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Safety and clinical benefit of cardiopulmonary rehabilitation in complex congenital heart disease

Seguridad y beneficio de la rehabilitación cardiopulmonar en cardiopatías congénitas complejas

To the Editor,

Cardiopulmonary rehabilitation (CR) in patients who have undergone surgery for congenital heart defects (CHDs) is rarely undertaken in Spain, despite its beneficial effects and the fact that physical activity is recommended for CHDs by the European scientific societies.[1]

An interventional, experimental, prospective, phase I study was conducted (with no randomization for rehabilitation program assignment) to evaluate program safety and functional improvement in 24 young patients (median age, 19 [range, 9-31] years) with complex CHDs that had been treated surgically. This phase 1 study was designed with safety as its primary endpoint and avoided the need to calculate the sample size. The intervention consisted of a 3-month program of twice-weekly CR sessions in groups of 4 or 5 individuals. Each 1-hour session included personalized exercise consisting of warmups, respiratory physiotherapy, aerobic exercise (treadmill, bicycle, and/or videogames), cooldowns, and stretches. Assessments and monitoring were performed in a session with a cardiologist, a physical therapist, a rehabilitation therapist, a psychologist, and a nurse. The program incorporated health instruction, nutritional support, and psychological orientation, with family participation. In addition to ultrasound and electrocardiography, patient assessment included forced spirometry, 6 minute walk test, ergospirometry, and quality of life surveys[2,3] before and after the program. Patients were not enrolled if they had syndromal CHDs or major comorbidities that could affect or influence the parameters assessed. All patients signed an informed consent form.

Categorical variables are shown as percentages, and continuous variables are shown as the median (range). Nonparametric tests were used to compare dependent paired proportions (McNemar) or ordinal variables (Wilcoxon). A P value $< .005$ was considered significant.

The patient sample is described in table 1. The number of scheduled sessions was 24, with a median adherence of 23.5 (range, 9-31). Patient #18 was treated by pulmonary valve replacement, whereas the others required no therapeutic or medical intervention of any kind. No adverse cardiovascular events or electrocardiographic or echocardiographic changes were reported before or after the program.

The course of the various parameters assessed before and after CR is shown in table 2. Upon completion of the program, the most significant cardiopulmonary changes were: *a)* increased inspiratory muscle strength and increased maximal inspiratory pressure; *b)* greater exertional capacity and tolerance to exercise, with increase in distance walked in the 6-minute walk test; longer exertion time (more than 1 minute) and tendency toward better heart rate recovery in the first minute after exertion, as a possible improvement in autonomic nervous system regulation; *c)* improvement in maximal aerobic capacity, with a significant increase in peak O_2 uptake (VO_2, expressed as % theoretical); *d)* improvement in aerobic physical performance, considered a higher VO_2 in the anaerobic threshold; *e)* improvement in cardiocirculatory response, as shown by the lower resting heart rate (with no drug-induced changes), increase in predicted maximal VO_2 as an indirect estimator of cardiac output, and in predicted O_2 pulse as a parameter to estimate systolic volume at maximal exertion; *f)* improvement in ventilatory efficiency in exercise, with a decrease in the slope of the plot line for ventilation per minute and CO_2 production (VE/VCO_2 slope), with a higher number of patients showing a ratio < 30, considered normal for patient age and sex. Furthermore, these improvements were achieved in the absence of other changes in ventilatory efficiency and ventricular function variables, as shown by similar values for respiratory equivalents (VE/VCO_2, VE/VO_2), end-tidal partial pressure of CO_2, slope of VO_2 efficiency, ventilatory reserve, and echocardiographic measurements of ventricular function before and after the program. These data were consistent with subjective assessments of the New York Heart Association functional class, which reported 18 patients in class I (75%) and 6 in class II (25%) at baseline. By completion of the program, functional class had improved in 4 patients and worsened in 2, for a total of 20 patients in class I (83.3%) and 4 (16.7%) in class II. Last, quality of life questionnaire scores were normal, regardless of the grade of CHD complexity, with no differences between baseline status and the end of the program. The usefulness of the program was highly rated by patients and their families.

Due to medical and surgical advances, it is estimated that more than 85% of children with CHDs in Spain will reach adulthood.[4] However, CHD patients who have undergone surgery have lower progressive functional capacity, which increases their morbidity and mortality. In this context, efficient resources for improvement, such as CR, have been implemented; however, they are not widely used in Spain, and there is only 1 published report on experience with 8 patients who had CHDs and pulmonary hypertension,[5] with increased functional class and exercise capacity in the 6 minute walk test and no adverse events.

The importance of our study is that it is the first to demonstrate the benefits of a CR program in Spain for young people with complex CHDs treated by surgery and that it includes a thorough assessment with ergospirometry. The main limitations of the study are the small, heterogeneous sample and the lack of a control

Table 1
Characteristics of patients undergoing the cardiac rehabilitation program

Sex	Age, y	BMI	CHD	Surgery/Residual Lesions	Medication	Number of Sessions
Male	17	23.35	PA-IVS	RV-PA conduit, mild PI	No	27
Female	21	23.14	PA-IVS	Transannular patch, severe PI, moderate TR	No	17
Female	19	21.56	PA-IVS	RV-PA conduit, moderate conduit stenosis, moderate TR	Aspirin	24
Female	26	20.52	Tricuspid atresia	Glenn, Fontan, chronic Fontan failure	Aspirin, diuretics, BB	21
Male	22	22.09	d-TGA	Arterial switch, VSD closure, mild PS	No	27
Male	26	26.2	d-TGA	Mustard, closed baffle leak, sinus node syndrome	Aspirin	28
Male	25	19.91	d-TGA	Mustard, systemic ventricular dysfunction	No	24
Male	31	20.43	d-TGA	Mustard, systemic ventricular dysfunction, sinus node syndrome, pacemaker	Aspirin, BB	31
Female	14	13.2	d-TGA	Arterial switch, VSD and ASD closure; arch, AoV, and pulmonary repair; PVR	ACEI	27
Female	11	16.44	d-TGA	Arterial switch, moderate DPL, mild AoR	No	26
Male	19	22.85	d-TGA	Mustard, sinus node syndrome	Aspirin, BB	14
Male	13	24.6	d-TGA	Arterial switch, VSD closure, aortic arch dilatation, moderate DPL	No	24
Male	27	19.63	Fallot	Complete correction, PVR	No	21
Male	28	25.02	Fallot	Palliative fistula, complete correction, PVR	Aspirin	27
Male	31	29.92	Fallot	Complete correction, restrictive VSD, mild PI	No	30
Female	20	20.24	Fallot	Complete correction, severe PI	No	16
Male	10	17.36	Fallot	Complete correction, mild RV dilatation, severe PI, mild PS	No	23
Female	9	18.02	Fallot	Transannular patch, VSD closure, RV dilatation, moderate PI	No	16
Female	23	25.15	Fallot	Complete correction with conduit, severe PI, RV dysfunction, CATCH 22	Aspirin	15
Female	28	15.45	Type 1 truncus	RV-PA conduit, conduit expansion, DPL with severe PI	No	10
Female	9	21.36	Type 1 truncus	Truncal valve repair, RV-PA conduit, severe valve regurgitation	No	25
Male	16	24.66	Fallot-type DORV	VSD closure, infundibular resection, severe PI	No	12
Male	19	18.49	Fallot-type DORV	VSD closure, infundibular resection, moderate PI	No	9
Female	12	16.49	Fallot-type DORV	VSD closure, infundibular resection, moderate PS	No	21

ACEI, angiotensin-converting enzyme inhibitor; AoR, aortic regurgitation; AoV, aortic valve; ASD, atrial septal defect; BB, beta-blockers; BMI, body mass index; CHD, congenital heart defect; DORV, double-outlet right ventricle; d-TGA, dextro-transposition of the great arteries; DPL, double pulmonary lesion; PA-IVS, pulmonary atresia with intact ventricular septum; PI, pulmonary insufficiency; PS, pulmonary stenosis; PVR, pulmonary valve replacement; RV, right ventricle; RV-PA, right ventricle-pulmonary artery; TR, tricuspid regurgitation; VSD, ventricular septal defect.

Table 2
Parameters assessed in forced spirometry, 6 minute walk test, and ergospirometry, before and after the cardiopulmonary rehabilitation program

	Before CR	After CR	*P*
Forced spirometry parameters			
Patients, n	24	23	
FVC, % theoretical	84 (48-110)	86 (60-120)	.106
Patients with FVC > 80% theoretical	13 (54.2)	13 (54.2)	1.000
FEV_1, % theoretical	87.5 (45-112)	84 (59-117)	.795
Patients with FEV_1 > 80% theoretical	17 (70.8)	14 (58.3)	.125
FEV_1/FVC	105.9 (78.3-121.1)	104.1 (76.7-119.3)	.128
Patients with FEV_1/FVC > 70% theoretical	24 (100)	23 (100)	1.000
FVC, % theoretical	84 (48-110)	86 (60-120)	.106
6 minute walk test parameters			
Patients, n	24	22	
Distance walked, m	524.5 (415-735)	640 (475-840)	< .001
Ergospirometry parameters			
Patients, n	24	24	
Exercise time, min	10.1 (6.1-12.3)	11.3 (6.4-13.2)	.002
Direct METs, VO_2/3.5 mL/kg/min	8.1 (4.1-12.4)	8.9 (3.9-11.2)	.094
Resting HR, bpm	92.5 (60-122)	86.5 (60-116)	.068
Maximum HR, bpm	177 (143-197)	179 (158-202)	.721
Maximum HR, % theoretical	87.3 (73.8-98.3)	89.1 (78.7-96.9)	.648
Reserve HR, bpm	86.5 (54-107)	92.5 (58-113)	.069
Patients with HR decrease > 12 bpm in 1st minute	24 (100)	24 (100)	1.000
Resting SBP, mmHg	115 (90-130)	107 (90-125)	.052
Resting DBP, mmHg	70 (45-90)	61.5 (50-90)	.819
Maximum SBP, mmHg	150 (100-180)	143.5 (105-185)	.896
Maximum DBP, mmHg	80 (50-90)	80 (60-100)	.955
Double product	25 500 (18 700-33 300)	25 570 (17 490-33 670)	.670
VO_{2max}, mL/kg/min	28.2 (14.3-43.4)	31 (13.8-39.3)	.091
$VO_{2máx}$, % theoretical	69.2 (45.5-99.5)	71.5 (50-103.3)	.042
AT, mL/kg/min	17.1 (9.2-24.6)	18.1 (10.6-25.5)	.045
AT, % theoretical	60.5 (30.5-77)	67.2 (42-83)	.050
Patients with AT > 60% (normal)	12 (50)	18 (75)	.031
AT HR, bpm	123 (73-156)	125.5 (90-153)	.077
RER > 1.10	23 (95.8)	23 (95.8)	1.000
PO_{2max}*, mL/beat	7.9 (5-16.4)	8.1 (4.9-16.4)	.182
PO_{2max}*, % theoretical	76 (48.2-124)	76 (58-118)	.039
VE/VCO_{2slope}*	30 (22.3-38.8)	28.3 (19-37.2)	.021
Patients with VE/VCO_{2slope}* < 30% (normal)	11 (47.8)	14 (60.9)	.375
Equivalent for CO_2 (VE/VCO_2)	29.2 (23-42.4)	29.5 (20.9-40.5)	.764
Equivalent for O_2 (VE/VO_2)	36.5 (28-51.9)	37 (29.1-54.8)	.449
$PetCO_{2resting}$, mmHg	31 (21-40)	32 (22-37)	.503
$PetCO_{2max}$, mmHg	33 (24-42)	33 (23-47)	.612
OUES	1.4 (0.4-3.4)	1.3 (0.6-3.3)	.617
OUES, % theoretical	62 (18.4-92.6)	56.4 (31-97)	.693
VR	42.5 (0-69)	37.5 (6-58)	.853
Patients with VR > 20% (normal)	17 (70.8)	21 (87.5)	.219
Quality of life			
Number of PedsQL questionnaires, child self-report	7	7	
PedsQL score, child self-report	1775 (1300-1850)	1700 (1550-1950)	.225
Number of PedsQL questionnaires, parent-proxy	4	5	

Table 2 *(Continued)*
Parameters assessed in forced spirometry, 6 minute walk test, and ergospirometry, before and after the cardiopulmonary rehabilitation program

	Before CR	After CR	*P*
PedsQL score, parent-proxy	1700 (1550-1900)	1775 (1175-2075)	.144
Number of NSS-36 questionnaires, young adults	14	15	
SF-36 score, young adults	103 (94-110)	103 (87-115)	.779

AT, anaerobic threshold; CR, cardiopulmonary rehabilitation; DBP, diastolic blood pressure; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; HR, heart rate; O_2P, oxygen pulse; OUES, oxygen uptake efficiency slope; PedsQL, Pediatric Quality of Life Inventory Cardiac Module, version 4.0 used in our study for pediatric patients (age 8 to 18 years) and their parents; $PetCO_2$, end-tidal partial pressure of CO_2; SBP, systolic blood pressure; SF-36, Short Form Health Survey; VCO_2, carbon dioxide production; VE, minute ventilation; VO_2, oxygen uptake; VR, ventilatory reserve.
* Patient #9 was excluded from this analysis due to Fontan circulation (this parameter is interpreted differently between cyanotic and noncyanotic patients).

group. Implementation of the program was a challenge, as difficulties were encountered for administration to understand that CR should focus on comprehensive prevention units open to all heart diseases, rather than only coronary patients. We show that, despite these difficulties, CR could be a cost-effective tool capable of improving functional capacity and quality of life in complex CHDs. In our experience, CR has helped to support our patients and their families and enabled them to understand their limits and to encourage improvements in their functional capacity.

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Truncating titin variants in dilated cardiomyopathy: not only LVEF recovery, but also maintenance

Miocardiopatía dilatada asociada a variantes tipo truncamiento en titina: no solo recuperación de la FEVI, también mantenimiento

To the Editor,

Truncating titin variants (TTNtv) are the main genetic cause of dilated cardiomyopathy (DCM).[1] These variants have been associated with a mild and treatable form of DCM[2] (the need for a 'second hit' such as chemotherapy or alcohol abuse has been even suggested),[3] but also with an increased risk of arrhythmias/sudden death.[4,5] The latter has aroused concerns about a lower threshold for defibrillator implantation, as practiced in other genetic forms of DCM.

The titin (TTN) gene encodes 364 exons that undergo alternative splicing to produce different isoforms. In the adult myocardium, 2 major TTN isoforms, *N2BA* and *N2B*, are mainly expressed. Most of truncating TTN variants affect these cardiac TTN isoforms, being predominantly located at the A-band.

We present a retrospective single referral-center cohort study exploring the phenotype and prognosis of TTNtv-DCM patients compared with a well-defined control group composed of carriers of variants in other DCM-related genes.

We selected 129 adult patients with DCM/hypokinetic nondilated cardiomyopathy and genetic testing. Of these, 47 tested positive (ie, pathogenic or likely pathogenic variant according to the American College of Medical Genetics and Genomics guidelines), 56 negative,