Impact of Sacubitril/Valsartan on Right Heart Failure

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Summary
Sacubitril/valsartan improves mortality and morbidity in patients with heart failure with reduced ejection fraction. However, its impact on right heart failure remains unknown. We experienced a 70-year-old man who was started on sacubitril/valsartan to treat his right heart failure with moderate tricuspid regurgitation. Following the 3-month sacubitril/valsartan treatment, a functional and geological improvement was observed in the right heart as well as amelioration of his congestive symptoms. Sacubitril/valsartan might improve right heart failure in addition to conventionally-proven left heart failure. Further large-scale studies are warranted to validate our findings.

Key words: Neprilysin inhibitor, Chronic heart failure, ARNI

The PARADIGM-HF trial demonstrated that sacubitril/valsartan was superior to enalapril in improving the composite endpoint of cardiovascular death and heart failure readmissions in patients with heart failure with reduced ejection fraction. Sacubitril/valsartan activates the natriuretic peptide system by inhibiting neprilysin and suppresses the renin-angiotensin-aldosterone system. Observational studies have demonstrated that sacubitril/valsartan ameliorates left ventricular diastolic dysfunction, facilitates left ventricular reverse remodeling, improves exercise capacity, and reduces the costs of hospitalization.

However, little is known about the impact of sacubitril/valsartan on right heart failure. Given the physiological mechanism, sacubitril/valsartan might also be effective in patients with right heart failure. We experienced a patient who received sacubitril/valsartan to treat his right heart failure.

Case Report

On admission: A 70-year-old man, previously hospitalized twice to treat decompensated heart failure with preserved ejection fraction probably due to hypertensive heart disease and chronic atrial fibrillation, was admitted to our institute complaining of dyspnea on effort, appetite loss, and bilateral edema in his lower limbs. He was assigned to New York Heart Association functional class III. He was taking 1.25 mg of bisoprolol, 2.5 mg of enalapril, 25 mg of eplerenone, 20 mg of furosemide, and 15 mg of tolvaptan. He also required intermittent IV furosemide administration at every clinic visit.

He was 166 cm tall and his body weight was 69 kg. His blood pressure was 103/72 mmHg and pulse rate was 81 bpm (irregular). Chest X-rays showed a cardio-thoracic ratio of 58%. He had pitting edema in both lower limbs.

The serum total bilirubin level was 2.2 mg/dL, estimated glomerular filtration ratio was 50 mL/minute/1.73 m², and plasma NT proB-type natriuretic peptide level was 577 pg/mL.

Transthoracic echocardiography revealed a left ventricular end-diastolic diameter of 36 mm and left ventricular ejection fraction of 60%. The tricuspid annular plane systolic excursion was 11.9 mm, the right ventricular fractional area change 34.2%, the right atrial area 55.6 cm², and the right ventricular end-diastolic area was 27.2 cm² (Figure 1A). The tricuspid regurgitation grade was moderate and the inferior vena cava diameter was 30 mm without any respiratory change (Figure 2A).

In-hospital course: Following the 2-day IV furosemide therapy, an invasive hemodynamic assessment was performed. Coronary angiography showed no significant stenosis in his coronary artery. There was no in-stent restenosis in the left anterior descending artery. Right heart catheterization showed the mean right atrial pressure was 10 mmHg, pulmonary capillary wedge pressure 11 mmHg, cardiac index 1.97 L/minute/m², and pulmonary artery pulsatility index was 1.2, and there was no dip and plateau sign in the right ventricular pressure wave.

Two days following the termination of enalapril, 100 mg of sacubitril/valsartan was initiated. His systolic blood pressure remained around 100 mmHg without any symptoms. The estimated glomerular filtration ratio and serum potassium level remained unchanged. He was discharged on day 5.

Three months follow-up: Medications remained unchanged during the observational period, except for the termination of intermittent IV furosemide. His dyspnea...
and appetite loss improved to New York Heart Association functional class II. Body weight decreased to 68 kg (-1 kg from the index discharge). His cardio-thoracic ratio in the chest X-rays decreased to 54%. The plasma NT proB-type natriuretic peptide level remained at 538 pg/mL, serum total bilirubin decreased to 1.2 mg/dL, and his estimated glomerular filtration ratio increased to 56 mL/minute/1.73 m².

Follow-up transthoracic echocardiography showed the left ventricular end-diastolic diameter was 34 mm and the left ventricular ejection fraction was 67%. His tricuspid annular plane systolic excursion improved to 12.5 mm and the right ventricular fractional area change also increased to 38.2%. The right atrial area decreased to 52.1 cm² and the right ventricular end-diastolic area also decreased to 25.8 cm² (Figure 1B). The tricuspid regurgitation grade improved to mild to moderate and the inferior vena cava diameter remained 28 mm, but the respiratory change recovered (Figure 2B). Given the extensive improvement in his heart failure symptoms, he decided not to undergo follow-up hemodynamic assessments.

Discussion

Decrease in preload on right ventricle: We observed an improvement in right heart failure during the 3-month sacubitril/valsartan therapy, secondary to the hypertensive left heart disease. Several mechanisms have been hypothesized, but one of the dominant effects of a neprilysin inhibitor, such as sacubitril, would be a decrease in preload on the right ventricle due to natriuresis and venous dilatation. In our patient, body weight decreased by 1 kg and

Figure 1. Four-chamber echocardiography at baseline (A) and 3 months following the administration of sacubitril/valsartan (B). RA indicates right atrium; and RV, right ventricle.

Figure 2. Color Doppler echocardiography showing tricuspid regurgitation (white arrow) at baseline (A) and 3 months following the administration of sacubitril/valsartan (B).
his right heart failure symptoms improved following the 3-month sacubitril/valsartan therapy.

**Improvement in renal function:** Renal function improved slightly, probably due to the discontinuation of intermittent IV furosemide administration owing to the natriuresis of the neprilysin inhibitor. An improvement in renal function would ameliorate systemic congestion and heart failure symptoms, like in our patient (i.e., improvement in cardio-renal syndrome). Longer treatment might be required to achieve further improvement in renal function.

**Reverse remodeling of the right ventricle:** We observed both functional and geological reverse remodeling in the right heart during the 3-month sacubitril/valsartan therapy, and not the left heart, although they were partial. Reverse remodeling in the left ventricle during sacubitril/valsartan therapy has been reported, and most likely is a result of suppression of the renin-angiotensin-aldosterone system and sympathetic nerve activity and an afterload reduction by arterial dilatation. However, few studies have investigated the impact of sacubitril/valsartan on the right heart.

Correale and colleagues observed an improvement in right ventricular function in patients with reduced left ventricular ejection fraction. It is uncertain whether the improvement in right ventricular function was derived secondarily from the left ventricular reverse remodeling (afterload reduction in right ventricle) or directly from the right ventricular reverse remodeling.

**Future concerns:** Further studies are warranted to validate our findings by investigating patients with pure right heart failure. Of note, the efficacy of sacubitril/valsartan might vary depending on the etiology and severity of the heart failure. Our patient had secondary right heart failure probably due to transient pulmonary congestion that was normalized by heart failure therapy. On the contrary, severe ischemic cardiomyopathy with a broad scar in the right ventricle might be refractory to sacubitril/valsartan. The degree of reverse remodeling in the right heart was partial in our patient. As observed in left heart failure, patients with less advanced right heart failure may be more suitable candidates for sacubitril/valsartan therapy.

**Disclosure**

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