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CASE REPORT

# Use of sacubitril/valsartan in acute decompensated heart failure: a case report

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## Abstract

Refractory heart failure typically requires costly long-term, continuous intravenous inodilator infusions while patients await mechanical circulatory support or cardiac transplantation. The combined angiotensin receptor blocker–neprilysin inhibitor, sacubitril/valsartan, is a novel therapy that can increase levels of endogenous vasoactive peptides. This therapy has been recommended as an alternative agent in patients with chronic heart failure with reduced ejection fraction and New York Heart Association class II–III symptoms. Here, we report a case of a patient with refractory stage D heart failure with reduced ejection fraction who was successfully weaned off continuous intravenous inodilator support using sacubitril/valsartan after prior failed attempts using standard therapies.

**Keywords** Cardiomyopathy; Systolic dysfunction; Inodilator therapy; Heart failure; Reduced ejection fraction

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## Introduction

Heart failure (HF) is responsible for over 1 million hospitalizations annually in the USA with total costs exceeding $30bn in 2012.[1] Treatment goals in acute decompensated HF include improvement of symptoms, identification of precipitating factors, optimization of volume status, titration of oral vasodilator and short-term intravenous inotropic and vasodilator (inodilator) therapies, and patient education.[2] However, costly long-term, continuous inodilator infusions may be required for refractory HF (stage D) patients with severe systolic dysfunction, depressed cardiac output, and end-organ mal-perfusion while awaiting mechanical circulatory support (MCS) or heart transplantation (HT).[2] The angiotensin receptor blocker–neprilysin inhibitor, sacubitril/valsartan, is a novel therapy that can increase levels of endogenous vasoactive peptides.[3,4] 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 and angiotensin receptor blockers in patients with chronic HF with reduced ejection fraction (HFrEF) and New York Heart Association class II–III symptoms.[5,6] We report a case of stage D HFrEF weaned off continuous inodilator support using sacubitril/valsartan after failed attempts using standard therapies.

## Case report

In June 2016, a 47-year-old woman with HIV-associated cardiomyopathy and prior admissions for acute decompensated HF was transferred to the National Institutes of Health Clinical Center (NIH CC) with progressive volume overload, ascites, and dyspnoea. She was diagnosed with HIV in 2013 and HFrEF in 2015 but was poorly compliant with medical therapies that included antiretroviral therapy, carvedilol, lisinopril, spironolactone, and furosemide. Further workup in early 2015 revealed an echocardiogram with EF of 20% and cardiac angiography with no significant coronary disease. In April 2016, she was admitted to an outside facility where an echocardiogram showed left ventricular (LV) dysfunction with EF of 10–15%. She was treated with intravenous

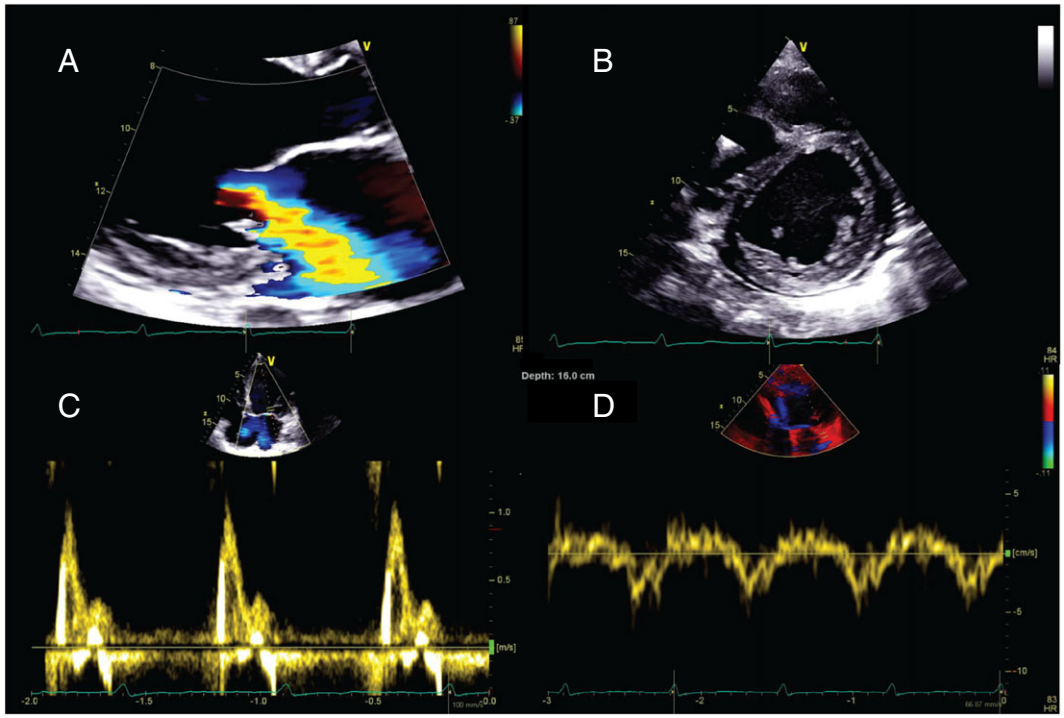
diuretics, implanted with an internal cardiac defibrillator, and discharged on carvedilol, lisinopril, and furosemide with unknown compliance. Electrocardiogram did not meet the criteria for cardiac resynchronization therapy. Following discharge, she continued to have progressive anasarca and was admitted 1 month after discharge. She required a dobutamine infusion in addition to a paracentesis for ascites. Echocardiogram showed diffuse LV hypokinesis with EF 20%. She was discharged on diuretics, and antiretroviral therapy was continued. However, 1 month antecedent to transfer to the NIH, she was readmitted to an outside facility with decompensated HF, associated congestive hepatopathy, and progressive renal dysfunction. Diuretic therapy was unsuccessful, prompting IV dobutamine again to augment perfusion. Clinical status remained tenuous, and dobutamine was discontinued, and the patient was advised to transition to hospice care for end-stage HF. However, she desired continued aggressive medical care, and the NIH was contacted.

She was transferred to the NIH CC while receiving carvedilol, spironolactone, furosemide, and an antiretroviral regimen of tenofovir disoproxil fumarate/emtricitabine, atazanavir, and ritonavir. Physical examination was notable for blood pressure 96/70 mmHg, pulse 83 b.p.m., $O_2$ saturation 96% on room air, anasarca, and cool peripheral extremities. Notable admission labs included sodium 120 mmol/L and pro-brain natriuretic peptide 8358 pg/mL.

At the NIH CC, she was treated with intravenous furosemide; however, this was held for hypotension and acute oliguria. She was transferred to the intensive care unit for inodilator support. An echocardiogram demonstrated dilation of all cardiac chambers with LVEF 11% (normal $>$ 53%), severe mitral regurgitation (*Figure 1A*), septal flattening suggesting right ventricular (RV) volume overload (*Figure 1B*), grade III diastolic dysfunction, and lateral E/e' ratio 23, suggesting an elevated LV filling pressure (*Figure 1C, D*). The tricuspid annular plane systolic excursion (not shown) was consistent with reduced RV systolic function.

Right heart haemodynamics revealed secondary pulmonary hypertension with mean pulmonary artery pressure 34 mmHg, volume overload with pulmonary capillary wedge pressure 20 mmHg, vasoconstriction with a high systemic vascular resistance (SVR) at 1599 dyn·s·cm$^{-5}$, and a low cardiac output state with cardiac index (CI) 1.3 L/min/m$^2$ and mixed venous oxygen saturation ($SVO_2$) 44%. She was started on dobutamine (2.5 μg/kg/min) and nitroglycerin (20 μg/min). Spironolactone (25 mg) was continued and carvedilol discontinued. Dobutamine was titrated to 7.5 μg/kg/min guided by haemodynamics. Her urine output increased to 200–300 mL/h; SVR decreased to 987 dyn·s·cm$^{-5}$; and CI and $SVO_2$ improved to 2.6 L/min/m$^2$ and 64%, respectively (*Figure 2*). She achieved a fluid balance of −4.6 L by Day 3.

**Figure 1** Transthoracic echocardiogram on admission. Imaging showed severe mitral regurgitation (A) and diastolic septal flattening suggestive of right-sided volume overload (B). Doppler imaging on admission showed a restrictive mitral inflow pattern (C) and diminished tissue Doppler velocities (D).





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Oral afterload reduction was initiated with captopril (Day 4), which was titrated to 50 mg t.i.d., and hydralazine (HYZ) and isosorbide dinitrate (ISDN) both at 10 mg t.i.d. (Day 5). On this regimen, nitroglycerin was discontinued (Day 6), and dobutamine was weaned to 2.5 μg/kg/min (Day 6). However, this resulted in a decrease in CI from 2.6 to 2.2 L/min/$m^2$. (*Figure 2*). HYZ and ISDN were increased to 50 and 20 mg, respectively. On Day 8, her total fluid balance was −19 L, and she had lost 15 kg. Haemodynamics revealed mean pulmonary artery pressure 31 mmHg, pulmonary capillary wedge pressure 16 mmHg, SVR 486 dyn·s·$cm^{-5}$, CI 4.4 L/min/$m^2$, and $SVO_2$ 73%. Dobutamine was weaned off (Day 9); however, within 10 h, she developed anuria with a drop in CI to 1.8 L/min/$m^2$ (*Figure 2*). Dobutamine was resumed, and HYZ and ISDN were increased to 75 and 40 mg t.i.d., respectively. The decision was made to trial sacubitril/valsartan following a 48 h captopril washout period.

On Day 12, sacubitril/valsartan was initiated at the mid-range dose of 49/51 mg b.i.d. Concerns over tachyphylaxis prompted a transition from dobutamine to milrinone (Day 12) titrated to 0.375 μg/kg/min. Because she was off dobutamine and was euvolemic, metoprolol tartrate was added (Day 13). Milrinone was successfully weaned off (Day 14) once sacubitril/valsartan approached a steady-state dose. The patient maintained adequate blood pressure and urine output. Subsequent changes to her medication regimen included increasing sacubitril/valsartan to the maximum dose of 97/103 mg b.i.d. (Day 15) and the addition of digoxin 0.25 mg o.d. (Day 15). She displayed no clinical or laboratory signs of infection for the duration of her intensive care unit admission.

The patient was transferred to the ward (Day 17) and transitioned to metoprolol succinate 100 mg o.d. with digoxin discontinued. Upon discharge, her pro-brain natriuretic peptide decreased to 788 pg/mL. An echocardiogram performed 41 days after discharge revealed an increase in LVEF to 35%, improved LV diastolic dimension (from 64 to 56 mm), and systolic dimension (from 58 mm to 42 mm), and markedly decreased mitral regurgitation (*Figure 3A*). There was no further evidence of septal flattening or LV diastolic dysfunction (*Figure 3B*), and there was normalization of LV filling pressures with a lateral E/e' ratio of 9 (*Figure 3C, D*). The tricuspid annular plane systolic excursion (not shown) suggested improved RV systolic function. At 10 months after discharge, she has not been readmitted and on clinic visits has been without signs of decompensated HF.

**Figure 2** Hospital course. Abbreviations: IV, intravenous; PO, by mouth; sPAP, systolic pulmonary artery pressure; dPAP, diastolic pulmonary artery pressure; mPAP, mean pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; CO, cardiac output; CI, cardiac index; $SVO_2$, mixed venous oxygen saturation; SVR, systemic vascular resistance; MAP, mean arterial pressure; PVR, pulmonary vascular resistance; CVP, central venous pressure.

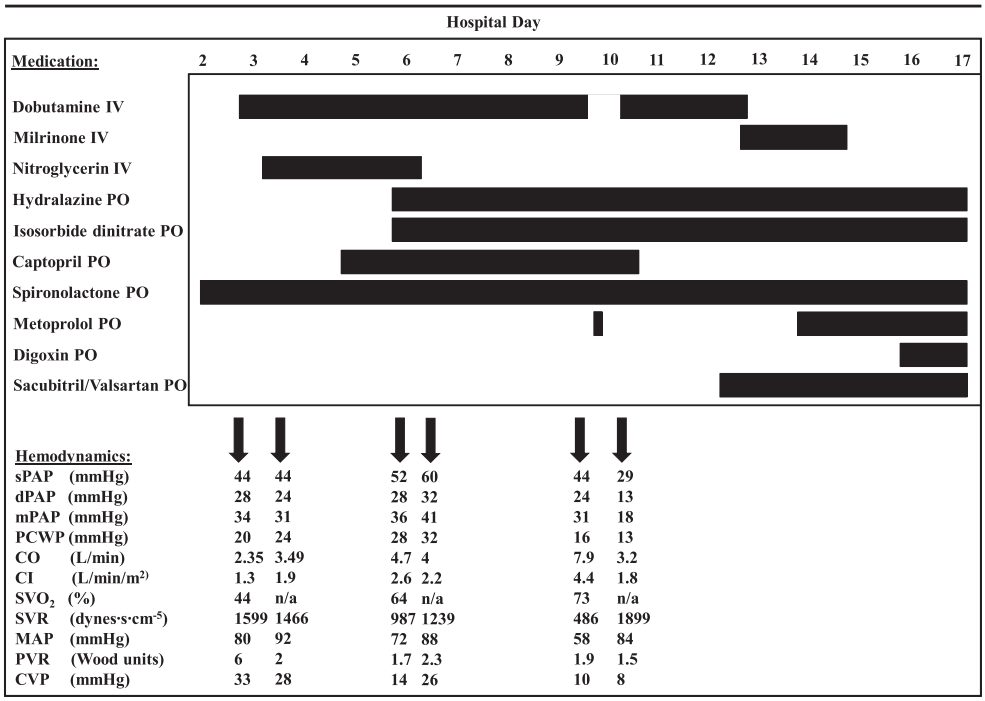



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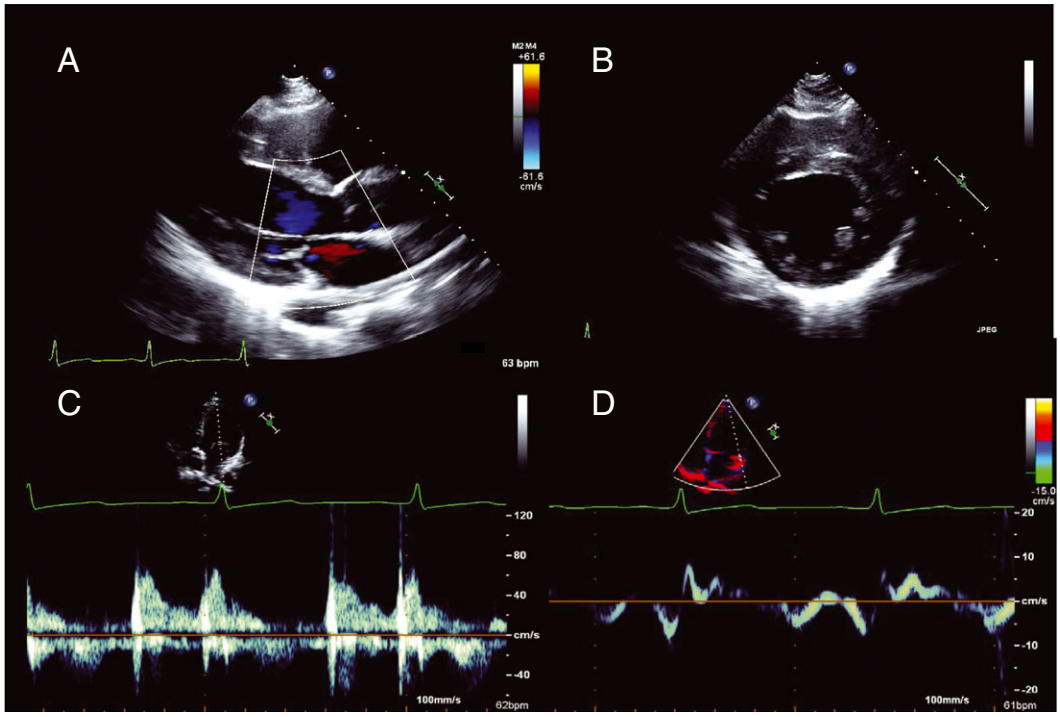
**Figure 3** Transthoracic echocardiogram after discharge from the hospital. Imaging showed trace mitral regurgitation (A) and no evidence of septal flattening (B). Doppler imaging showed normalization of the mitral inflow pattern (C) and similar tissue Doppler velocities (D).




## Discussion

In a patient with HIV-associated cardiomyopathy and stage D HFrEF, we describe the successful use of sacubitril/valsartan combined with goal-directed medical therapy to liberate the patient from inodilator dependence. To our knowledge, this is the first reported use of sacubitril/valsartan for this indication. Sacubitril/valsartan was shown to be superior to enalapril in reducing mortality and HF hospitalizations in patients with chronic HFrEF.[5] Sacubitril/valsartan also demonstrated fewer rates of inodilator agents (31% risk reduction) and MCS or HT (22% risk reduction).[7] These secondary outcomes were evident within 30 days of randomization, suggesting early effects of sacubitril/valsartan.

Despite optimization of medical therapy and haemodynamics, our attempts to wean dobutamine were complicated by hypoperfusion. Sacubitril/valsartan enabled the discontinuation of inodilators after traditional afterload reduction methods with an angiotensin-converting enzyme inhibitor failed. The neprilysin inhibitor's ability to increase levels of endogenous vasoactive peptides may have provided additional benefits towards maintaining improved organ perfusion once off inodilator support. However, it is important to mention that the medication's potency in reducing SVR and blood pressure may also be a limitation to its use in advanced HF, particularly if blood pressures are marginal. Clinical trials are needed to assess the efficacy and limitations of sacubitril/valsartan in patients with advanced HF. One such study under enrollment is the Entresto in Advanced Heart Failure (LIFE Study).

During end-stage HF, it can be challenging to wean inotropes. Chronic inotrope infusions may be the only option for stage D HFrEF patients optimally treated with goal-directed medical therapy and not candidates for MCS or HT. If home inotropes are chosen, a discussion must take place with the patient regarding the palliative nature and potentially harmful consequences, including increased risk of death.[2] Given the long-term favourable findings of sacubitril/valsartan and our experience with this patient, sacubitril/valsartan may be a potential cost-effective option for inotrope-dependent patients who are not candidates for MCS and HT.

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## Conflict of interest

None declared.

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