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Case Report

Reduction in pulmonary artery pressures with use of sacubitril/valsartan

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ABSTRACT

Pulmonary hypertension due to left heart disease (PH-LHD) frequently complicates heart failure with reduced ejection fraction (HFrEF). Specific therapies for PH have not offered an advantage in patients with PH-LHD. The combined angiotensin receptor blocker–neprilysin inhibitor (ARNI), sacubitril/valsartan, is a novel therapy that can increase levels of natriuretic peptides (NPs). The resulting action on natriuresis and vasodilation may play an important role in the reduction of pulmonary pressures. Here, we report how the use of ARNI in two patients with HFrEF has resulted in an improvement in PH and, consequently, in clinical status and prognosis.

<**Learning objective:** Sacubitril/valsartan (ARNI) is the newest neurohormonal agent approved for therapy in heart failure with reduced ejection fraction (HFrEF). Pulmonary hypertension (PH) due to left heart disease (PH-LHD) is frequent in patients with HFrEF and is associated with a reduced functional class and poor prognosis. The use of ARNI has been associated with a relevant reduction in pulmonary pressures in two cases of PH-LHD.>

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Introduction

Pulmonary hypertension due to left heart disease (PH-LHD; World Health Organization group 2) is frequently encountered in patients with heart failure with reduced ejection fraction (HFrEF) and is associated with functional class impairment and high mortality [1,2]. Although it is the most common etiology of PH worldwide, restricted proven therapies are known to decrease its associated morbidity and mortality.

Treatment with sacubitril, a neutral endopeptidase that degrades endogenous vasoactive peptides, increases circulating levels of natriuretic peptides (NPs), which have been shown to facilitate natriuresis and vasodilation [3]. It could be considered that the action of sacubitril on NPs may produce an effect on PH-LHD both at post-capillary level, acting on natriuresis, and at pre-capillary level, generating vasodilation.

We report here two cases of stage D HFrEF with reduction of pulmonary artery pressures in PH-LHD using combined angiotensin receptor blocker–neprilysin inhibitor (ARNI).

Case reports

Patient 1

Patient 1 was a 42-year-old male patient who came to our attention in March 2016 for worsening HF in the emergency room of our hospital. Cardiovascular history included prior acute anteroseptal myocardial infarction in 2014 treated with primary angioplasty with a drug-eluting stent for the left anterior descending coronary artery; for the recognition of a persistent severe left ventricular systolic dysfunction, the implantation of a bicameral cardioverter defibrillator in 2015 in primary prevention was necessary.

The patient was under treatment with candesartan 8 mg/day, acetyl salicylic acid 100 mg, furosemide 125 mg/day (he had independently increased the dosage), canrenone 50 mg/day, nitroglycerin transdermal patch 10 mg, and bisoprolol 5 mg/day.

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He complained of shortness of breath on mild efforts and non-productive cough. Physical examination showed a few crackles at both lung bases, jugular venous distention, mild peripheral edema, and an S3 sound on heart examination. Blood pressure was 85/60 mmHg; heart rate 78/min; oxygen saturation 94%. Laboratory examinations showed an acute renal insufficiency (creatinine 3.78 mg/dl).

An echocardiography revealed a severe left ventricular dilatation, ejection fraction was 25%, moderate mitral regurgitation, severe tricuspidal regurgitation, and increased peak systolic right ventricular (RV)-right atrial (RA) gradient (60 mmHg) (Table 1A.a and Fig. 1A, B).

A dopamine infusion at 4 mcg/kg/min dosage was started; sartan and nitroglycerine were suspended. The clinical conditions progressively improved and the renal function values also decreased; therefore, dopamine was weaned off. At this point a right heart catheterization (RHC) revealed a combined pre- and post-capillary PH partially reversed after sodium nitroprusside infusion (2 mcg/kg/min), volume overload with pulmonary capillary wedge pressure (PCWP) 31 mmHg, and a low cardiac output state with cardiac index (CI) 1.5 L/min/m^2; an echocardiography was also repeated (Table 1A.b).

The patient was put on a waiting list for heart transplant and was discharged with the following medical therapy: valsartan 80 mg b.i.d., bisoprolol 7.5 mg/day, furosemide 100 mg/day, canrenone 25 mg/day, acetyl salicylic acid 100 mg/day and febuxostat 80 mg/day.

For heart transplant checklist, a RHC and an echocardiography were repeated in October 2016 showing moderate PH with elevated PCWP and RA pressure (Table 1A.b). Therapy with ARNI was initiated at the dose of 24/26 mg b.i.d. considering persistent New York Heart Association (NYHA) III, stationary normal blood pressure values (110/70 mmHg), and renal function.

After 20 days, the patient reported a significant improvement in quality of life; therefore, ARNI dosage was increased to 49/51 mg b.i.d. and after 1 month to optimal dosage of 97/103 mg b.i.d.

Therapy was well tolerated and was continued with high compliance. At 6 months, the patient showed improved echocardiography and hemodynamic parameters (Table 1A.c and Fig. 1C). NYHA class switched from III to I and the patient was temporarily delisted.

Patient 2

Patient 2 was a 64-year-old male who came to our attention in January 2015 for clinical evaluation at our HF Center. Cardiovascular history included prior acute anterolateral myocardial infarction in 2014, complicated by cardiogenic shock with temporary necessity of intra-aortic balloon pump; the culprit lesion (left anterior descending coronary artery) was treated with primary angioplasty with a drug-eluting stent. For detection of ventricular-sustained tachycardia after 3 weeks, the implantation of a bicameral cardioverter defibrillator in secondary prevention was necessary.

The patient was under treatment with ramipril 10 mg/day, acetyl salicylic acid 100 mg, furosemide 100 mg/day, bisoprolol 5 mg/day, canrenone 50 mg/day, and allopurinol 150 mg/day. He complained of shortness of breath on moderate efforts (NYHA III). Physical examination did not show abnormal sounds at pulmonary and cardiac auscultation; blood pressure was 110/70 mmHg; heart rate 70/min; and oxygen saturation 95%. An echocardiography revealed a moderate left ventricular dilatation, ejection fraction was 33%, moderate mitral regurgitation, mild tricuspidal

Table 1 Evolution of the patients' hemodynamic parameters before and after sacubitril/valsartan initiation.

A. Evolution of the patient's hemodynamic parameters (case report 1)

Parameters	a	b	c
Echocardiography			
LVEF (%)	24	25	28
LVEDVI (ml/mq)	96	97	95
LVEDD (mm)	69	67	63
MR	2+	2+	1+
TR	3+	2+	1+
Peak RV-RA gradient (mmHg)	60	52	35
LAVI (ml/m^2)	54	53	38
TAPSE (mm)	13	14	19
E/A ratio	3.2	3.1	0.7
Right heart catheterization			
SBP (mmHg)	85	95	105
HR (beats)	78	70	66
sPAP (mmHg)	64	55	44
mPAP (mmHg)	43	38	29
dPAP (mmHg)	34	26	20
PCWP (mmHg)	31	25	18
CI (l/min/m^2)	1.5	1.7	2.1
RAP (mmHg)	13	11	3
SVO_2 (%)	58.7	62.7	67.2
RVSWI (g/m^2/beat)	8.7	8.9	10.6
RAP/PCWP	0.42	0.44	0.17
PVR (Wood unit)	4	3.8	2.6
DPG (mmHg)	3	1	2
Laboratory examinations			
NT-proBNP (ng/l)	2114	1788	595

B. Evolution of the patient's hemodynamic parameters (case report 2)

Parameters	a	b
Echocardiography		
LVEF (%)	33	34
LVEDVI (ml/mq)	89	88
LVEDD (mm)	61	60
MR	2+	2+
TR	2+	1+
Peak RV-RA gradient (mmHg)	75	36
LAVI (ml/m^2)	49	42
TAPSE (mm)	18	19
E/A ratio	2.6	0.8
Right heart catheterization		
SBP (mmHg)	120	110
HR (beats)	70	68
sPAP (mmHg)	98	45
mPAP (mmHg)	57	32
dPAP (mmHg)	39	24
PCWP (mmHg)	30	21
CI (l/min/m^2)	1.9	2.1
RAP (mmHg)	7	4
SVO_2 (%)	58.9	64.7
RVSWI (g/m^2/beat)	11.7	7.5
RAP/PCWP	0.23	0.19
PVR (Wood unit)	6.6	2.7
DPG (mmHg)	9	3
Laboratory examinations		
NT-proBNP (ng/l)	1349	694

LVEF, left ventricular ejection fraction; LVEDVI, left ventricular end diastolic volume index; LVEDD, left ventricular end diastolic diameter; MR, mitral regurgitation; TR, tricuspid regurgitation; Peak RV-RA gradient, peak systolic right ventricular-right atrial gradient; LAVI, left atrial volume index; TAPSE, tricuspid annular plane systolic excursion; SBP, systolic blood pressure; sPAP, systolic pulmonary artery pressure; mPAP, mean pulmonary artery pressure; dPAP, diastolic pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; CI, cardiac index; RAP, right atrial pressure; SVO_2, mixed venous oxygen saturation; RVSWI, right ventricular stroke work index; HR, heart rate; PVR, pulmonary vascular resistance; DPG, diastolic pulmonary vascular pressure gradient; NT-proBNP, N-terminal pro-brain natriuretic peptide.

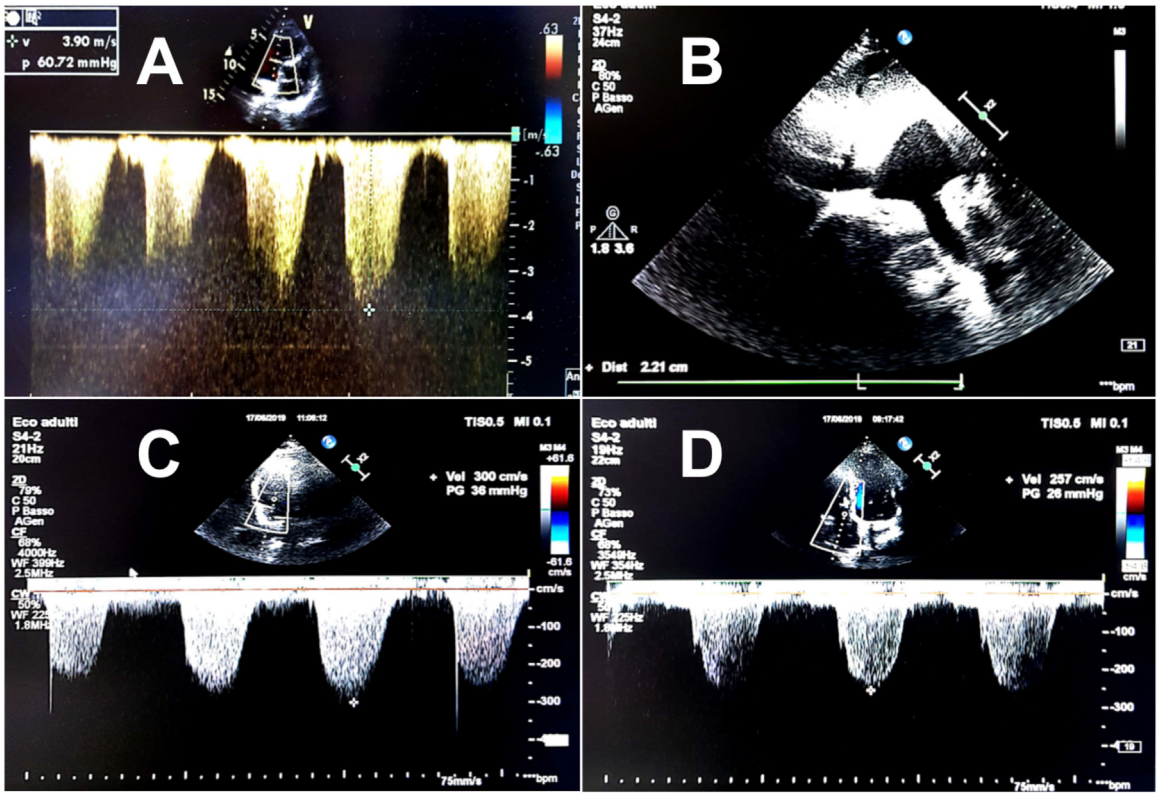

Fig. 1. The patient presented with high right ventricular-right atrial (RV-RA) peak gradient (A) with elevated estimated right atrial pressure (dilatation of the inferior vena cava) (B); after angiotensin receptor blocker–neprilysin inhibitor was started, a progressive reduction in RV-RA peak gradient was documented at 6 (C) and 12 months (D), respectively.

regurgitation, and high peak systolic RV-RA gradient (75 mmHg) (Table 1B.a and Fig. 2A, B). A chest X-ray showed mild pulmonary congestion and mild enlargement of left heart chambers; a spirometry revealed normal respiratory volumes with mild reduction of diffusing capacity for carbon monoxide (DLCO).

We admitted the patient to our Division of Cardiology for invasive examinations. The RHC revealed a severe post-capillary PH (Table 1B.a); diagnosis of combined post- and pre-capillary PH (Cpc-PH) was done, in consideration of diastolic pressure gradient (DPG) >7 mmHg and pulmonary vascular resistance (PVR) >3 WU. A high-resolution thorax computed tomography scan ruled out parenchymal lung disease and a ventilation/perfusion lung scan ruled out chronic thromboembolic PH.

At discharge, the patient was prescribed a higher dose of furosemide (150 mg/day).

He underwent a RHC after six months; hemodynamic data were substantially unchanged. We decided to start ARNI at the dosage of 49/51 mg. After 1 month of therapy, the patient reported a significant improvement in quality of life, and ARNI was increased to optimal dosage of 97/103 mg b.i.d.

In six months NYHA class switched from III to I. Therapy was well tolerated and was continued with high compliance. The last echocardiography examination (Fig. 2C, D) and a recent RHC showed a marked improvement (Table 1B.b).

Discussion

We describe the successful use of ARNI combined with standard medical therapy to improve the hemodynamic profile of two patients with two cases of combined post- and pre-capillary PH-LHD.

Chronic elevation of the left-sided filling pressure may result in pulmonary arterial endothelial dysfunction, decreased nitric oxide availability, increased expression of endothelin-1, upregulation of neurohormones, and vascular remodeling, leading to a 'disproportionate' increase of the pulmonary artery pressures (PAP), and thus resulting in an elevated DPG and PVR [4,5]. DPG, defined by the difference between diastolic PAP and PCWP, is assumed to be less dependent on stroke volume and loading conditions, and was shown to correlate with pulmonary vascular remodeling in PH-LHD.

These findings led to the current terminology and classification of post-capillary PH as either isolated post-capillary PH (Ipc-PH), if the DPG is <7 mmHg and/or PVR ≤ 3 WU, or combined post- and pre-capillary PH (Cpc-PH), if the DPG is ≥7 mmHg and/ or PVR [4]. Recently, a more simple classification of PH-LHD by PVR alone has been proposed [6].

In Patient 1, we waited to undertake ARNI in consideration of the previous acute renal failure event probably determined by hypotension and consequent low perfusion pressure at the glomerular level (for combined effect of candesartan, nitroderivative, and furosemide). Once the situation has shown stability for several months, we decided to try this therapy; the renal function remained stably normal even with maximum dosage of the drug.

The significant improvement in filling pressures has had a significant clinical impact on the patient so as to justify the temporary suspension from the waiting list for cardiac transplantation. The reduction of the filling pressures was surprisingly documented not only by the parameters of the RHC (RA pressure, PCWP), but also by the echocardiography: in particular, not only the reduction of the E/A ratio but also the left atrial volumetry, a valid parameter of the memory of the diastolic dysfunction of the

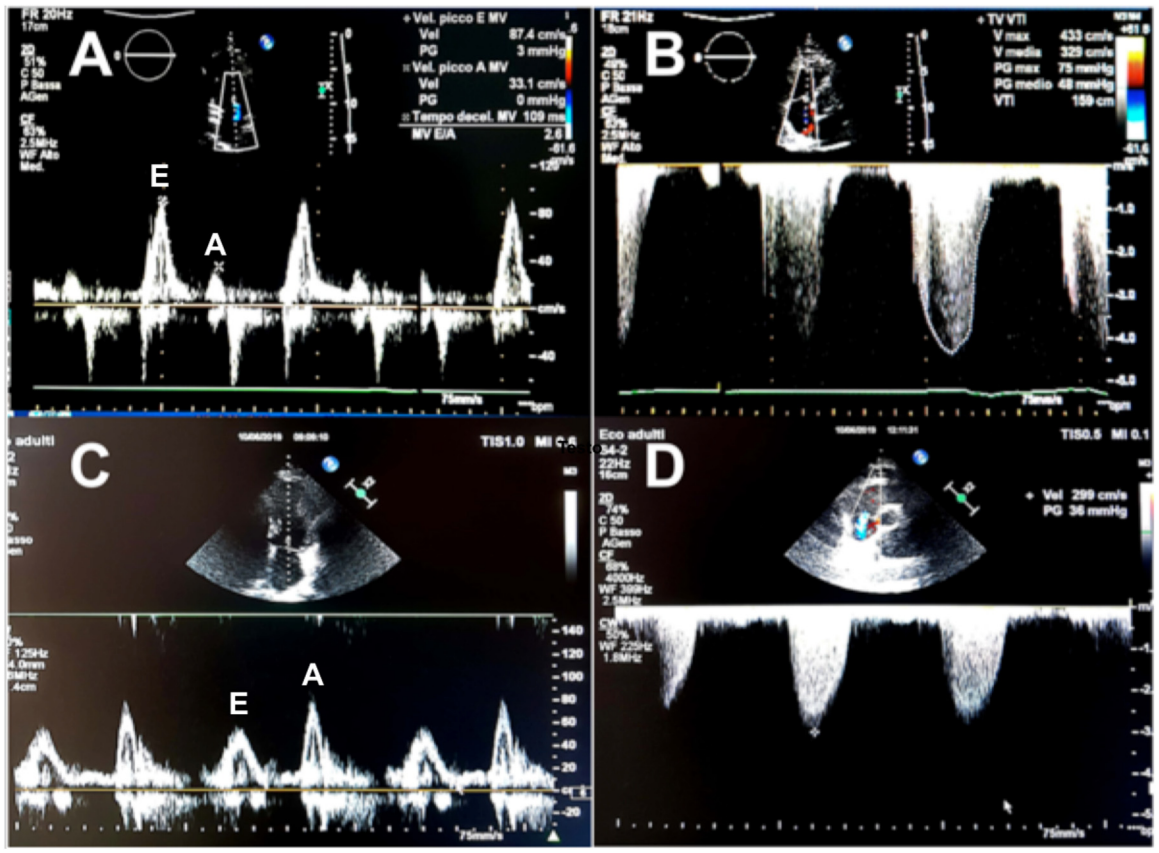

Fig. 2. This figure shows a "pseudonormal" transmitral flow pattern (A) and elevated right ventricular-right atrial (RV-RA) peak gradient (B) at the first examination of our patient; after treatment with angiotensin receptor blocker–neprilysin inhibitor, there was an improvement in transmitral pattern (C) represented by an impaired relaxation pattern of transmitral flow and a signifcant reduction in RV-RA peak gradient (D).

left ventricle [7]. The clear and evident improvement of the function of the right ventricle is also surprising: not only the echocardiography (tricuspid annular plane systolic excursion and two-dimensional measurements of the right ventricle) represented this evolution, but also the hemodynamic data supported this evidence considering the trend of the right ventricle stroke work index (RVSWI) and the RA pressure/PCWP ratio.

In the second patient, other causes of PH were excluded before starting treatment with ARNI. RHC presented mPAP >25 mmHg, PCWP > 15 mmHg, DPG > 7 mmHg, and PVR > 3 WU, and after treatment with sacubitril we have seen a significant improvement in all these parameters.

The final consideration is that in both patients the dose of furosemide was progressively reduced, confirming a considerable decrease in filling pressures.

Sacubitril augments circulating NPs levels by inhibiting their breakdown by neprilysin. The beneficial effects of NPs occur through a complex signaling system that involves up-regulation of intracellular cyclic guanosine monophosphate, which induces direct vasodilation, glomerular filtration increase, natriuresis promotion, reduction of renin secretion, and antihypertrophic and antifibrotic myocardial effects [8,9].

In the absence of targeted therapy for PH-LHD, sacubitril seems to dramatically improve outcomes in these patients. An ongoing trial will clarify the effects on pulmonary artery pressure reduction in patients with congestive HF, with an implanted hemodynamic monitor (CardioMEMS™ HF System, CardioMEMs, Atlanta, GA, USA), randomized to receive ARNI versus angiotensin-converting enzyme inhibitor/angiotensin receptor blocker [10].

Conflict of interest

The authors declare that there is no conflict of interest.

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