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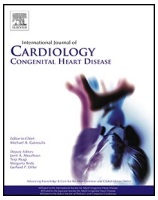

How does regular exercise improve cardiovascular function: Congenital heart disease and beyond

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ABSTRACT

Major advances in the fields of paediatric cardiology and cardiac surgery over the past decades have dramatically improved the survival of patients with congenital heart disease (CHD). Thus, care for CHD patients has shifted from managing short-term survival to having the best possible outcome in terms of long-term physical health, development and well-being. In this article, with a special focus on adult CHD (ACHD) population, we address the question: How does regular exercise improve cardiovascular function? We aim to underscore that regular exercise not only offers clinically relevant physiological benefits for patients living with a CHD condition but has also a positive effect on reducing the risk of future cardiovascular events.

1. Introduction

Major advances in the fields of paediatric cardiology and cardiac surgery over the past decades have dramatically improved the survival of patients with congenital heart disease (CHD) [1–3]. Currently, ~97 % of children born with CHD are expected to survive into adulthood and over 70 % of those will live to reach the age of 60 years [4]. With an aging population, the numbers of adults with CHD (ACHD) had equalized or even exceeded the corresponding numbers of children, changing thus the prevalence of CHD across the life-span [1]. Hence, care for CHD patients has shifted from managing short-term survival to having the best possible outcome in terms of long-term physical health, development and well-being [1,5].

Promotion of an active lifestyle and exercise engagement is increasingly recognized as pivotal for optimizing long-term health in the general population and CHD patients [6–8]. As patients with CHD age, they are prone to long-term complications of the congenital heart defect per se (anatomic and hemodynamic complications), in addition to acquired comorbidities (primarily atherosclerotic cardiovascular disease, ASCVD) that may be more pronounced in this subgroup of patients [9]. A more active lifestyle (including regular exercise) and health education programs seem to prevent and/or reduce some of these long-term cardiovascular (CV) complications in ACHD patients [10,11]. Most importantly, these prevention strategies and adapted physical exercise as medicine for primary and secondary prevention, ought to be implemented from the first decades of life and on, as the onset of acquired diseases starts early in life in patients with CHD [12].

In this article, with a special focus on ACHD population, we address the question: How does regular exercise improve CV function? We aim to underscore that regular exercise not only offers clinically relevant physiological benefits for patients living with a CHD condition but has also a positive effect on reducing the risk of future CV events. Initially, definitions of various concepts related to physical activity, exercise and sport are given. Subsequently, we review in ACHD patients the beneficial effects of exercise on long-term complications, present the potential mechanisms for benefit and discuss the interventions that have been adopted to optimize activity levels.

2. Physical activity, exercise and sport

The types of exercise that can be performed in different settings are: 1. physical activity, 2. sports (competitive and non-competitive), and 3. exercise training. Physical activity and sports are different constructs that seem to coincide. The term physical activity is defined as regular exercise in daily life with no competitive component, that increases energy expenditure above the basal level, whereas exercise training is a planned and structured period of physical activity with the intention of maintaining or improving physical fitness components (cardiorespiratory endurance, muscular endurance, flexibility, and body composition). In the European Council Charter, sport is defined as 'all forms of physical activity, which through casual or organized participation, aim at

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Abbreviations:

ACHD	Adult congenital heart disease
ASCVD	atherosclerotic cardiovascular disease
CHD	congenital heart disease
CV	cardiovascular
FEV	Forced Expiratory Volume
FVC	Forced vital capacity
HR	Heart Rate
PA	Pulmonary Atresia
TGA	Transposition of the great arteries
ToF	Tetralogy of Fallot
VO_2peak	Maximal Oxygen Uptake
NT-proBNP	N-terminal pro b-type natriuretic peptide
QOL:	Quality of life
NYHA	New York Heart Association
6MWD	Six-Minute Walk Test

expressing or improving physical fitness and mental well-being, forming social relationships, or obtaining results in competition at all levels'. Recreational sports can be non-competitive or competitive in nature with the distinction that in competitive sports participants have a strong desire to exert themselves physically to their limits.

All exercise activities can be characterized according to their static (need for strength) and dynamic (need for endurance) components, as reviewed by Mitchell et al. [13]. Moreover, the mode of exercise training can be categorized into two metabolic categories: aerobic and anaerobic. Aerobic exercise depends primarily on the oxidative energy-generating process and may be limited by the function of the cardiovascular, respiratory, and musculoskeletal systems. If one of these systems is deficient to meet energy demands, the body relies on less efficient anaerobic systems. Thus, anaerobic metabolism is activated under a number of physiological conditions, including exposure to low oxygen and/or during intense exercise when energy demands exceed the capacity of the mitochondria to generate ATP. Last but not least, the benefits of exercise are dependent on the dose of exercise. The dose of exercise can be described using the so-called FITT factors: frequency, intensity, time, and type of activity. Current literature provides a surprisingly heterogeneous spectrum of ranges and definitions concerning levels of exercise intensity based on parameters such as: 1. the percentage of maximal oxygen uptake capacity, 2. oxygen consumption, 3. heart rate reserve and 4. maximal heart rate. Exercise intensity can be described from very light to heavy. It is important to recognize that even activities of lighter intensity provide significant CV health benefits even if there are no changes in measures of exercise capacity.

3. Beneficial effects of exercise

Most patients with CHD are less active than healthy peers and do not participate in regular exercise programs. Indeed, despite current evidence suggesting that exercise is beneficial for patients with CHD and that adverse effects of exercise are rare, patients with CHD have reduced levels of fitness and reduced health-related quality of life (QOL) [14–18]. This limited physical activity seems to be multifactorial and the result of exercise intolerance due to the congenital heart defect per se (residual haemodynamic problems, arrhythmias, chronotropic impairment, myocardial perfusion abnormalities, pericardial disease, medication) as well as psychosocial factors (parental overprotection or restraints imposed by patients' social surroundings) [19,20].

The numerous benefits of frequent and sustained physical activity, as well as the risks of inactivity and sedentary life for people with and without heart disease, have been documented extensively in the literature [19,21,22]. Indeed, exercise seems to have a beneficial effect on the function of different body organs such as the heart, lungs, blood, vessels, and skeletal muscles (Fig. 1) [6–8]. In CHD patients, a small but growing body of evidence has demonstrated that physical activity is beneficial for the vast majority of patients, improving CV function and cardiorespiratory fitness, with potential implications for prognosis [11]. Moreover, it seems that patients with CHD who participate in sports from an early age have a significantly lower chance of becoming sedentary adults with potential prognostic implications.

3.1. In congenital heart disease

The beneficial effects of exercise have been reported in a variety of patient cohorts with ACHD (Table 1) including systematic reviews and metanalysis [10,11,23–38].It should be noted that these studies are limited by: 1) the small sample size, 2) the limited randomized controlled data, 3) the age group variation, 4) the high heterogeneity amongst studies assessing cardiorespiratory fitness, physical activity and QOL, and 5) the grouping of CHD patients based on the anatomical lesion rather than the functional status. Besides the aforementioned limitations, findings from these studies can help to conduct and structure future studies with a view to guide clinical practice.

Most of these studies ACHD have focused on aerobic exercise. Aerobic dynamic (endurance) exercise has a better outcome on most health parameters when the effects are compared with isolated resistance exercise as it is well known that a volume-loaded circulation is healthier than a pressure-loaded one. Overall, a consistent finding was that all types of physical activity interventions (including physical activity promotion, exercise training and inspiratory muscle training), when compared to usual care, may have a beneficial effect on cardiorespiratory fitness and physical activity and a rather small impact on QOL. In particular, exercise training seems to have beneficial effects on 1) cardiac function (improving N-terminal pro b-type natriuretic peptide, NT-proBNP levels), 2) exercise capacity (mean Maximal Oxygen Uptake, VO2peak) and 3) muscle strength. A recent systematic review in the setting of all CHD patients, in line with previous reports, showed that physical exercise training resulted in an 8 % (2.6 ml/kg/min) mean VO2peak improvement following exercise interventions [11]. Still, whether this modest improvement in cardiorespiratory fitness has prognostic implications, remains uncertain and requires confirmation in larger studies and in different CHD cohorts. Last but not least, it appears that peripheral adaptations (improved skeletal muscle oxidative capacity) as well as improved respiratory muscle oxygenation seem to play an important role in cardiorespiratory fitness.

3.2. In acquired heart disease

Acquired heart disease not only represents the leading cause of death at the global general population level but also is a growing concern in ACHD [9,39,40]. In these patients, acquired CV disease, primarily ASCVD, comes on top of the preexisting CHD and further complicates the outcome. Patients with CHD seem to show excess CV risk and in particular: 1. more pronounced risk factors for ASCVD, 2. premature onset of ASCVD, 3. higher burden of ASCVD, and 4. increased morbidity and mortality following CV events. The increased risk is prominent for complex CHD but is also significant for mild conditions.

The relationship between conventional risk factors (cigarette smoking, systemic hypertension, dyslipidemia, overweight/obesity, diabetes and metabolic syndrome, and sedentary lifestyle) and ASCVD is well established. At least one modifiable risk factor is present in up to 80 % of ACHD, with systemic hypertension, overweight/obesity and type 2 diabetes being the most prevalent. Systemic hypertension has a higher prevalence in ACHD patients compared to the general population and seems to be spanning the entire age spectrum. Besides specific lesions related to secondary hypertension such as coarctation of the aorta, other CHD-related factors seem to contribute to the genesis of hypertension in ACHD patients including arterial stiffness, endothelial dysfunction,

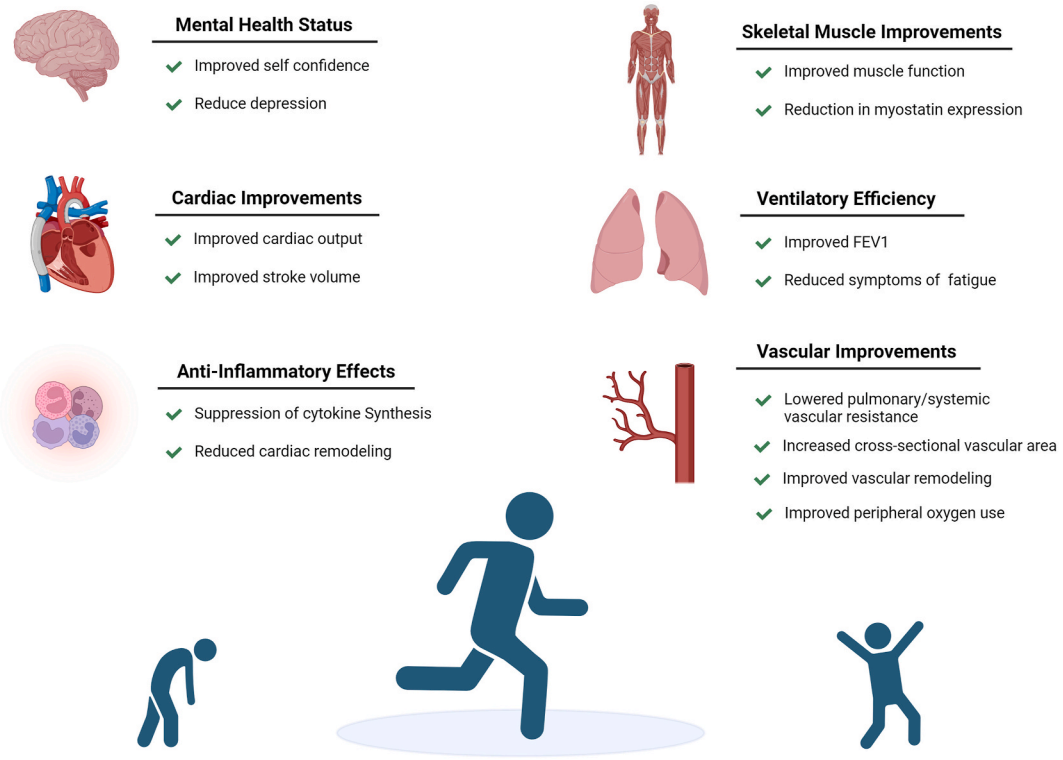

Fig. 1. Beneficial effects of exercise.

chronic kidney disease, and sleep apnea syndrome. Type 2 diabetes, overweight and obesity also occur in CHD patients and mostly in relatively young patients with complex underlying disease. Being overweight or obese leads not only to an unfavorable metabolic profile (and consequently an increased CV risk profile) but contributes also to sedentary lifestyle. A sedentary lifestyle is also a rather common CV risk factor in CHD patients. A study conducted by Dua et al. found that even up to 100 % of patients with complex CHD do not achieve the minimum requirements of daily physical activity.

Research has been done to evaluate the effect of exercise on health [41]. Positive results from exercise have been well demonstrated in controlling all CV risk factors regardless of underlying disease, age, or gender. Physical activity leads to better blood pressure control, favorably affects the lipid profile, and promotes more efficient body weight control. A beneficial effect is also noted at biochemical and cellular level. All this might lead to a clinically significant reduction of the patient's CV risk profile. Even though no long-term outcome studies in CHD have been conducted, data are extrapolated from the general population to CHD patients.

The ESC Guidelines on CV disease prevention and the 2020 ESC Guidelines on ACHD population provide only scarce information on the management of CV risk factors in ACHD patients [3,39,40]. A recently published clinical consensus statement of the ESC Working Group on ACHD in collaboration with the European Association of Preventive Cardiology and the European Association of Percutaneous Cardiovascular Interventions, provides general preventive measures regarding ASCVD for ACHD patients, as well as an expert opinion concerning the screening and management of conventional major risk factors in this patient population [9]. In this clinical consensus statement, the authors encourage regular exercise training for at least 30 min of exercise 4–5 times a week as a general preventive measure regarding acquired heart ACHD.

4. Mechanism of benefit of exercise training

During physical activity and exercise, several hemodynamic changes occur. Oxygen delivery must be augmented to meet increased metabolic demands [16]. Increasing cardiac output is one of the fundamental ways in which oxygen delivery is augmented. While limited studies have measured the effects of exercise and training on cardiac output and stroke volume directly, increases in post-training oxygen during peak exercise, an indirect measure of cardiac output, suggest that exercise may improve stroke volume in some patients with CHD, but these findings require confirmation in larger studies and in different CHD cohorts (Table 1).

The underlying mechanisms for the beneficial effects of exercise on cardiorespiratory fitness are not fully elucidated. It seems that besides a direct myocardial training effect, exercise seems to be implicated in 1) muscular and molecular effects on blood vessels (lowering thus systemic and pulmonary vascular resistance, increasing vascular cross-sectional area and decreasing afterload), 2) inducing of marked anti-inflammatory response (suppression of cytokine synthesis and other mediators of heart failure leading to adverse cardiac remodeling) 3) improving peripheral oxygen utilization 4) improving vascular remodeling (reduces vascular stiffness reversing some of the endothelial dysfunction), 5) improving skeletal muscle function and wasting (by reducing myostatin expression) and 6) improving ventilatory efficiency. Further research though is needed to elucidate the relevance of each of these mechanisms. It is also of great interest whether exercise training leads to epigenetic changes.

5. Exercise recommendations and rehabilitation in with congenital heart disease

It is crucial, therefore, that people with ACHD lead an active lifestyle [26,28,42,43]. To that end and to best improve physical activity, cardiorespiratory fitness and QOL, the ESC has provided recommendations with a unified protocol for dictating physical activity in ACHD

Table 1
Exercise intervention characteristics and outcome in adult patients with congenital heart disease.

Source	Type of CHD	Age (mean ± SD, years)	No of patients (n)	Sessions/week	Intensity	Time/session (minutes)	Duration	Mode	Main outcomes
Fritz C. et al., 2020 [20]	Fontan	30.5 ± 8.1	20	7	Individualized	3 sets/10–30 repetitions	6 months	Respiratory	↔ VO2peak ↔ VO2peak predicted ↔ VCO2 slope ↔ FVC ↔ FVC predicted ↔ FEV1 ↔ FEV1 predicted
Van Dissel AC. et al., 2019 [21]	ToF TGA Fontan PA Other	39.9 ± 8.6	17	≥3	Heavy intensity (80 % HR reserve)	45 min	6 months	Aerobic, resistance	↑ VO2peak ↔ QOL ↔ NT-proBNP
Opotowsky AR. et al., 2018 [22]	ToF TGA Fontan PA Truncus arteriosus Ebstein anomaly	47.5 ± 9.0	13	2	–	60 min	12 weeks	Aerobic, resistance	↑ VO2peak ↔ QOL
Bhasipol A. et al., 2018 [23]	Eisenmenger's syndrome ToF with palliative shunt Single ventricle Other	30.9 ± 10.2	11	1 (hospital-based phase) 5 (home-based phase)	Very light to heavy intensity (40–70 % max HR)	Hospital-based: Home-based: 30 min	12 weeks	Aerobic	↑ 6MWD ↑ O2 pulse ↑ CWRET ↔ VO2peak ↔ peak VE/VCO2 slope
Novakovic M. et al., 2018 [24]	ToF	38.5 ± 8.7	18	2–3 (36 sessions)	Interval training: Heavy intensity (80 % max HR) Continuous training: Moderate training (70 % max HR)	Internal training: 32 min Continuous training: 26 min	12–18 weeks	Aerobic	Interval training: ↑ VO2peak ↑ vascular function ↓ NT-proBNP ↓ fibrinogen Continuous: ↑ QOL
Sandberg C. et al., 2017 [25]	Complex CHD	31.3 (26.9–36.6)	16	3	Moderate to high intensity interval (BORG 15–16.29)		12 weeks	Aerobic	↔ QOL ↑ VO2peak ↑ Peak workload
Avila P. et al., 2016 [26]	ToF	35 (28–42)	13	1–2	Heavy to very heavy intensity (70–80 % max HR)	30–40 min	12 weeks	Aerobic, resistance	↑ VO2peak ↑ metabolic equivalent ↑ exercise duration ↓ ventricular arrhythmias
Shafer KM. et al., 2015 [27]	TGA	34 ± 10	12	1st month 1: 1/week (base training) 3/week (steady state) 2 nd month: 1/week (base training 3/week (steady state) 1/week (interval) 3rd month: 1/week (base training") 3/week (steady state) 2/week (interval)	1st month: Moderate to high intensity 2 nd month: Moderate to very heavy intensity	1st month: Base training: 60 min Steady state: 30 min 2 nd month: Base training: 60 min Steady state: 35 min Interval training: 28 min 3rd month: Base training: 60 min Steady state: 40 min Interval training: 56 min	12 weeks	Aerobic	↑ VO2peak ↔ NT-proBNP

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Table 1 (*continued*)

Source	Type of CHD	Age (mean ± SD, years)	No of patients (n)	Sessions/week	Intensity	Time/session (minutes)	Duration	Mode	Main outcomes
Becker-Grunig T. et al., 2013 [28]	PAH-CHD	48 ± 11	20 (at 3 weeks) 15 (at 15 weeks)	In-hospital rehabilitation Aerobic: 7 Respiratory muscle and resistance training: 5 Home-based aerobic: 5	Moderate and heavy intensity (60–80 % max HR)	Hospital-based: 90 min Home- based: ≥30 min	15 weeks	Aerobic, resistance, respiratory, mental training	↑ 6MWD ↑ maximal workload ↑ VO2peak ↑ QOL
Cordina R. et al., 2013 [29]	Fontan	31 ± 4	6	3	High intensity (80 % one repetition maximum)	60 min	20 weeks	Resistance	↑ strength, ↑ VO2peak ↑ skeletal muscle mass ↑ stroke volume
Westhoff-Bleck M. et al., 2013 [30]	TGA	29.3 ± 3.1	19	Weeks 1–6: 3 × /wk. Week 7–24: 5 × /wk	Moderate intensity (50 % VO2peak)	Week 1–3: 10 min Week 4–9: 15 min Week 9–12: 20 min Week 13–24: 30 min	24 weeks	Aerobic	↑ VO2peak ↑ maximal exercise time ↑ workload ↓ NYHA class ↔ QOL ↔ NT-proBNP
Winter MM. et al., 2012 [31]	Systemic right ventricle	31 + 10	28	3	Very Heavy intensity (90 % max HR)	32 min	10 weeks	Aerobic	↑ VO2peak ↓ Resting systolic blood pressure ↔ QOL ↔ NT-proBNP
Dua JS. et al., 2010 [32]	Coarctation of the aorta Marfan TGA Fontan ToF Eisenmenger's syndrome Other	18–63 (range)	50	5	–	5–10 min if < 3 METS 10–20 min if 3–5 MET 20–30 min if > 5 METS +10 %/week in every group	10 weeks	Aerobic	↑ QOL
Therrien J. et al., 2003 [33]	ToF	35 ± 9.5	9	3	Moderate and heavy intensity (60–85 % VO2peak)	30–40 min	12 weeks	Aerobic	↑ VO2peak
Minamisawa S. et al., 2001 [34]	Fontan	19 ± 4	11	2–3	Moderate and heavy intensity (60–80 % max HR)	25–35 min	2–3 months	Aerobic	↑ VO2peak

FEV: Forced Expiratory Volume, FVC: Forced vital capacity, HR: Heart Rate, PA: Pulmonary Atresia, TGA: Transposition of the great arteries, ToF: Tetralogy of Fallot, VO2peak: Maximal Oxygen Uptake, NT-proBNP: NT-proBNP, QOL: Quality of life, NYHA: New York Heart Association, 6MWD: Six-Minute Walk Test.

patients [8]. These recommendations are based on haemodynamic and electrophysiological parameters, rather than focusing on specific anatomical defects, which do not correlate to exercise associated risks. They provide a step-wise evaluation, which is based on the assessment of five parameters (Fig. 2): 1. ventricular function, 2. pulmonary artery pressure, 3. aorta dimensions, 4. presence of arrhythmias, and 5. arterial oxygen saturation at rest and during exercise. The physician should assess each one parameter in turn, assign the individual patient in a specific route, and decide on the type of exercise recommended based on the static component, while the dynamic component is replaced by the relative intensity based on individual exercise performance on cardio-pulmonary exercise testing [8,44]. In the context of competitive sports, ESC recommendation for competitive sports recognize that athletes will push themselves to their limits (maximum intensity) and as such provide sport disciplines are divided in four major groups (skill, power, mixed, and endurance).

Beside the safe engagement of ACHD in physical activity and competitive sports, exercise training is a potent therapy to improve well-being and cardiorespiratory fitness, with potential implications for prognosis [11]. This has led to exercise becoming an increasingly important adjunct to medical therapy in the management of this group who frequently have significant exercise limitation and complex medical issues. However, there is currently limited evidence-based guidance that has been published regarding appropriate exercise prescription in adults with CHD.

6. Conclusions

With an aging population, care for CHD patients has shifted from managing short-term survival to having the best possible outcome in terms of long-term physical health, development and well-being. Physical activity and exercise engagement is increasingly recognized as pivotal for optimizing long-term health in the general population and CHD patients. Prevention strategies and adapted physical exercise as medicine for primary and secondary prevention, ought to be implemented from the first decades of life and on, as the onset of acquired diseases starts early in life in patients with CHD.

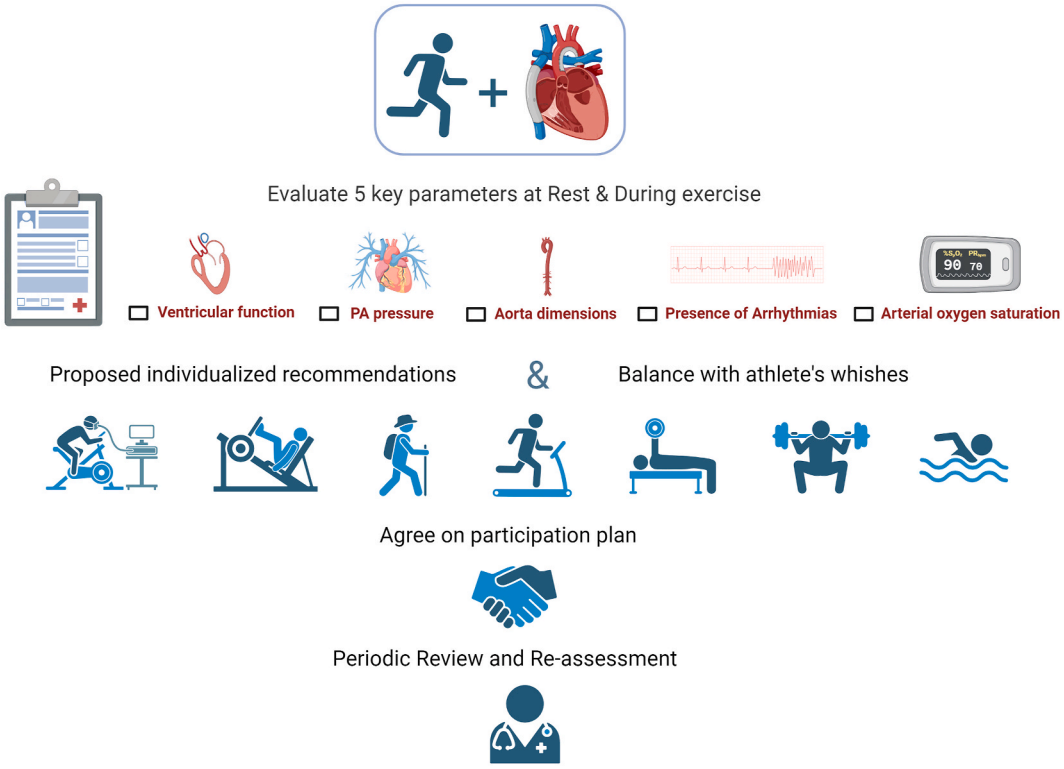

Fig. 2. Step-wise approach for dictating physical activity in ACHD patients.

CRediT authorship contribution statement

M. Drakopoulou: Writing – review & editing, Writing – original draft. **P.K. Vlachakis:** Writing – original draft. **A. Apostolos:** Writing – original draft. **K. Tsioufis:** Writing – review & editing. **K. Toutouzas:** Writing – review & editing.

Declaration of competing interest

There are no conflicts of interest.

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