


Acute pulmonary pressure change after transition to sacubitril/valsartan in patients with heart failure reduced ejection fraction

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Abstract

Aims Sacubitril/valsartan combines renin–angiotensin–aldosterone system inhibition with amplification of natriuretic peptides. In addition to well-described effects, natriuretic peptides exert direct effects on pulmonary vasculature. The effect of sacubitril/valsartan on pulmonary artery pressure (PAP) has not been fully defined.

Methods and results This was a retrospective case-series of PAP changes following transition from angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB) to sacubitril/valsartan in patients with heart failure reduced ejection fraction and a previously implanted CardioMEMS™ sensor. Pre-sacubitril/valsartan and post-sacubitril/valsartan PAPs were compared for each patient by examining averaged consecutive daily pressure readings from 1 to 5 days before and after sacubitril/valsartan exposure. PAP changes were also compared between patients based on elevated trans-pulmonary gradients (trans-pulmonary gradient ≥ 12 mmHg) at time of CardioMEMS™ sensor implantation. The cohort included 18 patients, 72% male, mean age 60.1 ± 13.6 years. There was a significant decrease in PAPs associated with transition from ACEI/ARB to sacubitril/valsartan. The median (interquartile range) pre-treatment and post-treatment change in mean, systolic and diastolic PAPs were -3.6 ($-9.8, -0.7$) mmHg ($P < 0.001$), -6.5 ($-15.0, -2.0$) mmHg ($P = 0.001$), and -2.5 ($-5.7, -0.7$) ($P = 0.001$), respectively. The decrease in PAPs was independent of trans-pulmonary gradient ($F(1,16) = 0.49, P = 0.49$).

Conclusions In this retrospective case series, transition from ACEI/ARB to sacubitril/valsartan was associated with an early and significant decrease in PAPs.

Keywords Heart failure; Pulmonary hypertension; Remote monitoring; Heart failure reduced ejection fraction; Implantable monitors; Nephilysin

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Jeffrey S. Tran and Ofer Havakuk contributed equally to this study.

Background

Sacubitril/valsartan embodies a novel neurohormonomodulatory approach to the treatment of heart failure with reduced ejection fraction (HFrEF). It combines renin–angiotensin–aldosterone system antagonism with amplification of the natriuretic peptide system, conferring many beneficial compensatory effects in HFrEF.¹ The superior clinical response to sacubitril/valsartan is generally attributed to

peripheral vasodilation, reverse remodelling, and sustained natriuresis.^{2,3}

Natriuretic peptides are also expressed in the pulmonary vascular bed and have been shown to mediate multiple pulmonary vascular effects including vasorelaxation, antiproliferation, and reverse remodelling.^{4,5} Active natriuretic peptide levels are increased by the neprilysin inhibitor sacubitril. Although pulmonary hypertension (PH) is associated with worse clinical outcomes in HFrEF, the clinical

actions of sacubitril/valsartan on pulmonary vascular pressure have not yet been described.

Aims

In this study, we used the CardioMEMS™ system (Abbott Vascular, Inc.), a wireless haemodynamic monitoring device enabling ambulatory assessment of pulmonary artery pressure (PAP), to measure the effect of sacubitril/valsartan initiation on PAPs in patients with HFrEF previously treated with ACEI or ARB.

Methods

This was a retrospective case-series of ambulatory HFrEF patients who had previously received a CardioMEMS device, in whom sacubitril/valsartan was initiated at the discretion of the treating physician. Haemodynamic data at device implantation and the timing of conversion from ACEI or ARB to sacubitril/valsartan at the 24 mg/26 mg dosage were abstracted from the medical record. Up to three consecutive daily PAP readings from 1 to 5 days before and after sacubitril/valsartan initiation were collected from the Merlin website and averaged to yield pre-values and post-values for each subject. Patient records were audited to verify that other interventions that might have influenced PAPs measurement (e.g. addition of new diuretic drugs and change in diuretic dose) had not occurred during the observation period.

Haemodynamic data pre-sacubitril/valsartan and post-sacubitril/valsartan exposure were compared via Wilcoxon signed-rank testing. Patients were also separated into two groups based on trans-pulmonary gradient (TPG) at

CardioMEMS implantation, with $TPG \geq 12$ suggestive of mixed pre-capillary and post-capillary PH and $TPG < 12$ consistent with post-capillary PH. Between-group comparisons of implant haemodynamics were performed with Wilcoxon rank-sum testing. Within-group comparisons of pre-exposure and post-exposure were made via Wilcoxon signed-rank testing. A two-way repeated-measures ANOVA was performed to assess the effect of TPG on the magnitude of changes in pulmonary artery mean pressures (PAMP). Data management and statistical analyses were conducted using STATA 14.2. The study was approved by the Institutional Review Board.

Results

We identified 18 subjects who had previously received a CardioMEMS device and were subsequently transitioned from ACEI or ARB to sacubitril/valsartan. All had a left ventricular ejection fraction $<40\%$ (mean 23.4 ± 6.9), 28% were women, and the mean age was 60.1 ± 13.6 years (*Table 1*). Relevant comorbidities included atrial fibrillation/flutter (44%) and chronic obstructive pulmonary disease (75%). Medication regimens, apart from transition to sacubitril/valsartan, remained unchanged during the observation period.

At device implantation, median [interquartile range (IQR)] PAMP and pulmonary capillary wedge pressure were 33 (28, 37) mmHg and 21 (17, 29) mmHg, respectively (*Table 1*). There were 47 independent measurements prior and 51 measurements following the first sacubitril/valsartan dose. Two patients on ACEI were started on sacubitril/valsartan after a 24 h washout period. The remainder were on an ARB and transitioned directly to sacubitril/valsartan.

Table 1 Baseline characteristics

	All subject $N = 18$	$TPG < 12$ $n = 12$	$TPG \geq 12$ $n = 6$
Age	60.1 ± 13.6	59.1 ± 13.4	32.0 ± 15.0
BMI	32.1 ± 11.6	31.5 ± 11.6	33.4 ± 12.7
EF	23.4 ± 6.9	22.2 ± 6.9	26.0 ± 6.8
PCWP	21 [17,29]	22 [18,32]	21 [12, 23]
eGFR	48 [37, 59]	50 [40,60]	35 [30, 40]
Atrial fibrillation	7 (44)	5 (42)	2 (33)
Beta-blocker	14 (89)	10 (83)	4 (67)
Hydralazine	2 (13)	1 (8.3)	1 (17)
Nitrate	2 (13)	1 (8.3)	1 (17)
MCA	10 (63)	6 (50)	4 (67)
Loop diuretic	15 (94)	11 (92)	4 (67)
Thiazide diuretic	5 (31)	3 (25)	2 (33)

BMI, body mass index; EF, ejection fraction; eGFR, estimated glomerular filtration rate; MCA, mineralocorticoid antagonist; PCWP, pulmonary capillary wedge pressure; TPG, trans-pulmonary gradient.

Descriptive statistics summarizing baseline demographic, haemodynamic, and medication data in all patients and in groups defined by $TPG \geq 12$. Data are presented as mean \pm standard deviation when normally distributed and as median [interquartile range] when not normally distributed. Medication frequency is presented as number (percentage). Haemodynamic data were obtained at time of CardioMEMS implantation.

There was a significant decrease in PAMP, pulmonary artery systolic pressure, and pulmonary artery diastolic pressure associated with sacubitril/valsartan initiation (Table 2, Figure 1). The median (IQR) changes in PAMP, pulmonary artery systolic pressure, and pulmonary artery diastolic pressure after sacubitril/valsartan initiation were -3.6 ($-9.8, -0.7$) mmHg ($P < 0.001$), -6.5 ($-15.0, -2.0$) mmHg ($P = 0.001$), and -2.5 ($-5.7, -0.7$) ($P = 0.001$), respectively.

At CardioMEMS implantation, six patients had a TPG ≥ 12 . The median (IQR) pulmonary vascular resistance (PVR) at baseline was significantly higher in this group compared with the rest of the cohort: 357 (320, 548) vs. 137 (73, 172) dynes respectively, $P = 0.001$. Pulmonary capillary wedge pressure did not differ significantly between the high and low TPG groups (21 (12, 23) vs. 22 (18, 32) mmHg, respectively, $P = 0.32$).

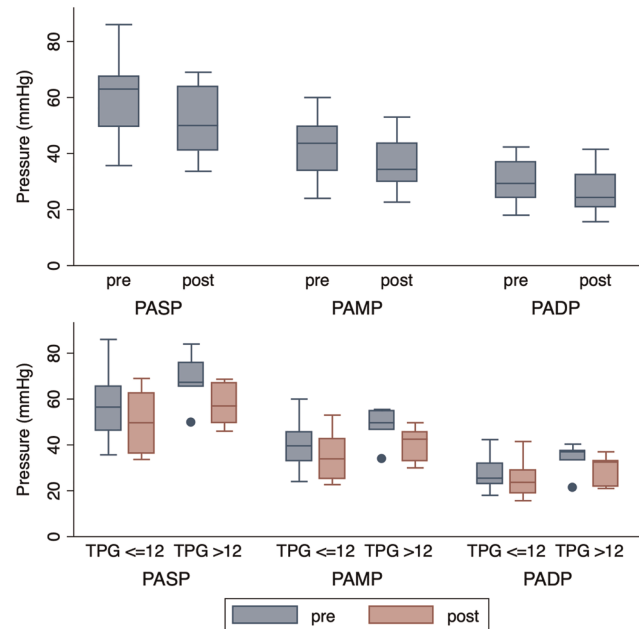
Patients demonstrated declines in PAPs after sacubitril/valsartan initiation regardless of their baseline TPG, with median (IQR) PAMP change of -4.5 ($-9.8, -3.3$) mmHg in the high TPG group and a median (IQR) change of -2.5 ($-10.4, -0.7$) mmHg in the low TPG group (Table 2, Figure 1). Based on repeated-measures ANOVA, there was no significant association between TPG group and magnitude of PAMP changes ($F(1,16) = 0.49$, $P = 0.49$).

Eleven (64.7%) patients, including the majority (5/6) of the high TPG patients, demonstrated a 'hyperacute response', which we defined as a >1 standard deviation reduction in PAMP within 48 h of sacubitril/valsartan initiation. Baseline characteristics of this sub-group did not differ significantly from the other patients, and there was no significant difference in PAPs or PVR as measured at right heart catheterization between the groups.

Discussion

In this observational study, the combination drug sacubitril/valsartan significantly and acutely reduced PAPs in ambulatory patients with HFrEF and elevated PAPs. This effect was seen in patients with low TPG and relatively normal PVR and in those with elevated TPG and PVR.

Figure 1 Pulmonary artery pressure changes after sacubitril/valsartan exposure. A box plot illustration of pulmonary artery pressures pre-sacubitril/valsartan and post-sacubitril/valsartan initiation. The box ranges indicate 25th/50th/75th quartiles. Dots indicate outside values. The plot above indicates pulmonary artery pressures pre and post initiation while the plot below indicates pulmonary artery pressures pre-initiation and post-initiation, divided into groups based on TPG ≥ 12 . PADP, pulmonary artery diastolic pressure; PAMP, pulmonary artery mean pressure; PASP, pulmonary artery systolic pressure; TPG, trans-pulmonary gradient.



The prevalence of PH in HF is reported to be 40–75% as diagnosed with right heart catheterization.^{6,7} PH in patients with HFrEF is associated with considerably increased morbidity and mortality.⁸ This association has been specifically confirmed in CardioMEMS-implanted HF patients, where those with concomitant PH were found to have higher rates of HF-related hospitalizations and mortality compared with those patients without.⁶ While the presence of PH with HFrEF has prognostic importance, no PH directed therapies have been demonstrated to clearly improve clinical outcomes in these patient.⁷

Table 2 Pulmonary pressure changes

	All patients $N = 18$			TPG ≤ 12 ($n = 12$)			TPG > 12 ($n = 6$)		
	Pre-initiation	Median change	P value	Pre-initiation	Median change	P value	Pre-initiation	Median change	P value
PAMP	43 (34, 50)	-3.6 ($-9.8, -0.7$)	<0.001	40 (33, 46)	-2.5 ($-10.4, -0.7$)	0.013	48 (34, 55)	-4.5 ($-9.8, -3.3$)	0.028
PASP	61 (50, 67)	-6.5 ($-15.0, -2.0$)	0.001	57 (46, 65)	-5.0 ($-14.3, -1.7$)	0.015	66 (50, 76)	-7.8 ($-17.0, -4.3$)	0.035
PADP	28 (22, 37)	-2.5 ($-5.7, -0.7$)	0.001	26 (23, 32)	-2.5 ($-6.3, -0.5$)	0.013	35 (21, 38)	-2.8 ($-4.5, -1.0$)	0.028

PADP, pulmonary artery diastolic pressure; PAMP, pulmonary artery mean pressure; PASP, pulmonary artery systolic pressure; TPG, trans-pulmonary gradient.

Pulmonary artery pressure data pre-sacubitril/valsartan initiation, in all patients and in groups defined by trans-pulmonary gradient (TPG) ≥ 12 . Data are presented as median (interquartile range). P values were obtained from Wilcoxon signed-rank testing.

Preclinical HF models have shown reverse remodelling, improved myocardial structure and function, and reduced left ventricular end-diastolic pressure in animals exposed to sacubitril/valsartan compared with either valsartan or placebo.^{9,10} These effects have also been demonstrated among HFrEF patients treated with sacubitril/valsartan.¹¹ Other unique effects of this drug combination are its early and sustained effect on increased natriuresis and diuresis, through increased levels of natriuretic peptides.¹ These mechanisms may explain the reduction in PAPs observed in our cohort through an amelioration of left heart-related, post-capillary PH. However, there is also considerable evidence supporting a direct role of natriuretic peptides and neprilysin inhibition on pulmonary vascular tone.

Natriuretic peptides are secreted and degraded in the lungs, and a number of studies have shown that their concentration is increased in the setting of PH.¹² In a study using a rodent model of hypoxemia-induced PH, sacubitril/valsartan was shown to significantly reduce right ventricular pressure and right ventricular dilatation.¹³ Zern *et al.* described five inotrope-dependent HFrEF patients listed for heart transplant in whom sacubitril/valsartan initiation resulted in reduced PVR within 24 h.¹⁴ A proof of concept trial of acute neprilysin inhibition for PAH demonstrated a swift 14% fall in PVR.¹⁵ An analogous response may underlie the acute declines seen in our study. The strong correlation between PH and the risk of morbidity and mortality in HF may broaden the implication of these findings.^{6,7}

This study is limited chiefly by its small size and retrospective nature. The observation window was short in duration,

and due to adjustments in other therapies over the long term, we could not determine if these changes were sustained. Additionally, the pre-capillary and post-capillary PH vs. post-capillary PH distinction was made at the time of CardioMEMS implantation, and some patients designated as post-capillary PH may have progressed to combined pre-capillary and post-capillary PH prior to sacubitril/valsartan initiation. Despite such limitations, our findings suggest an attribute of sacubitril/valsartan deserving of more investigation.

In summary, an acute fall in PAPs was demonstrated with initial transition to sacubitril/valsartan from ACEI or ARB. Additional studies are needed to define the clinical relevance of this observation and to elucidate its therapeutic implications.

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Conflict of interest

Dr David M Shavelle is a consultant for Abbott Vascular, Inc. All other authors report no conflict of interest and have no financial disclosures. This research received no external funding support.

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