The power of optimal medical therapy using Angiotensin Receptor-Neprilysin inhibitor (ARNI) in acute decompensated heart failure, sparing a critical patient open-heart surgery with a device therapy

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Abstract

Timely use of Sacubitril/Valsartan has the potential to significantly improve cardiac function and dramatically reduce secondary mitral regurgitation (MR) severity even in patients presenting with acute decompensated heart failure (HF), not only in compensated chronic HF patients. The outstanding impact of echocardiography is obvious in monitoring improvement of cardiac function and MR severity in patients with heart failure with reduced ejection fraction (HFrEF). We report a relevant case of an elderly patient who presented with acute decompensated HF with severe bi-ventricular dysfunction and severe MR. He was previously on optimal medical therapy (OMT), however still symptomatic. Coronary angiogram (CAG) depicted three vessel coronary artery disease (CAD). Patient advised to undergo coronary artery bypass graft surgery (CABG) with mitral valve repair, then followed by implantation of a cardiac resynchronization therapy defibrillator device (CRT-D) if no LV function improvement observed after revascularization. Patient's ECG showed a QRSd [?] 125 ms, hence a good candidate for CRT. Two weeks after starting Sacubitril/Valsartan the LV EF improved from 15% to 40%. Severe MR reduced to grade II and there was dramatic improvement of patient's symptoms from NYHA class IV to NYHA class I. NT-proBNP reduced from 9,000 pg/ml to 800 pg/ml. Following an elective percutaneous coronary intervention (PCI), LV EF further improved to 50%. The patient was symptoms-free with preserved LV EF on follow up for 18 months later. This case report documents the swift echocardiographic and symptom improvement in an elderly patient with decompensated end-stage HF when Sacubitril/Valsartan started during the acute setting

Introduction

Sacubitril/Valsartan is a first-in-class combination of angiotensin receptor blocker (ARB) and neprilysin inhibitor. It is now recommended for the treatment of chronic heart failure with reduced ejection fraction (HFrEF) that remains symptomatic despite optimal treatment as per international guidelines. (1)

Compared with enalapril, sacubitril/valsartan reduced the composite endpoint of cardiovascular death or HF hospitalization and is recommended as an alternative for angiotensin-converting enzyme inhibitors (ACEI) and (ARB) in patients with HFrEF and New York Heart Association (NYHA) class II–III symptoms. (2, 3)

In the randomized controlled trial PRIME (Pharmacological Reduction of Functional, Ischemic Mitral Regurgitation) sacubitril/valsartan treatment resulted in a greater reduction of Mitral Regurgitation (MR)

associated with HF compared to valsartan alone. (4)

In our patient, who presented with acute decompensated HF, dramatic reduction in secondary MR severity as well as significant left ventricular (LV) function improvement were achieved after using Angiotensin Receptor-Neprilysin inhibitor (ARNI)

Case Report

Herein we describe a case report of a low body weight 74-year old male patient who presented with acute decompensated heart failure (HF) with both end-stage systolic and diastolic HF including right ventricular (RV) failure.

He is previously known to have type II Diabetes Mellitus (DM), Hypertension and previous presumed diagnosis of Dilated Cardiomyopathy (DCM) in another facility on non-optimal medical therapy (OMT) for the past two years.

On presentation patient was orthopneic and in dyspnea NYHA functional class IV over the past 10 days.

Initial work up was done. 2D echo showed severe LV dysfunction, with estimated LV ejection fraction (EF) of 15-20% (Video_1), with global hypokinesia and akinesia of apex, inferior and lateral wall and a picture of ischemic dilated cardiomyopathy (IDCM) with severe RV dysfunction demonstrating interventricular septal flattening more during diastole due to RV volume overload (Video_2, Figure_1) with associated severe pulmonary hypertension (PH) and an estimated systolic pulmonary artery pressure (PAPs) of 80 mm Hg (Figure_2). There was grade IV severe MR (Video_3 & 4, Figure_3 & 4) and torrentially significant tricuspid regurgitation (TR) (Video_5 & 6, Figure_5 & 6) with illustrated hepatic vein systolic flow reversal on Pulsed wave doppler (PWD) (Figure_7, Video_7).

Restrictive pattern grade III diastolic dysfunction with elevated LV filling pressure by Tissue doppler imaging (TDI) was noted (Figure_8 & 9).

Lung ultrasound (LUS) demonstrated frequent B-lines on both lungs (Video_8) denoting pulmonary interstitial edema and volume overload.

The patient was admitted in the coronary care unit (CCU) and started on Frusemide infusion after an IV bolus dose of 40mg, besides Spironolactone, Ramipril, Rosuvastatin, Empagliflozin and Aspirin.

Patient had sinus rhythm on Electrocardiogram (ECG) with Interventricular conduction delay and a duration of QRS complex [?] 125 ms (Figure_10).

Chest X-Ray showed signs of pulmonary congestion (Figure_11).

N-terminal pro B-type natriuretic peptide (NT-proBNP) was over 9,000 pg/ml. Serum potassium 3.8 mmol/L, serum sodium 141 mmol/L, Hemoglobin 14 gm/dl, serum Creatinine 107 Umol/L and calculated creatinine clearance of 45 ml/min.

Patient improved on medical therapy. And then on day four during admission coronary angiography (CAG) was done and revealed triple vessel disease with significant 90% long diffuse tight lesions in proximal to mid left anterior descending (LAD) artery, critical 90% lesion in both obtuse marginal (OM) branches of left circumflex (LCX) artery and chronic total occlusion (CTO) of right coronary artery (RCA) with retrograde filling from LAD and LCX arteries (Video_9 & 10).

In view of severe grade IV MR, triple vessel disease and severe LV and RV dysfunction; we recommended coronary artery bypass graft surgery (CABG) combined with mitral valve repair (MVr), then followed by implantation of a cardiac resynchronization therapy defibrillator (CRT-D) device if no LV function improvement observed after coronary revascularization plus OMT.

Patient had a QRSd [?] 125 ms on ECG, and hence is a good candidate for a CRT-D device therapy after coronary revascularization in case LV dysfunction persisted.

While waiting for myocardial viability stress test to be done before revascularization and with efforts to improve LV function, we started maximally tolerated doses of different ACEI and ARBs including Enalapril, Ramipril and Valsartan, as well as Beta-blockers including Nebivolol, Metoprolol and Carvedilol. This is in addition to Mineralocorticoid receptor antagonists (MRA) and sodium-glucose cotransporter-2 (SGLT-2) inhibitors, aspirin and high doses of loop diuretics.

Patient could not afford Sacubitril/Valsartan due to cost burden.

He experienced recurrent hospitalization due to acute decompensated heart failure. After hospital discharge, he showed up every other day in hospital for Furosemide injection to alleviate his HF symptoms. Patient was in Dyspnea NYHA class IV with symptoms at rest and significant orthopnea and PND with dramatic impairment of his life quality.

Three weeks later during repeated CCU admission Sacubitril/Valsartan was offered to the patient after we ensured a 36-hour washout period which is required when switching from ACEI to Sacubitril/Valsartan. Started on a dose of 24mg/26mg PO BID.

We observed a dramatic improvement in symptoms from NYHA class IV to NYHA class II that occurred 5 days only after starting Sacubitril/Valsartan during CCU setting. Then further improvement to NYHA class I occurred after 2 weeks of treatment.

After discharge from hospital patient was walking 4 kilometers daily with exceptionally good effort tolerance and no symptoms. He stopped showing up in the hospital for Furosemide injections.

In addition, there was a major favorable change in his quality of life.

NT-proBNP reduced from above 9,000 pg/ml on admission to 800 pg/ml after two weeks.

Screening 2D echo on hospital discharge showed dramatic improvement of LV function. LV EF improved from 15-20% to 40-45% with significant reversal of LV remodeling (Video_11, Figure_12).

MR severity improved from grade IV to grade II (Video_12 & 13, Figure_13), and severe TR improved to mild grade I (Video_14, Figure_14) with no hepatic vein systolic flow reversal on PWD. In addition, PAPs fell from 80 mm Hg to normal value of 30 mm Hg (Figure_15).

The patient's diastolic function improved from grade III to grade I with normal LV filling pressure (Figure_16).

Sacubitril/Valsartan dose then increased to 49 mg/51 mg PO BID

Three weeks later, myocardial perfusion scintigraphy using nitrate-augmented ^{99m}Tc-Sestamibi showed evidence of viable myocardial perfusion of the LAD and LCX/OM territories. However, there was non-viable myocardial perfusion in the RCA territory.

Due to the fact that our patient showed improvement of myocardial function and dramatic reduction of MR severity after treatment with Sacubitril/Valsartan, we found that revascularization by percutaneous coronary intervention (PCI) is a more convenient option for the fragile low body weight elderly patient with a much lower overall operative risk than that of surgery, and in addition that he will no longer need MVr for secondary MR.

Elective PCI done successfully to LAD and LCX/OM arteries with no peri-operative events (Video_15 & 16).

The patient showed further improvement of LV function post PCI. LV EF improved from 35-40% to 50% on follow up 2D echo (Video 17). He was completely asymptomatic and with particularly good effort tolerance.

The patient maintained preserved LV EF on follow up for 18 months later while on Sacubitril/Valsartan.

Discussion

Our case is demonstrating the tremendous effect of ARNI on the left ventricular function and remodeling that is noticed in the improvement of the ejection fraction together with the improvement in symptoms.

In 2016, the U.S. Food and Drug Administration (FDA) approved a new drug for the treatment of heart failure, the scientific evidence that has supported the approval of this new drug was mainly obtained from the results of the PARADIGM-HF trial which was a prospective comparison of ARNI with ACEI to determine impact on mortality and morbidity in patients with heart failure. (2)

Then, in 2019 another major trial was published by Velazquez EJ et al. that tested ARNI in patients with acute decompensated heart failure and they concluded that the initiation of ARNI in those patients led to a greater reduction in the NT-proBNP levels as well as less side effects like hypotension, hyperkalemia and angioedema. (5)

Many case reports and case series reports have been published with similar observation of the improved ejection fraction after using ARNI, one of them was published by Pandey et al. in 2017 where he included 60 HFrEF individuals and noticed the improvement of their EF from 27.3% to 37.5% after a period of one year (P<0.001). (6)

Later on, another prospective study was published by Bayard et al. in 2019, he included 52 patients and after only 3 months of follow up he noticed an improvement of the ejection fraction from 32.6 ± 5% to 36 +- 6% ($p < 0.0001$) and this was also associated with improvement of the LV dimensions and volumes. (7)

One of the studies that aimed to evaluate changes in left ventricular ejection fraction (LVEF) in patients with heart failure and reduced LVEF treated with ARNI was recently conducted in Taiwan by Liu EW et al. where he enrolled 93 patients and prescribed ARNI as both first line and second line therapy and he found that the mean LVEF improved from 35 +- 6.1% to 50 +- 8.8% at 6 months use of sacubitril/valsartan ($p < 0.001$). (8)

Conclusion

Appropriate and timely use of Sacubitril/Valsartan has the potential to significantly and swiftly improve LV function even in patients with acute decompensated HF, not only in chronic HF patients.

Based on these improved outcomes, it is necessary to make a change in clinical practice to early implement this lifesaving therapy in acute decompensated HF patients.

Usually when medications improve quality of life, the patient's adherence increases. Our patient was highly adherent to his medications after he experienced the significant improvement of his symptoms.

The outstanding impact of multimodality imaging and precisely 2D Echocardiography is obvious in monitoring improvement of cardiac function and deciding for revascularization

Echocardiography is the most useful test providing immediate information, including improvement of systolic and diastolic function of LV and RV, chamber size, and reduction in severity of valvular regurgitation and pulmonary pressure with OMT including ARNI as in our patient.

A cknowledgement

None.

Statement of Ethics

Patient has given his written informed consent to publish his case (including publication of images).

Disclosure Statement

The authors have no conflicts of interest to declare.

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None.

Author Contributions

Dr. Fady Gerges was treating the patient under his care and performed his echo studies and initiated and modified his medical treatment with regular follow up through 18 months, in addition to admitting the patient in CCU for receiving proper management.

Dr. Austin Komaranchath and **Dr. Faiz Al bakshy** had performed PCI to LCX/OM arteries with revision of manuscript.

Dr. Wissam Al Sahli had performed staged PCI to LAD artery with revision of manuscript.

Dr. Abdallah Almaghraby had contributed in writing the discussion/conclusion with revision of manuscript

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Legend of figures

Figure_1

2D transthoracic echocardiogram on admission, PSAX view at MV level showing interventricular septal flattening on diastole due to RV volume overload

Figure_2

Transthoracic echocardiogram with continuous wave doppler (CWD) interrogation across the tricuspid valve on admission showing RV systolic pressure (RVSP) of 66 mm Hg with severe pulmonary hypertension

Figure_3

2D transthoracic echocardiogram with color doppler on admission, A2C view showing a central jet of severe grade IV MR

Figure_4

2D transthoracic echocardiogram with color doppler on admission, PLAX view demonstrating severe grade IV MR (before starting ARNi)

Figure_5

2D transthoracic echocardiogram with color doppler on admission, modified RV view depicting a central jet of severe grade IV TR

Figure_6

2D transthoracic echocardiogram with color doppler on admission, A4C view demonstrating severe grade IV TR and severe grade IV MR

Figure_7

Transthoracic echocardiogram with pulsed wave doppler (PWD) interrogation across hepatic Vein on admission illustrating hepatic vein systolic flow reversal due to severe TR

Figure_8

Transthoracic echocardiogram with pulsed wave doppler (PWD) interrogation across mitral valve on admission showing restrictive pattern grade III diastolic dysfunction

Figure_9

Transthoracic echocardiogram with tissue doppler imaging (TDI) interrogation across mitral valve annulus (septal mitral annulus) on admission showing reduced mitral annular velocity with high E/E' ratio of 36

Figure_10

Baseline 12-leads Electrocardiogram (ECG) showing sinus rhythm with wide QRS complex and Interventricular conduction delay with increased duration of QRS complex [?] 125 ms

Figure_11

X-ray chest (Antero-posterior) on hospital admission showing pulmonary congestion with cephalization of the pulmonary vessels, Kerley B lines with the "bat wing" pattern and patchy shadowing with increased cardiac size

Figure_12

Transthoracic echocardiogram showing LV Ejection fraction improvement to 45% by biplane method of disks (modified Simpson's) after two weeks of starting Sacubitril/Valsartan

Figure_13

2D transthoracic echocardiogram, A2C view showing reduction of MR severity to grade II after two weeks of starting Sacubitril/Valsartan

Figure_14:

2D transthoracic echocardiogram, A4C view showing marked reduction of severe grade IV TR to mild grade I TR

Figure_15

Transthoracic echocardiogram with continuous wave doppler (CWD) interrogation across the tricuspid valve two weeks after starting Sacubitril/Valsartan, showing RV systolic pressure (RVSP) dramatically improved to 30 mm Hg compared to 66 mm Hg on admission

Figure_16

Transthoracic echocardiogram with pulsed wave doppler (PWD) interrogation across mitral valve after initiating ARNi, showing improved LV diastolic function to grade I compared to grade III on admission

Legend of videos

Video_1

Transthoracic echocardiogram on admission, A4C view showing severe both LV and RV dysfunction with bi-atrial dilatation.

Video_2

Transthoracic echocardiogram on admission, PSAX view at MV level showing interventricular septal flattening more on diastole due to RV volume overload

Video_3

Transthoracic echocardiogram with color doppler on admission, A2C view showing a central jet of severe grade IV MR

Video_4

Transthoracic echocardiogram with color doppler on admission, PLAX view demonstrating severe grade IV MR (before starting ARNi)

Video_5

Transthoracic echocardiogram with color doppler on admission, modified RV view depicting a central jet of severe grade IV TR

Video_6

Transthoracic echocardiogram with color doppler on admission, A4C view demonstrating severe grade IV TR and severe grade IV MR

Video_7

Transthoracic echocardiogram with color doppler, subcostal view demonstrating hepatic systolic flow reversal due to severe TR and right-sided volume overload.

Video_8

Lung ultrasound on admission showing frequent B-lines on both lungs due to interstitial pulmonary edema.

Video_9

Coronary angiogram of Left coronary system demonstrating significant 90% long diffuse tight lesions in proximal to mid left anterior descending (LAD) artery, critical 90% lesion in both obtuse marginal (OM) branches of left circumflex (LCX) artery with significant retrograde filling from left system to right coronary artery (RCA)

Video_10

Coronary angiogram of Right coronary system demonstrating heavy calcification and tight lesions in proximal and mid RCA then followed by a 100% chronic total occlusion (CTO) of posterior left ventricular branch (PLV)

Video_11

Transthoracic echocardiogram, A4C view showing marked improvement of LV function two weeks after starting Sacubitril/Valsartan along with normalization of RV function. Estimated LV EF by eye-ball method is 40-45%

Video_12

Transthoracic echocardiogram, PLAX view on mitral valve showing marked reduction of MR severity two weeks after starting Sacubitril/Valsartan

Video_13

Transthoracic echocardiogram, A2C view showing reduction of MR severity to grade II after two weeks of starting Sacubitril/Valsartan. Akinetic and aneurysmal basal inferior wall demonstrated as non-viable RCA territory on myocardial perfusion.

Video_14

Transthoracic echocardiogram, A4C view showing marked reduction of severe grade IV TR to mild grade I TR with marked improvement of LV and RV function after starting Sacubitril/Valsartan

Video_15

Coronary angiogram of Left coronary system demonstrating successful PCI to LAD artery with TIMI III flow.

Video_16

Coronary angiogram of Left coronary system demonstrating successful PCI to LCX artery and OM branch with TIMI III flow.

Video_17

Transthoracic echocardiogram, A4C view demonstrating further LV function improvement after coronary revascularization by PCI. Estimated LV EF of 50%.

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