	0.34
Peak Work (W)					
Baseline	148.6 ± 56.6	134.9 ± 46.9	148.6 ± 60.3	159.0 ± 58.6	0.14
Δ	3.3 ± 16.5	−0.7 ± 18.0	3.0 ± 16.9	6.7 ± 14.3	0.21
$pVO_{2\text{-perkg}}$ (ml/kg/min)					
Baseline	22.0 ± 6.7	19.3 ± 5.7	22.0 ± 6.1	24.0 ± 7.3	0.005
Δ	0.6 ± 2.7	0.07 ± 2.1	0.0 ± 3.0	1.6 ± 2.7	0.004
Δ (ml/min/kg/year)	0.7 ± 2.9	0.06 ± 2.0	−0.07 ± 2.77	1.8 ± 3.2	0.002
$pVO_{2\text{-}\%\text{pred}}$ (%)					
Baseline	67.3 ± 16.7	61.2 ± 13.1	67.3 ± 12.8	71.9 ± 20.6	0.02
Δ	1.9 ± 9.9	0.5 ± 8.6	0.2 ± 9.7	4.6 ± 10.5	0.04
Δ (%pred/year)	1.9 ± 9.9	0.3 ± 8.0	−0.5 ± 9.0	5.2 ± 11.2	0.01
$pVO_{2\text{-abs}}$ (L/min)					
Baseline	1.6 ± 0.6	1.49 ± 0.53	1.64 ± 0.62	1.68 ± 0.60	0.29
Δ	0.03 ± 0.18	0.01 ± 0.17	0.00 ± 0.19	0.08 ± 0.19	0.07
Δ (%/year)	2.3 ± 14.4	1.6 ± 10.1	0.2 ± 12.2	6.6 ± 13.3	0.04
O_2 pulse (ml/beat)					
Baseline	10.6 ± 3.6	9.7 ± 2.9	10.9 ± 4.0	10.9 ± 3.6	0.19
Δ	0.1 ± 1.3	0.1 ± 1.4	0.0 ± 1.4	0.2 ± 1.2	0.62
Δ (%/year)	2.3 ± 14.4	2.0 ± 13.6	0.8 ± 12.8	3.8 ± 16.3	0.56
VE/VCO_2 Slope					
Baseline	28.2 ± 4.6	29.5 ± 4.4	27.9 ± 4.2	27.5 ± 5.0	0.02
Δ	−0.01 ± 4.16	−0.1 ± 5.4	´−0.4 ± 3.0	0.3 ± 4.0	0.37

CPX data at baseline and change in CPX data between both tests, based on PA classification at follow-up.

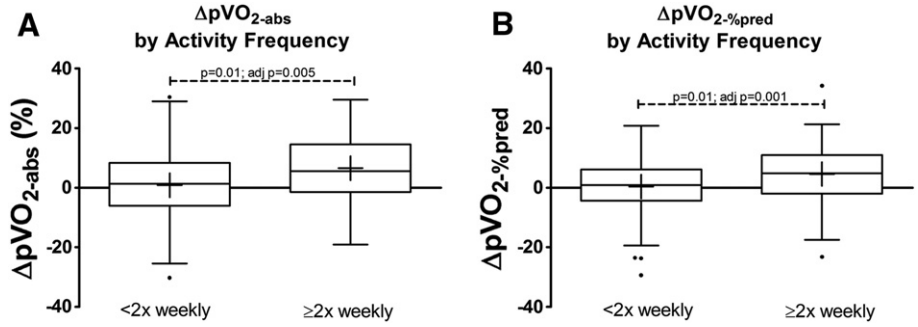

Fig. 2. Change in peak VO_2 by frequency of moderate or strenuous physical activity, <2 vs. ≥2 times per week. Panel A shows change in $pVO_{2\text{-abs}}$ while panel B shows change in $pVO_{2\text{-\%pred}}$ between exercise tests. P values represent linear regression adjusting for baseline $pVO_{2\text{-\%pred}}$.

increased PhysAct frequency was associated with improved $pVO_{2\text{-perkg}}$ (+1.6 ± 2.1 ml/min/kg).

4. Discussion

We found frequent PhysAct of at least moderate intensity to be associated with maintenance of superior exercise capacity in ACHD patients. Patients who sustained a high level of PhysAct were more likely to maintain or improve their pVO_2 and to lose weight during the interval between their exercise tests. In contrast, patients who participated in less frequent PhysAct were more likely to gain weight and their pVO_2 was more likely to decline. Furthermore, not only did frequent baseline PhysAct correlate with a more favorable change in pVO_2 over time, the subset of patients who increased physical activity frequency between tests appeared to derive benefit while those who became more sedentary saw a decline in pVO_2. The change in peak VO_2 was not attributable to weight loss per se, as adjustment for weight change in multiple regression models did not affect the relationship between PA and change in peak VO_2.

Our data support the concept that the aerobic capacity of ACHD patients is not limited solely by fixed cardiac factors. They also imply that the time-related decline in aerobic capacity, frequently reported in past longitudinal studies of ACHD patients, is modifiable. For many ACHD patients, regular PhysAct appears to have the potential to attenuate or reverse this debilitating decline.

Regular aerobic activity has pleiotropic effects, a number of which could account for these results. These include peripheral factors (e.g., increased numbers of mitochondria and up-regulation of aerobic enzyme pathways within skeletal muscle cells, increased muscle size and capillary density [15], enhanced muscle pump function [16] and beneficial changes in peripheral vascular beds) which may enhance oxygen extraction and/or cardiac output during exercise [17], and central factors (e.g. increase in myocardial mass and improvements in myocardial systolic and diastolic function) [18] which also may enhance myocardial reserve and improve enhanced cardiac output during exercise.

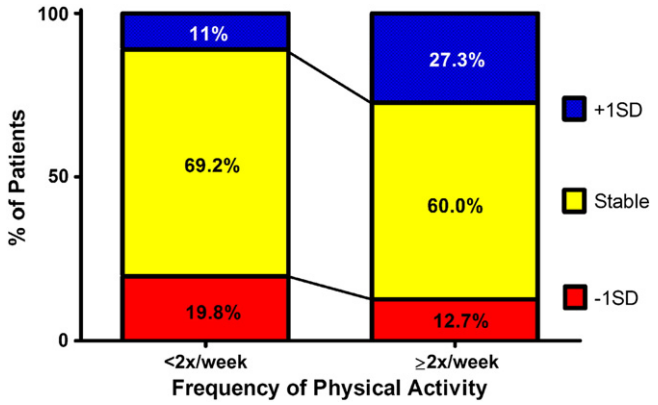

Fig. 3. Proportion of patients having >1SD (±11%) change in peak $VO_{2\text{-abs}}$ between exercise tests. Most patients had stable pVO_2, independent of PA frequency. However, approximately twice as many patients in the lower exercise frequency group had a >1SD decrease in pVO_2 compared with a >1SD increase. Conversely, among those engaging in frequent PA, more than twice as many improved their pVO_2 >1SD compared to the number that had equivalently decreased pVO_2.

Inadequate PhysAct is common among adults with CHD and >70% report moderate or extreme concern about participating in PhysAct [19]. This apprehension often stems from inappropriate advice or overprotection during childhood and adulthood. Historically, healthcare providers restricted PhysAct in patients with CHD [20], or did not provide specific exercise guidelines. A recent study of patients with aortic stenosis suggested, however, that exercise restriction does not prevent adverse outcomes, and the detrimental effects of exercise restriction on cardiovascular risk factors, exercise capacity and psychological well-being are often overlooked [21].

Our observations are consistent with experience in other populations. In the general population, regular PhysAct is associated with lower mortality, improved quality of life and reduction in the incidence of primary [22,23] and secondary [24] cardiovascular events. Interventions to increase PhysAct appears to provide benefit in a number of medical conditions including chronic heart failure [25], obesity [26], and diabetes [27].

The observed impact of frequent PhysAct on exercise capacity exceeds that reported for some ACHD surgical and interventional catheterization procedures [28,29]. The few studies of cardiac rehabilitation in ACHD have reported promising results vis-a-vis exercise capacity and quality of life [30–32]. Cardiac rehabilitation programs have also been extensively studied in patients with acquired heart disease, and have been shown to increase exercise capacity, reduce morbidity, mortality, and medical costs [33]. The number of patients with ACHD is increasing, and the healthcare costs of these patients are increasing even more quickly [34,35]. The impact of inexpensive lifestyle interventions such as providing an exercise prescription or referral to cardiac rehabilitation could improve the "natural history" and quality of life for many adults with CHD while at the same time lowering associated healthcare costs.

The finding that BMI and weight are significant clinical predictors of change in pVO_2 suggests that, in conjunction with specific exercise training, educational, nutritional and behavioral interventions may have independent benefit.

Our data support the need for prospective clinical trials to assess the impact of various strategies to increase PhysAct and improve aerobic capacity in this population. Most critically, it remains unclear whether improving $pVO_{2\text{-\%pred}}$ bestows a benefit in terms of quality of life, cardiovascular events, and mortality.

4.1. Limitations

Causality (i.e., frequent PhysAct causes ↑pVO_2 over time) cannot be inferred from these data. The fact that a change in lifestyle in terms of PhysAct frequency was associated with a corresponding change in

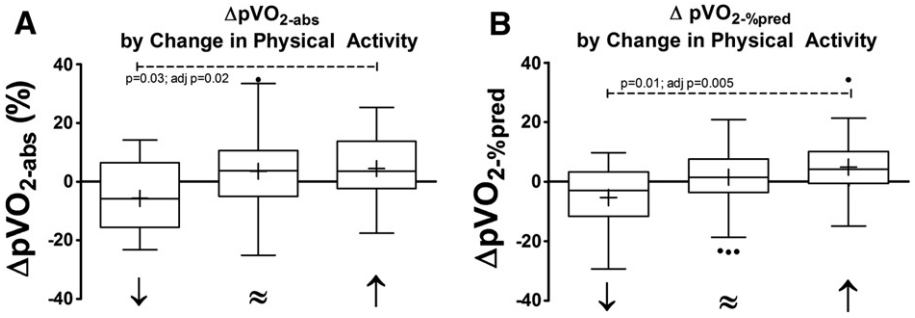

Fig. 4. Change in peak VO_2 by change in PA frequency (decreased="↓", stable="≈", increase="↑") between the baseline and follow-up CPX. Panel A shows %change $pVO_{2\text{-abs}}$. Panel B shows $\Delta pVO_{2\text{-\%pred}}$. P values represent linear regression adjusting for baseline $pVO_{2\text{-\%pred}}$.

pVO_2, provides some support for a causal relationship. It is also important to note that these data do not provide insights into the mechanisms by which frequent PhysAct results in ↑pVO_2. PhysAct frequency was extracted from clinical notes and assessment is therefore somewhat imprecise. It is possible that some patients might provide inaccurate descriptions of PhysAct frequency. Any misclassification, however, would generally tend to bias our results to the null (e.g., if sedentary patients reported frequent PhysAct, this would tend to minimize the apparent effect of frequent PhysAct). The observed baseline variation in pVO_2 and correlations between weight change and both PhysAct level and ΔpVO_2 supports the accuracy of PhysAct classification.

Patient characteristics differed between PhysAct groups. There were differences in baseline resting heart rate, pVO_2, and VE/VCO_2 slope. These characteristics tended to be "better" in the frequent PhysAct group. One might expect a more prominent decline in patients with higher baseline pVO_2 as a result of regression to the mean. Our data demonstrated this phenomenon; for each increase of 1 mL/kg/min in baseline $pVO_{2\text{-perkg}}$ there was a 0.056 mL/kg/min decline in $pVO_{2\text{-rel}}$ between tests ($p = 0.07$). The fact that we observed a strong relationship between PhysAct and ΔpVO_2, despite this supports the validity of our findings.

5. Conclusion

Adults with CHD who engage in frequent PhysAct maintain higher pVO_2 over time compared with sedentary patients. Given the strong prognostic significance of pVO_2 in this population, strategies to increase the frequency of PhysAct in the ACHD population may have the potential to positively impact morbidity and mortality. Further studies are needed to determine the effect of specific interventions to modify PhysAct on pVO_2 and clinical outcomes in adults with congenital heart disease.

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