CASE REPORT

Remote monitoring with cardiac implantable electronic device to follow up pharmacodynamic effects of sacubitril/valsartan treatment: A case report

Sacubitril/valsartan tedavisinin farmakodinamik etkilerinin kardiyak takılabilir elektronik cihaz aracılığı ile uzaktan takibi: Bir olgu sunumu

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Summary– Cardiac implantable electronic devices include remote monitoring tools intended to guide heart failure management. These tools allow for observation of some physiological functions, such as intrathoracic impedance (ITI), patient activity (PA), and heart rate variability (HRV). Sacubitril/valsartan is recommended in the current guidelines as foundational therapy for patients with heart failure and reduced ejection fraction. However, the effects of sacubitril/valsartan treatment on these physiological parameters remain unclear. To the best of our knowledge, this is the first case objectively documenting improvements in ITI, PA, and HRV values with sacubitril/valsartan treatment.

Özet– Takılabilir kardiyak elektronik cihazlar, kalp yetersizliği yönetimine yardımcı olabilen donanımlar içerir. Bu donanımlar, intratorasik empedans, hasta aktivitesi ve kalp hızı değişkenliği gibi fizyolojik fonksiyonların ölçümüne olanak verir. Güncel kılavuzlar düşük ejeksiyon fraksiyonlu kalp yetersizliğinin tedavisinde sacubitril/valsartan'ı önermektedirler. Bununla birlikte bu ilacın yukarıda sıralanan fizyolojik göstergeler üzerine etkisi bilinmemektedir. Bildiğimiz kadarı ile bu olgu sunumu, sacubitril/valsartan tedavisinin söz konusu fizyolojik göstergeler üzerine olan etkilerinin konu edildiği ilk bilimsel dökümandır.

Cardiac implantable electronic devices (CIEDs) can improve clinical outcomes in selected patients with heart failure and reduced ejection fraction (HFrEF) and can also collect valuable diagnostic information via continuous monitoring of several physiological variables. This information allows for assessment to determine signs of volume overload and to predict the onset of HF exacerbation, as well as monitoring the effects of any particular treatment.[1] Variables that are readily accessible from routine device interrogation include intrathoracic impedance (ITI), patient activity (PA), and heart rate variability (HRV).

The PARADIGM-HF trial demonstrated that sacubitril/valsartan treatment significantly reduced the primary endpoints of cardiovascular mortality, HF hospitalization, and all-cause mortality in patients with symptomatic HFrEF compared with enalapril.[2] Since then, sacubitril/valsartan has been recommended in current guidelines as foundational therapy for patients with symptomatic HFrEF.[3]

However, the temporal relationship between sacubitril/valsartan treatment and

Abbreviations:

ACC	*American College of Cardiology*
AHA	*American Heart Association*
ACEI	*Angiotensin-converting enzyme inhibitor*
ARNI	*Angiotensin receptor-neprilysin inhibitor*
ARB	*Angiotensin receptor blocker*
BNP	*Brain natriuretic peptide*
CIED	*Cardiac implantable electronic device*
ECG	*Electrocardiography*
ESC	*European Society of Cardiology*
HFrEF	*Heart failure with reduced ejection fraction*
HFSA	*Heart Failure Society of America*
HRV	*Heart rate variability*
ICD	*Implantable cardioverter-defibrillator*
ITI	*Intrathoracic impedance*
KCCQ	*Kansas City Cardiomyopathy Questionnaire*
LVEF	*Left ventricular ejection fraction*
MRA	*Mmineralocorticoid receptor antagonist*
PA	*Patient activity*
TTE	*Transthoracic echocardiography*

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these variables has not yet been reported. In this report, CIED interrogation in a patient with HFrEF due to ischemic cardiomyopathy is used to illustrate that relationship.

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A 59-year-old physician with HFrEF presented at the outpatient clinic with exertional dyspnea and fatigue. He had a past medical history of type 2 diabetes mellitus, hyperlipidemia, a coronary artery bypass graft operation 8 years prior, and had undergone dual chamber implantable cardioverter-defibrillator (ICD; Itrevia 5 DR-T, Biotronik, Berlin, Germany) implantation in May 2017. He was taking ramipril 10 mg and atorvastatin 40 mg daily, carvedilol 12.5 mg twice daily, furosemide 40 mg daily, spironolactone 25 mg daily, aspirin 100 mg daily, and intensive insulin therapy. The blood pressure measurement was 125/80 mm Hg, with 14 respirations per minute, and his heart rate was recorded as 88 beats per minute. He had a regular rhythm, apical 2/6° systolic murmur. A pulmonary exam revealed no inspiratory crackles. The extremities were without edema. An electrocardiogram (ECG) showed a sinus rhythm with rare premature ventricular complexes and poor R wave progression along with precordial leads. Transthoracic echocardiography (TTE) demonstrated an akinetic left ventricular septum, anterior wall, and apex with moderate mitral regurgitation. The left ventricular ejection fraction (LVEF) was calculated as 32% using the modified Simpson method. ICD interrogation demonstrated normal pacing, sensing, and therapy values with no preceding antitachycardia pacing or shock event. Counter histogram also revealed no atrial or ventricular pacing (Fig. 1). Serum renal and liver function tests were within normal limits, and the B-type natriuretic peptide level was 105 pg/mL (normal <35 pg/mL). After a comprehensive evaluation, the ramipril 10 mg treatment was replaced with sacubitril/valsartan 97/103 mg twice daily after 2 days of a washout period (June 2017). The patient returned to the outpatient clinic for a scheduled visit 6 months later and reported improvement in his symptoms of exertional dyspnea and fatigue as well as increasing his ordinary physical activities, such as jogging and cycling. No significant alteration was observed in a physical examination or ECG and TTE evaluations. Interrogation of his ICD revealed a stable increase in ITI (from 51 to 73 ohm) and HRV (from 42 to 66 millisecond) values (Fig. 2). This was accompanied by a marked improvement in the PA level (from 5% to13%/day). The patient reported no hospitalization

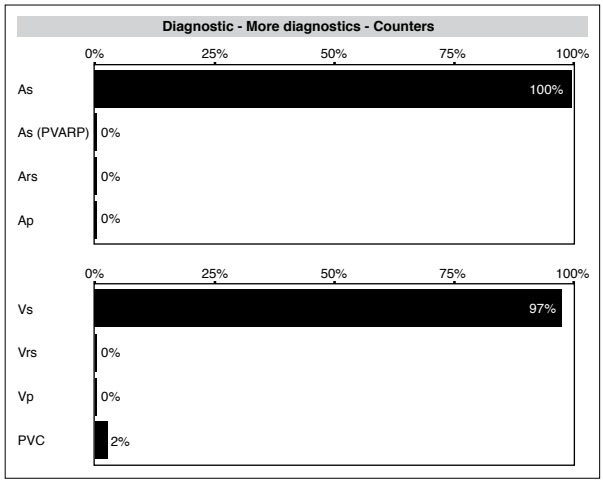

Figure 1. Event counter histogram. As denotes atrial sensing event, Vs denotes ventricular sensing event, and PVC denotes premature ventricular contraction event.

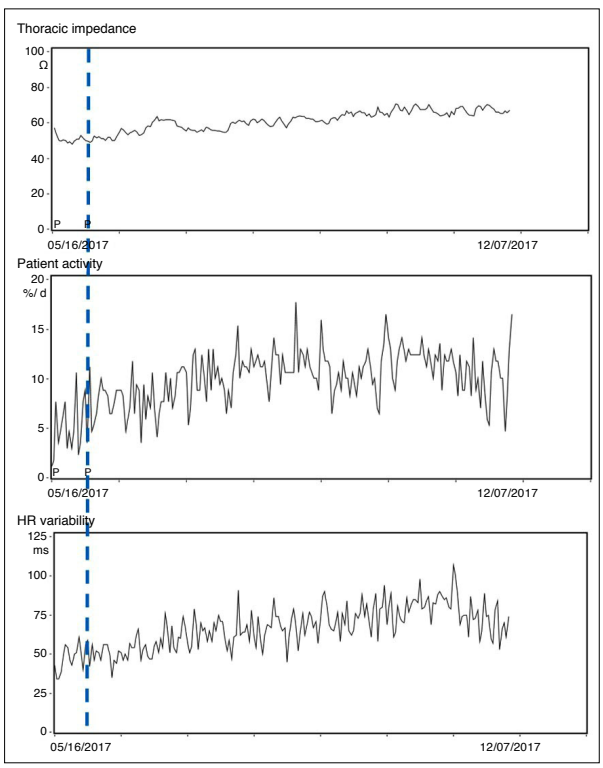

Figure 2. Temporal trends of intrathoracic impedance, heart rate variability, and patient activity values (horizontal lines). Vertical line represents the date of sacubitril/valsartan initiation.

event, change in drug therapy, or adverse drug reaction related with sacubitril/valsartan treatment during the 6-month period. Current treatment was continued without any alteration and another visit was scheduled for 6 months later.

DISCUSSION

Dual inhibition of the renin-angiotensin-aldosterone system and neprilysin represent a novel approach to treating patients with HFrEF. The PARADIGM-HF trial demonstrated the superiority of sacubitril/valsartan to enalapril in hard outcomes (death from any cause and death from cardiovascular causes).[2] In their 2016 focused update on HF guidelines, the American College of Cardiology (ACC), the American Heart Association (AHA), and the Heart Failure Society of America (HFSA) recommended replacing an angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blocker (ARB) with an angiotensin receptor-neprilysin inhibitor (ARNI) in patients with chronic symptomatic HFrEF, New York Heart Association class II or III, currently tolerating an ACEI or ARB, to further reduce morbidity and mortality (class I recommendation).[3]

On the other hand, the 2016 European Society of Cardiology (ESC) HF guidelines recommend the use of sacubitril/valsartan as an ACEI replacement to further reduce the risk of death and HF hospitalization in ambulatory patients with HFrEF (LVEF <35%) who remain symptomatic despite optimal treatment with ACEI, a beta-blocker, and a mineralocorticoid receptor antagonist (MRA) (class IB recommendation).[4] In contrast to ACC/AHA/HFSA guidelines, the ESC guidelines specify having an LVEF cut-off of 35% prior to initiation of sacubitril/valsartan, initial treatment with an MRA, and the patient should have elevated natriuretic peptide levels (i.e., plasma brain natriuretic peptide [BNP] ≥150 pg/mL) before initiating use of an ARNI.[4] ARNI treatment was initiated in this patient based on the ACC/AHA/HFSA guidelines, despite a BNP value that was below to ESC guideline cut-off. The PARADIGM Trial also demonstrated the greater effectiveness of ARNIs compared with enalapril with respect to physical capacity and symptoms and quality of life, which was measured with the Kansas City Cardiomyopathy Questionnaire (KCCQ).[2] Although previous studies have proven the validity of the KCCQ score in the HFrEF population, it has limitations, such as the absence of appropriate reference standards for the various domains, and patient perspective (subjectivity). The score also has a vulnerability in terms of physician-originated bias. Researchers and many physicians often rely on physiological variables, such as LVEF or N-terminal pro-BNP levels to monitor therapy in HFrEF population. However, such surrogate markers may not always be as useful as expected, due to lower temporal resolution and vulnerability to confounding factors.

CIEDs include remote monitoring tools intended to guide heart failure management. These tools allow for daily observation of particular physiological functions.[2] They are objective measurements with high temporal resolution that permit analysis of trends. In this case, the patient's self-reported improvements in symptoms and PA level were objectively confirmed by CIED monitoring functions. To the best of our knowledge, this is the first case documenting improvements in ITI, PA, and HRV levels with sacubitril/valsartan treatment using CIED reporting. These hypothesis-generating findings provide the rationale for further study focused on the effects of sacubitril/valsartan treatment in HFrEF patients who have a CIED. The CHILISALT Study (Changes in Intrathoracic Impedance during Sacubitril/Valsartan Treatment; NCT03359967) will be 1 study to obtain more information in this patient population.

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REFERENCES

1. Hawkins NM, Virani SA, Sperrin M, Buchan IE, McMurray JJ, Krahn AD. Predicting heart failure decompensation using cardiac implantable electronic devices: a review of practices and challenges. Eur J Heart Fail 2016;18:977–86. [CrossRef]
2. McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, et al.; PARADIGM-HF Investigators and Committees. Angiotensin-neprilysin inhibition versus enalapril in

heart failure. N Engl J Med 2014;371:993–1004. [CrossRef]
3. Papadimitriou L, Hamo CE, Butler J. Heart failure guidelines: What's new? Trends Cardiovasc Med 2017;27:316–23.[CrossRef]
4. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, et al.; Authors/Task Force Members; Document Reviewers. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail 2016;18:891–975.[CrossRef]

Keywords: Cardiac implantable electronic devices; heart failure; heart rate variability; intrathoracic impedance; physical activity; remote monitoring; sacubitril/valsartan.

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