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CASE REPORT

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Management of pulmonary hypertension associated with valvular heart disease with angiotensin-receptor neprilysin inhibitor

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Abstract

Pulmonary hypertension secondary to left-sided valvular disease (VHD-PH) is associated with high morbidity and mortality. Angiotensin-receptor neprilysin inhibitor (ARNI) is a novel pharmacotherapy, which reduces afterload with natriuresis and peripheral vasodilation. Our cases demonstrate that ARNI may also have a role in the treatment of combined pre- and postcapillary pulmonary hypertension that is independent of its effect on pulmonary capillary wedge pressure and cardiac output. Future prospective trials are needed to evaluate role of ARNIs in treatment of VHD-PH.

KEYWORDS
cardiopulmonary pharmacology and therapeutics, congestive heart failure, hemodynamics, pulmonary hypertension

INTRODUCTION

Pulmonary hypertension secondary to valvular disease of the left heart (VHD-PH) is associated with high morbidity and mortality.[1] Unfortunately, past studies evaluating pulmonary arterial hypertension pharmacotherapies in this population have found lack of benefits and, in some cases, risk of harm.[2] Angiotensin-receptor neprilysin inhibitor (ARNI) is a novel pharmacotherapy, which reduces afterload with natriuresis and peripheral vasodilation. Whether ARNI can also reduce pulmonary vasculature resistance is unknown. We present two cases of VHD-PH that improved after treatment with ARNI.

CASE 1

A 63-year-old woman with past medical history of rheumatic mitral valve (MV) stenosis despite percutaneous MV balloon valvuloplasty presented with progressive shortness of breath and New York Heart Association Class IIIB symptoms. The initial echocardiogram showed normal left ventricular ejection

fraction of 60%, MG of 7 mmHg at HR = 57 beats/minute, an estimated right ventricular systolic pressure of 100 mmHg, and difficult visualization of the right ventricle (appeared normal in size but unable to assess function). Given that the patient was volume overloaded on exam, she underwent several months of outpatient diuresis; however, continued to complain of New York Heart Association Class IIIB symptoms. Therefore, a right heart catheterization (RHC) was done, which showed that she had not only severe mitral stenosis (MG = 12 mmHg at a heart rate of 57 beats per minute) but also severe combined pre- and postcapillary PH (Cpc-PH, see Table 1). She was deemed to be a high-risk surgical candidate per our multidisciplinary heart team and was referred to the PH clinic for medical optimization. After 6 months of treatment with ARNI 49–51 mg twice daily, a repeat RHC showed significant improvement in Cpc-PH with a relatively similar pulmonary capillary wedge pressure (PCWP, Table 1). Given these improvements, she was deemed suitable for MV replacement and subsequently underwent mechanical MV replacement (St. Jude's 27 mm) with improvement in the mean gradient to 3 mmHg at a heart rate of 66 beats/min. At 6 months post-op, her symptoms resolved completely with a repeat echocardiogram demonstrating normal biventricular function (left ventricular ejection fraction = 65%–69%) and right ventricular systolic pressure of 36 mmHg.

CASE 2

A 59-year-old man with past medical history of MV endocarditis with remote bovine MV replacement in 1984 complicated by severe recurrent paravalvular leak and redo replacements in 1994 and 2014 who presented for routine follow-up appointment with worsening shortness of breath. The repeat echocardiogram demonstrated a well-functioning MV prosthesis and normal biventricular function (left ventricular ejection fraction = 60%), but RHC demonstrated elevated biventricular filling pressures with severe Cpc-PH (Table 1). After 2 months of diuresis, a repeat RHC showed persistent, severe Cpc-PH despite significant improvement in biventricular filling pressures, right atrial pressure decreasing from 19 to 9 mmHg and PCWP from 30 to

TABLE 1 Right heart catheterization results before and after angiotensin receptor neprilysin-inhibitor (ARNI) initiation and up-titration.

	Case 1		Case 2		
	RHC initial conditions	**RHC after ARNI 49–51 mg**	**RHC initial conditions**	**RHC after diuresis**	**RHC after ARNI 49–51 mg**
HR	57 beats per minute	64 beats per minute	74 beats per minute	80 beats per minute	73 beats per minute
BP	128/73 mmHg	169/98 mmHg	157/91 mmHg	134/79 mmHg	121/65 mmHg
MAP	91 mmHg	122 mmHg	113 mmHg	97 mmHg	84 mmHg
MVG	12 mmHg	N/A[a]	19 mmHg	9 mmHg	10 mmHg
RAP	7 mmHg	5 mmHg	30 mmHg	20 mmHg	17 mmHg
PAP	117/33 (66) mmHg	65/32 (46) mmHg	112/44 (67) mmHg	77/31 (46) mmHg	49/21 (24) mmHg
PCWP	25 mmHg	21 mmHg	37 mmHg	26 mmHg	7 mmHg
TPG	41 mmHg	25 mmHg	14 mmHg	11 mmHg	4 mmHg
DPG	8 mmHg	11 mmHg			
PVR	11.4 woods units	6.1 woods units	6.7 woods units	4.3 woods units	1.1 woods units
SVR	1866 dynes	2283 dynes	1213 dynes	1154 dynes	911 dynes
CO, CI	3.6 L/min, 1.8 L/min/m^2[b]	4.1 L/min, 2.0 L/min/m^2[c]	6.2 L/min, 2.8 L/min/m^2	6.1 L/min, 2.8 L/min/m^2	6.5 L/min, 3.0 L/min/m^2

Abbreviations: FCI, Fick cardiac index; FCO, Fick cardiac output; MVG, mean mitral valve gradient; MVR, mitral valve replacement; PAP, pulmonary arterial pressure; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure; RHC, right heart catheterization; TPG, transpulmonary gradient.

[a]Not available.

[b]Measured by Fick.

[c]Measured by thermodilution.

20 mmHg (Table 1). A pulmonary vasodilator challenge was considered at this time; however, given persistently elevated PCWP and concern for flash pulmonary edema, the decision was made to forego this test. Moreover, the patient was borderline hypotensive during sedation; thus, nitroprusside challenge was not performed. He was subsequently started on ARNI, titrated up to 49–51 mg twice daily, and 2 months later had almost complete resolution of his symptoms. A repeat RHC at this time showed significant improvement of pulmonary arterial pressures (PAPs) and pulmonary vascular resistance (PVR), again with relatively similar PCWP and cardiac output.

DISCUSSION

Evidence regarding the safety and efficacy of pulmonary vasodilators to treat patients with Cpc-PH have been inconsistent at best.[1] Although these therapies are being used currently as compassionate use in select patients with Cpc-PH, they are not currently recommended—even in the latest 2022 European Society of Cardiology and the European Respiratory Society Guidelines. This report is the first to describe treatment of Cpc-PH with ARNI along with invasive hemodynamic data showing successful reduction in PAPs and PVR. These cases add to the small body of literature regarding the use of ARNIs to treat Cpc-PH.[3,4] Case 1 is an example of severe VHD-PH which precluded operative management initially that eventually responded to ARNI allowing her to have surgical intervention for the culprit valve. Case 2 demonstrates Cpc-PH that failed to improve with diuretics, which improved significantly with ARNI. In both cases, there were significant reduction in PAPs and PVR with relatively unchanged PCWP and cardiac output. ARNI's potential in the treatment of *prohibitive* Cpc-PH, such as in preoperative risk reduction in Case 1, or in the treatment of *persistent* Cpc-PH, such as in postoperative residual PH management in Case 2, are important areas for future prospective trials.

Although there are no prior animal studies on Cpc-PH secondary to valve disease, animal models of hypoxia-induced PH have shown direct attenuation of pulmonary vascular wall thickening with ARNI, compared to lack of response with placebo or aldosterone receptor blocker treatment alone.[5] It is possible that the improvement in pulmonary hemodynamics after ARNI initiation is in part due to its effect on pulmonary vascular reverse remodeling. Another possible mechanism is ARNI's role in improving left atrial and ventricular compliance, which may lead to reduced pulsatile afterload and improved pulmonary arterial compliance. Future prospective trials are needed to better elucidate the mechanism of ARNI in treatment of Cpc-PH.

AUTHOR CONTRIBUTIONS

All authors: made a substantial contribution to the concept or design of the work; or acquisition, analysis or interpretation of data. Drafted the article or revised it critically for important intellectual content. Approved the version to be published. Participated sufficiently in the work to take public responsibility for appropriate portions of the content.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

ETHICS STATEMENT

Both patients provided verbal consent for personal information relating to the subjects to be published by SAGE Publishing, its licensees, and assigns.

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