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RESEARCH LETTER

Carvedilol for Treatment of Right Ventricular Dysfunction in Pulmonary Arterial Hypertension

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The safety and efficacy of carvedilol in patients with pulmonary arterial hypertension (PAH) is ambiguous.[1,2] We hypothesized that carvedilol may primarily be effective in patients with PAH with reduced RV systolic function.

We performed a single-center, open-label pilot study to test the safety and feasibility of carvedilol in 5 patients with PAH with RV ejection fraction (RVEF) <45% by cardiac magnetic resonance imaging, World Health Organization functional class II–III symptoms, mean pulmonary artery pressure >35 mm Hg, and stable dose of PAH-specific therapies for 3 months. Exclusion criteria included resting heart rate (HR) <60 beats per minute, second- or third-degree heart block, resting HR >110 beats per minute, systolic blood pressure <100 mm Hg, cardiac index (<2 L/min per m^2, mean right atrial pressure >15 mm Hg, or right heart failure within 30 days of enrollment. The primary efficacy end point was change in cardiac magnetic resonance imaging–derived RVEF. Primary safety outcome was absence of adverse events. Exploratory secondary end points included change in 6-minute walk distance (6MWD), serum NT-proBNP (N-terminal pro-B-type natriuretic peptide), serum catecholamine, invasive hemodynamics, and quality of life as assessed by the Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR) questionnaire after 6 months of carvedilol treatment. The trial protocol was approved by the institutional review board and registered at clinicaltrials.gov (NCT02120339). All patients gave informed consent. The data that support the findings of this study are available from the corresponding author upon reasonable request.

Carvedilol was started at 3.125 mg twice a day (BID), and uptitrated every 4 weeks as tolerated up until week 12 to a maximum of 25 mg BID. Dose escalation was halted, and/or the dose was decreased if the following occurred: systolic blood pressure <100 mm Hg, resting HR <60 beats per minute, or increasing diuretic requirements. Patients were continued on the maximum tolerated dose at week 12 for 3 additional months. The sign-rank test and Spearman rho test were used as appropriate. *P* values were reported but not used for inference. All statistical analyses were performed using Stata software Version 15.

Patients were median age 58 years (interquartile range [IQR], 46–67 years), female, had idiopathic PAH (n=2), scleroderma-PAH (n=2), or portopulmonary hypertension (n=1) and were World Health Organization functional class II (n=1) or III (n=4). All patients were treated with combination therapy with 2 patients on parenteral prostacyclin and 2 patients on inhaled prostacyclin. The median total daily dose of carvedilol was 18.75 mg (IQR, 9.375–25 mg). Uptitration was slowed because of asymptomatic bradycardia (n=1), asymptomatic hypotension (n=3), and fluid retention (n=1). Two patients completed the 6-month study. Three patients exited the study at 4 months because of PAH disease progression (n=1), syncope (n=1), and stroke and stress-induced cardiomyopathy (n=1). Two patients had increased oral diuretic requirements.

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Table 1. Baseline, Follow-Up, and Median (Interquartile) Change in Study Assessments for Patients

Characteristics	N	Baseline	Carvedilol	Median Change	*P* Value
Heart rate, beats per min	5	78 (74 to 80)	67 (57 to 70)	−5 (−21 to −4)	0.04
Systolic blood pressure, mm Hg	5	138 (120 to 140)	112 (111 to 117)	−17 (−29 to −3)	0.04
Diastolic blood pressure, mm Hg	5	78 (74 to 85)	67 (67 to 72)	−11 (−14 to −7)	0.04
6-Minute walk distance, m	4	336 (291 to 395)	382 (343 to 418)	47 (23 to 52)	0.07
Serum NT-proBNP, pg/mL	5	704 (661 to 2443)	1331 (998 to 1553)	511 (−627 to 890)	0.89
Serum norepinephrine, pg/mL	4	599 (422 to 878)	574 (426 to 791)	−26 (−181 to 97)	0.72
CAMPHOR Score	4	28 (16 to 38)	27 (19 to 31)	−1 (−7 to 3.5)	0.72
Cardiac MRI					
RV ejection fraction, %	5	34 (28 to 40)	42 (34 to 55)	5 (−7 to 15)	0.50
RV end systolic volume index, mL/m^2	5	57 (56 to 66)	63 (28 to 86)	5 (−22 to 7)	0.89
RV end diastolic volume index, mL/m^2	5	100 (82 to 114)	109 (62 to 127)	−9 (−20 to 17)	0.89
Stroke volume index, mL/m^2	5	44 (32 to 56)	40 (38 to 50)	−4 (−5 to 7)	0.89
LV end diastolic volume index, mL/m^2	5	53 (46 to 55)	52 (51 to 67)	11 (3 to 14)	0.10
Hemodynamics					
Mean RA pressure, mm Hg	5	7 (5 to 8)	9 (8 to 10)	3 (1 to 3)	0.10
Mean PAP, mm Hg	5	50 (46 to 50)	50 (50 to 53)	4 (−3 to 7)	0.49
Mean PCWP, mm Hg	5	10 (10 to 12)	10 (8 to 19)	1 (0 to 7)	0.28
Cardiac output, L/min	5	4.7 (4.5 to 5.3)	4.3 (4.2 to 4.5)	−0.3 (−0.8 to 0.3)	0.42
Cardiac index, L/min per m^2	5	2.5 (2.4 to 2.8)	2.2 (2.1 to 2.6)	−0.2 (−0.4 to −0.2)	0.22
PVR, Wood Units	5	8.4 (7 to 9)	9.7 (6.6 to 10.3)	0.7 (−1.8 to 1.1)	0.89
PAC, mL/mm Hg	5	1.4 (1.3 to 1.5)	1.2 (1.1 to 1.5)	−0.2 (−0.2 to 0.003)	0.69

CAMPHOR indicates Cambridge Pulmonary Hypertension Outcome Review; LV, left ventricle; MRI, magnetic resonance imaging; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PAC, pulmonary arterial compliance; PAP, pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; RA, right atrium; and RV, right ventricle.

Carvedilol reduced HR and systemic blood pressure (Table). The median change in RVEF was +5% (IQR, −7 to +15%, *P*=0.50), left ventricular end diastolic volume index was +11 mL (IQR, 3–14 mL, *P*=0.10), and 6MWD was +47 m (IQR, 23–52 m, *P*=0.07) (Table). There was no change in serum NT-proBNP, serum catecholamine, or quality of life (Table). On invasive hemodynamics, the median change in cardiac index was −0.2 L/min per m^2 (IQR, −0.4 to −0.2 L/min per m^2, *P*=0.22) with no change in pulmonary hemodynamics (Table). The correlation between changes in RVEF and 6MWD was 0.8 (*P*=0.24), serum NT-proBNP was −0.8 (*P*=0.09), and quality of life was −0.9 (*P*=0.05).

In this study, patients with PAH with RVEF <45% were able to tolerate only low doses of carvedilol. Carvedilol was associated with mild fluid retention and syncope with a trend towards improved 6MWD, higher left ventricular end diastolic volume index, and lower cardiac index.

Grinnan et al. reported a median tolerated dose of 18.75 mg BID, with 50% of patients reaching 25 mg BID.[1] Farha et al. reported a median tolerated dose of 12.5 mg BID with 40% of patients reaching 25 mg BID.[2] In contrast, none of our patients reached the 25 mg BID dose, likely because they had reduced RVEF (median 34%, IQR, 28%–40%) and advanced World Health Organization functional class (80% were functional class 3). No patients had worsening RV failure requiring hospitalization or intravenous diuretics. The stress-induced cardiomyopathy and related stroke in 1 patient were unrelated to carvedilol because beta-blockers are protective against stress-induced cardiomyopathy,[3] and the patient had a clear emotional stress preceding the event.

We did not observe an increase in RVEF, perhaps because of the small sample size and the fact that only 2 patients completed the 6-month study. The reduction in HR and systemic blood pressure suggest that we achieved clinically relevant adrenergic receptor blockade with low-dose carvedilol. The mechanism behind the trend towards improvement in 6MWD is unclear. There was a trend towards a positive relationship between change in 6MWD and serum NT-proBNP, suggesting carvedilol-induced improvement in RV function. Left ventricular end diastolic volume index increased with carvedilol, which has been associated with improved survival.[4] A randomized, placebo-controlled, multicenter study with a run-in phase and low target carvedilol dose would be a safe next step in studying carvedilol in patients with PAH with reduced RVEF.

ARTICLE INFORMATION

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