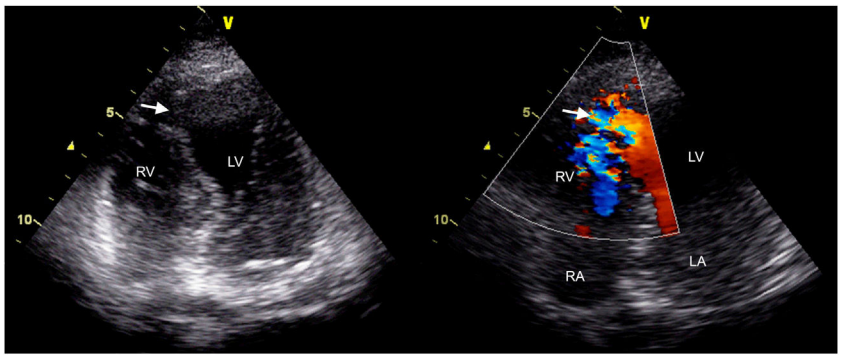

Figure 2. Four-chamber echocardiographic views showing the apical ventricular septal defect (white arrow). LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

lack of solid evidence, various protocols have been published by scientific societies,[5,6] which aim to ensure adequate treatment of the patient with STEMI in this context, with special emphasis also on protection against infection of the health personnel involved.

CONFLICTS OF INTEREST

M.Á. Arias is an associate editor of *Revista Española de Cardiología;* the journal has followed its established editorial procedure to guarantee impartial processing of the manuscript.

Alejandro Gadella, Miguel Ángel Sastre, Carolina Maicas, Luis Rodríguez-Padial, and Miguel Á. Arias*

Servicio de Cardiología, Complejo Hospitalario Universitario de Toledo, Toledo, Spain

*Corresponding author:
E-mail address: maapalomares@secardiologia.es (M.Á. Arias).

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Left ventricular assist devices in patients eligible for heart transplant with irreversible pulmonary hypertension

Dispositivos de asistencia ventricular izquierda en pacientes candidatos a trasplante cardiaco con hipertensión pulmonar irreversible

To the Editor,

Pulmonary hypertension (PH) in patients with heart failure and reduced ejection fraction is associated with a worse prognosis and increases the risk of complications and death in heart transplant (HTx) patients.[1] International HTx guidelines thus consider PH to be a relative contraindication for this procedure.[2] PH is defined by systolic pulmonary artery pressure $>$ 50 mmHg, transpulmonary gradient $>$ 12 mmHg, pulmonary vascular resistance $>$ 3 Wood units despite optimal medical therapy, and irreversibility following a vasodilator challenge.

The European heart failure guidelines[3] recommend left ventricular assist device (LVAD) implantation as a means of reducing PH and providing a bridge to HTx candidacy for patients with irreversible PH.[4] Despite not being recommended by the European PH guidelines,[5] pulmonary vasodilators, and sildenafil in particular, are also used either alone or in combination with LVADs in specialized HTx centers.[6]

To evaluate the effect of pulmonary vasodilators and LVAD implantation in HTx candidates with severe PH, we retrospectively reviewed the clinical outcomes of all such patients who underwent vasodilator testing at our hospital between January 2010 and August 2018. The primary objective was to analyze survival outcomes at 2 years following an initial vasodilator challenge.

Patients who met the reversibility criteria during the first vasodilator challenge were classified as eligible for HTx and added to the waiting list; those with a negative challenge were treated with sildenafil and/or LVAD implantation. They were administered a second challenge after 3 to 4 months and added to the HTx waiting list if they met the reversibility criteria. The

patients were thus divided into 3 groups: *a*) patients with reversible PH after the first vasodilator challenge, *b*) patients with irreversible HTP treated with centrifugal LVAD implantation (HVAD [Medtronic] or HeartMate 3 [Abbott]) (if they received this treatment before HTx), and *c*) patients with irreversible PH not treated with centrifugal LVAD implantation (ie, those who received a pulsatile LVAD (EXCOR [Berlin Heart] or sildenafil monotherapy).

Patient characteristics and right heart catheterization data at baseline are summarized in table 1, together with details of the treatments received. Quantitative variables are presented as median [interquartile range] and dichotomous variables as number and percentage. Between-group differences were calculated using the Kruskal-Wallis test for quantitative variables and the chi-square test for dichotomous variables.

Forty-seven patients were included: 28 with reversible PH and 19 with irreversible PH at baseline right heart catheterization. The breakdown of patients and their outcomes throughout the study period are shown in figure 1A. All 5 patients with irreversible PH treated with centrifugal LVAD implantation after the first vasodilator challenge survived to undergo a second challenge and met the reversibility criteria. Of the 14 patients who did not receive a centrifugal LVAD after the first challenge, just 10 were alive at the time of the second challenge and 8 of them met the reversibility criteria (57% vs 100% in the centrifugal LVAD group, $P = .07$). These differences can largely be explained by the high proportion of patients who did not undergo centrifugal LVAD implantation and who died before the second challenge.

The Kaplan-Meier 2-year survival curves comparing the 3 groups are shown in figure 1B. Mortality was higher in the group of patients with irreversible PH who did not receive a centrifugal LVAD (6 deaths) than in patients treated with centrifugal LVAD implantation (1 death) and patients with reversible PH after the first challenge (4 deaths) ($P = .019$). The subanalysis of patients who underwent HTx showed no significant differences ($P = .238$).

Table 1
Baseline characteristics and subsequent treatments

Baseline Characteristic	Reversible PH (n = 28)	Reversible PH with centrifugal LVAD implantation (n = 7)	Reversible PH without centrifugal LVAD implantation (n = 12)	*P*
Age, y	55.2 [47.1-65.1]	62.0 [55.3-63.7]	53.9 [44.3-63.6]	.41
Male sex	23 (82)	6 (86)	9 (75)	.81
Creatinine, μmol/L	111 [89-132]	130 [107-139]	97 [84-124]	.34
Atrial fibrillation	10 (36)	2 (29)	8 (67)	.14
Ischemic heart disease	17 (61)	5 (71)	10 (83)	.36
LVEF, %	26 [21-31]	27 [23-28]	30 [23-34]	.46
Baseline treatment				
β-Blockers	27 (96)	7 (100)	11 (92)	.66
ACEIs	19 (68)	4 (57)	8 (67)	.87
ARBs	4 (14)	2 (29)	3 (25)	.58
MRAs	27 (96)	7 (100)	11 (95)	.66
Nitrates	6 (21)	3 (43)	2 (17)	.40
Hydralazine	5 (18)	1 (14)	3 (25)	.82
Furosemide	23 (82)	7 (100)	12 (100)	.15
CRT	6 (21)	2 (29)	1 (8)	.50
Baseline right catheterization				
mBP, mmHg	74 [67-77]	81 [74-88]	82 [67-88]	.05
mPAP, mmHg	39 [35-42]	44 [38-53]	51 [47-58]	< .001
PCWP, mmHg	26 [20-32]	30 [12-32]	29 [24-33]	.52
Cardiac index, L/m^2	1.9 [1.6-2.5]	1.9 [1.4-2]	2.1 [1.7-2.8]	.41
sPAP, mmHg	62 [55-66]	70 [53-84]	79 [72-88]	.008
TPG, mmHg	13 [9-16]	21 [16-26]	22 [20-26]	< .001
PVR, WU	3.37 [2.7-4.6]	5.9 [5-8.7]	6.2 [4.9-8.2]	.001
Subsequent treatment				
Sildenafil	19 (68)	7 (100)	12 (100)	.02
Sildenafil dose, mg/d	60 [30-120]	240 [120-240]	120 [60-160]	.008
LVAD	5 (18) 2 EXCOR 1 HVAD 2 HeartMate 3	7 (100) 4 HVAD 3 HeartMate 3	3 (25) 3 EXCOR	< .001
Transplant at 2 y	21 (75)	6 (85.7)	6 (50)	.178
Time to transplant, d	171 [82-280]	219.5 [170-313]	57.5 [42-117]	.118

ARBs, angiotensin *II* receptor blockers; ACEIs, angiotensin conversion enzyme inhibitors; CRT, cardiac resynchronization therapy; GTP, mPAP-PCWP transpulmonary gradient; LVAD, left ventricular assist device; LVEF, left ventricular ejection fraction; mBP, mean blood pressure; mPAP, mean pulmonary arterial pressure; MRAs, mineralocorticoid receptor antagonists; PCWP, pulmonary capillary wedge pressure; PH, pulmonary hypertension; PVR, pulmonary vascular resistance [GTP/cardiac index]; sPAP, systolic pulmonary artery pressure; WU, Wood units.
Values are expressed No. (%) or as median [interquartile range].

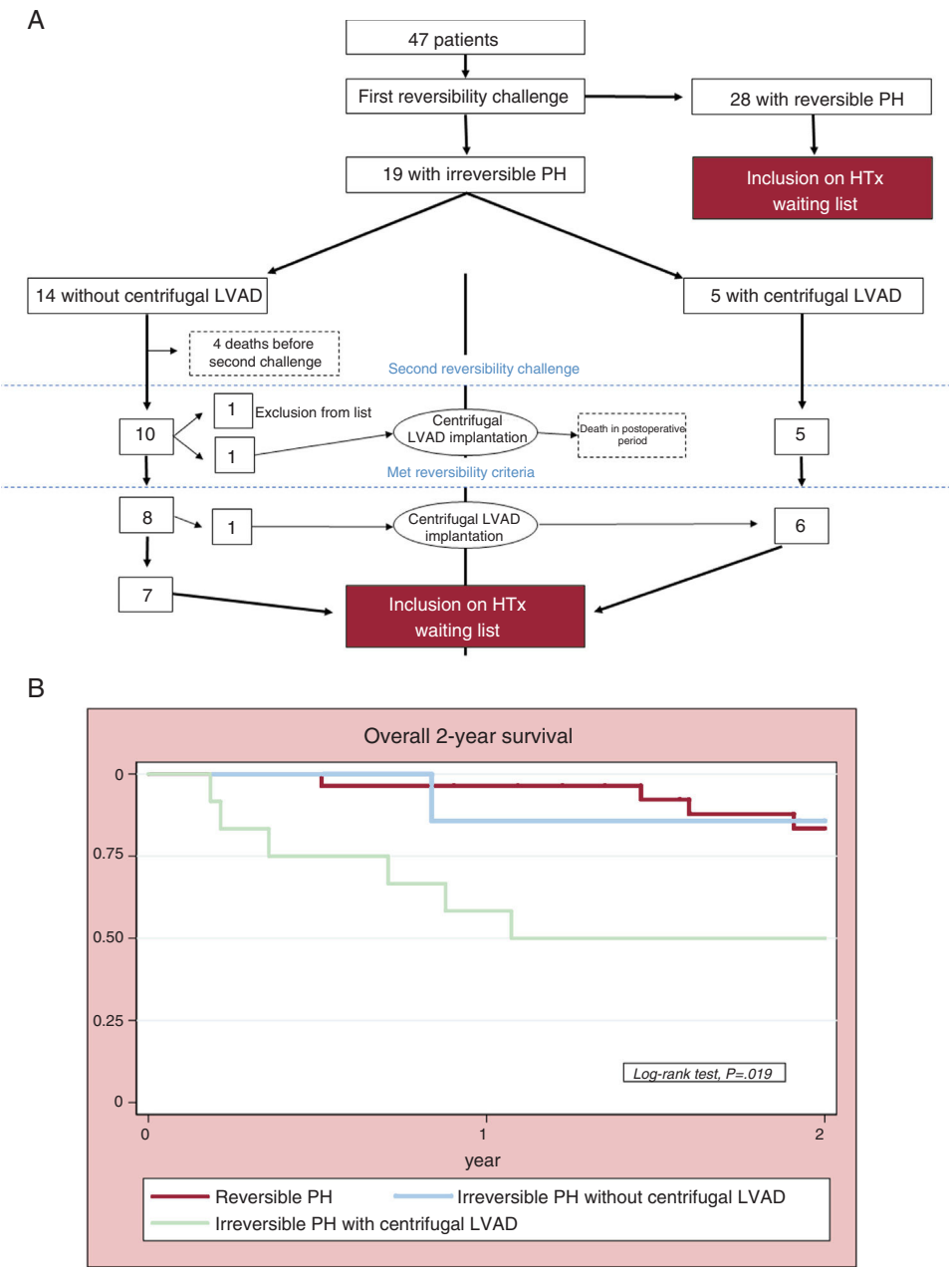

Figure 1. A. Flow chart showing the progression of patients up to inclusion on the HTx waiting list. B. Kaplan-Meier overall 2-year survival analysis by groups. HTx, heart transplant; LVAD, left ventricular assist devices; PH, pulmonary hypertension.

Despite the limitations of this small, single-center, observational study, our results show that HTx candidates with irreversible PH who undergo centrifugal LVAD implantation survive longer than patients not undergoing this procedure and have a similar prognosis to patients with reversible PH. The 2-year mortality rate in patients with irreversible PH not treated with centrifugal LVAD implantation was 50%. The higher survival rate in patients treated with centrifugal LVAD implantation can largely be attributed to their increased likelihood of meeting the reversibility criteria and being added to an HTx waiting list following this procedure. Our results also support previous findings showing that the combined use of sildenafil and centrifugal LVAD implantation is safe.[6]

Centrifugal LVAD implantation can safely and effectively reverse PH in HTx candidates with an initially negative vasodilator response, providing a bridge to HTx candidacy and a similar prognosis to that of patients with reversible PH.

CONFLICTS OF INTEREST

J. González-Costello has received consultancy fees from Abbott.

Fernando de Frutos,[a,*] Carles Díez-López,[a] José Carlos Sánchez-Salado,[a] Albert Miralles,[b] Nicolás Manito,[a] and José González-Costello[a]

[a]*Servicio de Cardiología, Hospital Universitari de Bellvitge, L'Hospitalet de Llobregat, Barcelona, Spain*
[b]*Servicio de Cirugía Cardiaca, Hospital Universitari de Bellvitge, L'Hospitalet de Llobregat, Barcelona, Spain*

*Corresponding author:
E-mail address: fdefrutos@alumni.unav.es (F. de Frutos).

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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