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Journal

Proceedings of UCLA Health, 26(1)

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Publication Date

2023-01-11

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CLINICAL VIGNETTE

B-type Natriuretic Peptide as a Diagnostic Marker in a Hospitalized Patient with Heart Failure Resuming Sacubitril/Valsartan

Stephanie Pintas, BA and Nasser El-Okdi, MD

Introduction

Sacubitril/Valsartan is a medication which promotes natriuresis in patients with chronic heart failure with reduced ejection fraction <40% (HFrEF). The pathophysiology of HFrEF is multifactorial and includes left ventricular systolic dysfunction with eccentric hypertrophy. Initially this leads to stretching of the ventricle and compensatory release of both atrial natriuretic peptide (ANP) and B-type natriuretic peptide (BNP) to enhance natriuresis.[1] Over time, this compensatory mechanism fails, and the decreased cardiac output leads to poor perfusion of end-organs and clinical decompensation.[1] Paradoxically, the kidneys recognize poor perfusion as low intravascular volume and upregulate the renin-angiotensin-aldosterone system (RAAS). This leads to an increase in vasoconstriction, blood pressure and sympathetic activation, further worsening forward flow from the heart and inducing volume overload. Eventually, RAAS upregulation induces cardiac remodeling, further decreasing ventricular functionality.[1-3]

Sacubitril/Valsartan is in a class of drugs called angiotensin receptor neprilysin inhibitors (ARNI). Sacubitril acts as a neprilysin inhibitor, increasing endogenous levels of ANP and BNP to promote diuresis, prevent cardiac modeling and decrease blood pressure (Figure 1).[1] The improvement in blood pressure occurs mainly through vasodilatory effects and attenuation in aldosterone levels to decrease sodium retention.[1] Valsartan acts mainly as an angiotensin II receptor blocker, decreasing levels of aldosterone to improve blood pressure and prevent cardiac remodeling.[1]

Prognostic Usefulness of BNP

During hospitalizations for acute heart failure exacerbations, BNP should not be used to guide management decisions for diuretics, which should be clinically based. However, BNP can provide prognostic risk of mortality and readmission. One study examining BNP levels at admission and discharge reported cut-off values above 1699 pg/ml on admission and 434.5 pg/ml at discharge were significantly associated with readmission within one year.[4] Further, BNP levels $\geq$431 pg/ml one month after discharge was associated with increased likelihood of death or heart failure related hospitalization at 1 year ($p < 0.001$).[5]

Special consideration must be taken in patients prescribed an ARNI. Sacubitril can increase endogenous levels of BNP, thus elevating blood concentration and may influence clinicians' assessment of volume overload status (Figure 1). In the PARADIGM-HF trial, patients randomized to sacubitril/valsartan had a 19% increase in BNP with 18% of patients with doubling and 6% tripling of BNP levels.[3]

N-terminal prohormone BNP (NT-proBNP) is a non-active prohormone released from the same molecule that produces BNP. Both BNP and NT-proBNP are released in response to pressure changes inside the heart, however NT-proBNP is not a substrate of neprilysin inhibition. In the PARADIGM-HF trial, NT-proBNP decreased by 28%, with <3% of patients having doubling or tripling levels.[3] The TRANSITION study also reported a 28% reduction in NT-proBNP in HFrEF patients started on sacubitril/valsartan in the hospital with >40% lower risk of rehospitalization or cardiovascular death at 26 weeks ($p = 0.007$).[6]

BNP will increase compared to NT-proBNP after sacubitril/valsartan initiation. However, both are comparable prognostic indicators of future cardiovascular events, with higher levels of both BNP and NT-proBNP correlating with increased cardiovascular events.[3] BNP elevation should not be attributed to drug initiation alone as higher levels correlate with worse outcomes. In the PIONEER-HF trial, both NT-proBNP and BNP levels decreased 4-8 weeks after in-hospital initiation of sacubitril/valsartan.[7] This effect is likely explained by improvement in heart failure disease activity. BNP levels should reach steady-state or decline after several months of maintenance dosing. PARADIGM-HF trial, demonstrated this at 8 months of treatment.[3]

This case study illustrates the management of a patient with HFrEF with acute exacerbation of heart failure. Further, the effect of initiating sacubitril/valsartan on BNP levels is discussed with the clinical course.

Patient Summary

The patient is an 83-year-old African American male with severe peripheral artery disease admitted with worsening right lower extremity pain and gangrenous toes. Pat medical history includes: right femoral to anterior tibial artery bypass, left femoral to posterior tibial artery bypass and multiple bilateral angioplasties and thrombolyses. Other chronic medical problems include: Stage IIIb, chronic kidney disease, coronary

artery disease with a drug eluting stent, and heart failure with reduced ejection fraction (25-30%). He was admitted with worsening right lower extremity pain. He was found to have critical leg ischemia from occlusion of the right femoral to anterior tibial artery bypass. He initially underwent angioplasty with thrombolysis and stenting of the bypass and subsequent transmetatarsal amputation of the right foot. Unfortunately, his right femoral to tibial bypass re-occluded requiring a second thrombolysis. This was complicated by retroperitoneal bleeding requiring several blood transfusions. Due to the multiple blood transfusions, the patient became acutely volume overloaded requiring IV furosemide diuresis with transition to oral furosemide. Goal-directed medical therapy (GDMT) was resumed for management of the patient's heart failure and he was discharged to SNF after one month. Unfortunately 2 months later, he was readmitted with bacteremia severe volume overload and expired.

Date	Significant Events
04/07/2022	Patient admitted.
04/08/2022	**BNP 2,819 pg/mL.** Receives furosemide and metolazone.
04/10/2022	Thrombolysis of right bypass graft.
04/12/2022	Right lower extremity angiogram with angioplasty and stent of proximal and distal bypass anastomoses. **BNP decreases to 1,047 pg/mL.**
04/14/2022	Right transmetatarsal amputation (TMA). Furosemide held.
04/15/2022	tPA lysis and catheter placement of right bypass graft with significant bleeding. Furosemide held.
04/16/2022	Lysis of distal anterior tibial artery with 1 unit of packed red blood cells (pRBCs) transfused. Patient transferred to ICU.
04/18/2022	**Transthoracic echocardiogram with ejection fraction of 25-30%.**
04/19/2022	Receives 5 units of pRBCs. **BNP decreases to 334 pg/mL.**
04/20/2022	CT abdomen/pelvis angiography demonstrates bilateral retroperitoneal hematomas with prompt embolization.
04/23/2022	**BNP increases to 2,720 pg/mL. Carvedilol resumed.**
04/25/2022	Patient transferred to Medicine floor. IV furosemide increased.
04/26/2022	**Patient resumes ½ tablet of Sacubitril-valsartan 49-51 mg once daily.** IV furosemide increased.
04/27/2022	**BNP increases to 3,613 pg/mL.** IV furosemide increased.
04/28/2022	Receives 1 blood transfusion. Switched from IV furosemide to oral furosemide, **resumed spironolactone.**
04/29/2022	Receives 1 blood transfusion. **Resumed dapagliflozin.**
05/05/2022	Patient transferred to skilled nursing facility.
07/15/2022	Patient admitted with hypothermia, with *Stenotrophomonas maltophilia* bacteremia of right TMA.
07/25/2022	Patient develops cardiac arrest with pulseless electrical activity and expires.

Table 1. Hospital Course

Discussion

Our patient had multiple medical comorbidities with clinically complex management of HFrEF. The patient's admission BNP was 2,819 pg/mL and increased to 3,613 pg/mL prior to discharge (Figure 3). Although the patient's sacubitril/valsartan was restarted, it is unlikely that resuming this medication had a significant impact on the increasing BNP. The patient was restarted on low dos sacubitril/valsartan 49/51 mg, which is a lower dose than used in previous trials which started patients on 200 mg twice daily.[3,6,7] These trials reported a clinically significant rise in BNP several weeks after initiation with sacubitril/valsartan. Resuming sacubitril/valsartan is unlikely to significantly increase BNP in this patient after one dose. While the rise in BNP in this case is multifactorial, impacting factors include multiple blood transfusions, the patient's age and medical comorbidities, impaired kidney function, and a poor ejection fraction. The BPN elevation is more likely a marker of clinical decompensation, supported by increased weight at discharge (Figure 2) and expiration at a subsequent hospitalization.

Conclusion

BNP levels may not be an accurate measurement of successful diuresis in HFrEF patients with acute decompensation and volume overload when initiating sacubitril/valsartan. It is important to assess BNP levels at the beginning and end of a hospitalization as a predictor of successful diuresis, risk of future hospitalizations, and 1-year mortality. While BNP levels may rise with sacubitril/valsartan, this effect should not be attributed to medication alone. BNP levels should stabilize or decrease after long-term treatment with sacubitril/valsartan. Careful consideration must be exercised when interpreting BNP levels in HFrEF patients started on sacubitril/valsartan during an acute heart failure exacerbation. Initial increase in BNP warrants clinical assessment of possible worsening disease status. Higher BNP and NT-proBNP at hospital discharge both correlate with worsened clinical outcomes for HFrEF patients taking sacubitril/valsartan. If available, NT-proBNP concentration may be a more useful diagnostic marker as it is not degraded by neprilysin. Overall, BNP concentration is only one factor predicting HFrEF disease status in patients taking sacubitril/valsartan. Other factors, including demographics, medication dosing and medical comorbidities must be considered when determining the clinical status and medical management of a patient with heart failure with reduced ejection fraction.

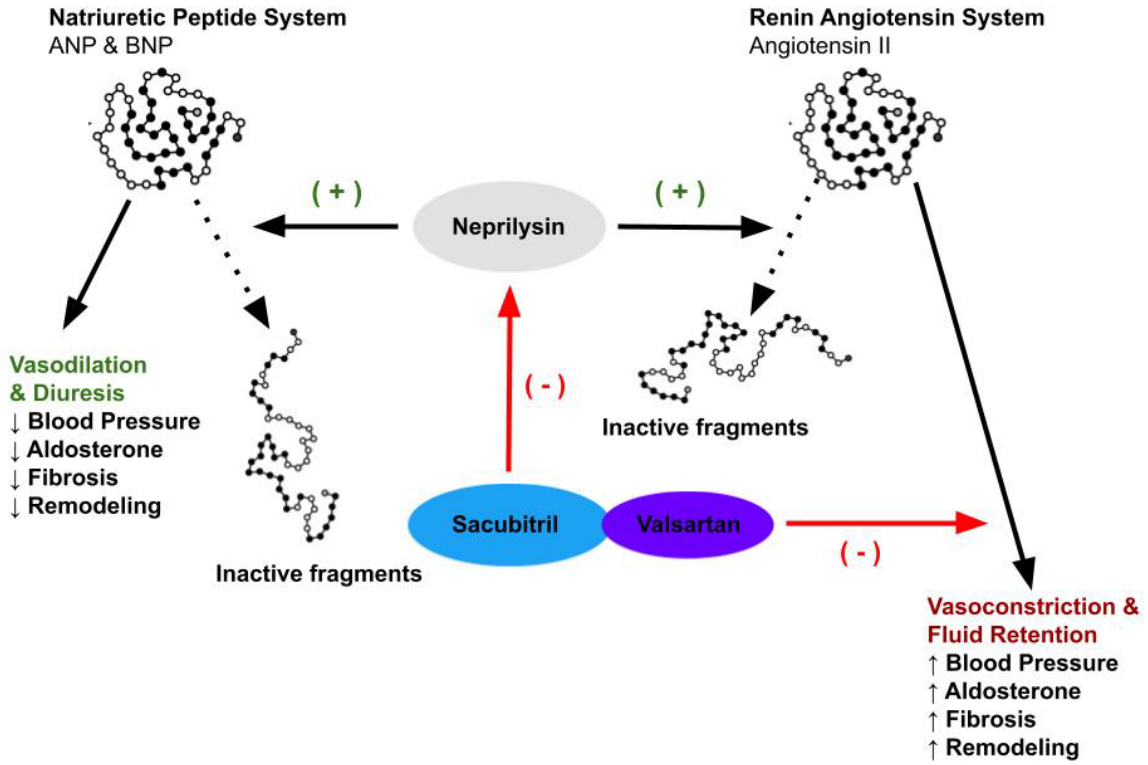

Figure 1. Unique Mechanism of Sacubitril/Valsartan. Sacubitril is a neprilysin inhibitor, increasing endogenous levels of ANP and BNP. It prevents breakdown of angiotensin II, thus an ARB (valsartan) must be used in combination. Because sacubitril increases levels of bradykinin, it must not be combined with ACE inhibitors due to the increased risk of angioedema.

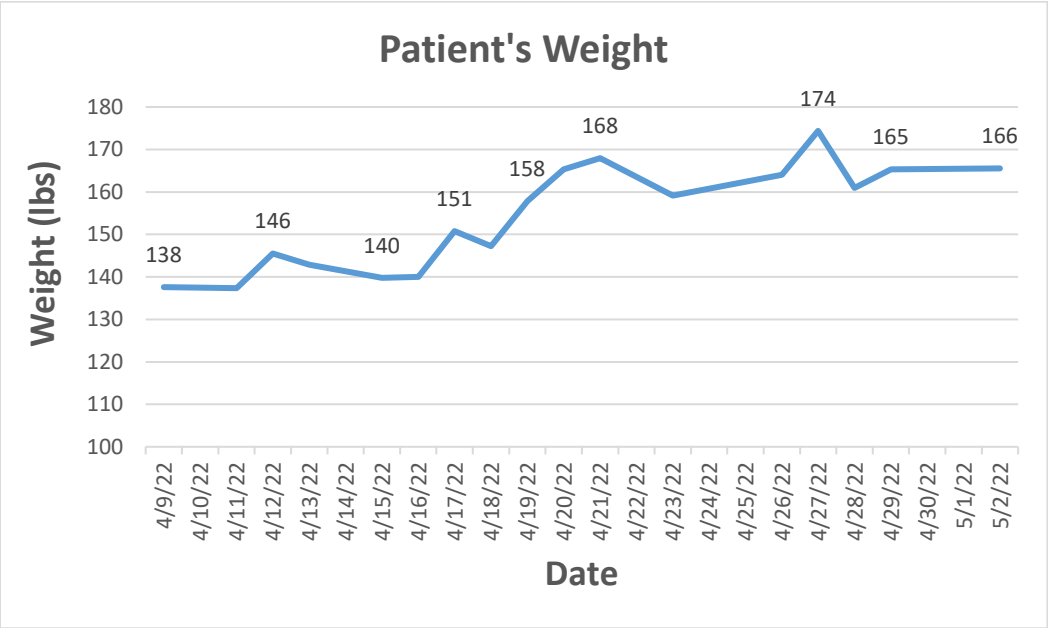

Figure 2. Weight throughout hospital admission. Despite diuresis, the patient's general uptrend in weight is one sign of worsening volume status.

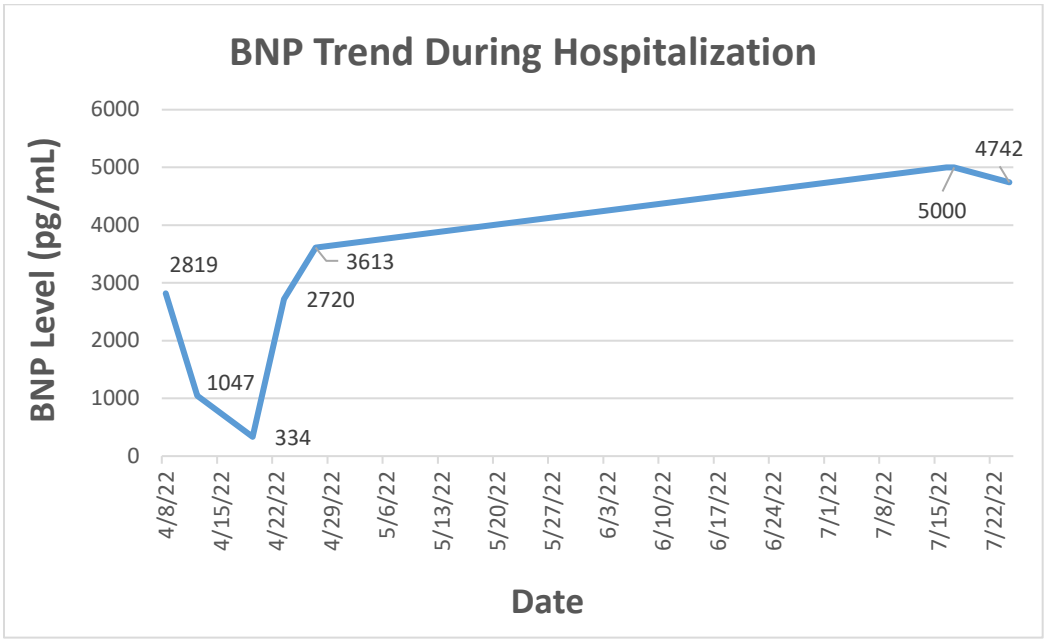

Figure 3. Trend in BNP During Hospitalization.

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