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CASE REPORT
Heart failure

Crossing the chasm: caution for use of angiotensin receptor-neprilysin inhibition in patients with cardiogenic shock– a case report

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Background Vasoplegia has been reported in patients receiving angiotensin receptor-neprilysin inhibitors (ARNI) with heart failure with reduced ejection fraction (HFrEF). We present a case of vasoplegic shock after initiation of ARNI in a hospitalized 65-year-old man recovering from cardiogenic shock (CS) and acute kidney injury (AKI).

Case summary A 65-year-old man with HFrEF presented to a community hospital with CS with evidence of poor perfusion with a lactate of 5.6 mmol/L and creatinine (Cr) 125 µmol/L. He was treated with intravenous furosemide infusion. Subsequently, his lactate normalized but he developed an AKI with a Cr of 176 µmol/L. He was then started on ARNI and beta blockers. Over the next 24 h, he developed a vasoplegic shock necessitating multiple vasopressors and a transfer to a tertiary academic centre. With supportive therapy, his vasoplegic shock improved and he was discharged home.

Discussion PARADIGM-HF found that the introduction of an ARNI in patients with ambulatory symptomatic HFrEF reduces the risk of death and heart failure hospitalization. Most recently, PIONEER-HF showed that ARNI reduced N-terminal pro-B-type natriuretic peptide levels at 4 and 8 weeks, without significantly different rates of medication-related adverse effects. However, thus far, no clinical trials have examined the role of ARNI in CS. Our case report highlights the risk of vasoplegic shock caused by initiation of ARNI in patients hospitalized with CS especially in whom renal and hepatic impairment is present.

Keywords Heart failure • Cardiogenic shock • Angiotensin receptor-neprilysin inhibitor • Case report

Learning points

- Among ambulatory patients with heart failure with reduced ejection fraction, angiotensin receptor-neprilysin inhibitors reduced all-cause mortality and heart failure hospitalization.
- Angiotensin receptor-neprilysin inhibitors can cause vasoplegic shock when initiated in patients hospitalized with heart failure.

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Introduction

After the results of PARADIGM-HF showed reduction in death and heart failure hospitalization with the use of angiotensin receptor-neprilysin inhibitors (ARNI), major heart failure guidelines included ARNI in the algorithm for treating patients with heart failure with reduced ejection fraction (HFrEF).[1–4] PIONEER-HF showed a reduction in N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels in patients hospitalized with acute decompensated heart failure (ADHF). Although this trial enrolled a small percentage of patients who were on inotropes during the index admission, it excluded patients with renal impairment [estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2].[5] We present a case of vasoplegic shock after initiation of ARNI in a hospitalized 65-year-old man recovering from cardiogenic shock (CS) and acute kidney injury (AKI).

Timeline

Case presentation

A 65-year-old man with a previously established diagnosis of non-ischaemic cardiomyopathy [left ventricular ejection fraction (LVEF) 20%], on guideline-directed medical therapy (bisoprolol 5 mg PO o.d., candesartan 4 mg PO o.d.) with a primary prevention implantable cardioverter-defibrillator, presented to a community hospital with persistent epigastric abdominal pain. Prior to this, he was New York Heart Association (NYHA) class II. Five days prior to this admission, he was discharged with abdominal pain of uncertain cause after oesophagogastroduodenoscopy and colonoscopy showed no evidence of gastrointestinal pathology and computed tomography angiography showed patent mesenteric vessels. His comorbid illnesses include paroxysmal atrial fibrillation (treated with apixiban), previous cerebrovascular accident, hypertension, dyslipidaemia, and depression. At the time of admission, he had re-presented with abdominal pain and fatigue. His medications were unchanged. His blood pressure was 112/81 mmHg heart rate of 70 b.p.m. (irregularly irregular) and

Day of admission	Events
-5	• Day of discharge from community hospital with abdominal pain of uncertain cause after having non-contributory oesophagogastroduodenoscopy, colonoscopy, and computed tomography angiography
0	• Presented to hospital with generalized abdominal pain and fatigue • Physical examination consistent with congestive heart failure • Transthoracic echocardiography: left ventricular function of 11% and mild right ventricular dysfunction • Started on intravenous (IV) furosemide; home medications, bisoprolol and candesartan, held
8	• Acute kidney injury (AKI) and elevated liver enzymes noted • Lactate normalized, vitals stable (103/66 mmHg and heart rate 86 b.p.m.) • Started on bisoprolol 2.5 mg PO o.d. and sacubatril/valsartan 24/26 mg PO b.i.d.
9	• Developed hypotension requiring norepinephrine and dobutamine • Worsening AKI
10	• Transferred to our tertiary academic centre • Right heart catheterization performed • Diagnosed with vasoplegic shock secondary to sacubatril/valsartan after sepsis and adrenal insufficiency ruled out • Supported with above vasopressor/inotrope
14	• Vasoplegic shock resolved and norepinephrine weaned off • Creatinine improved to normal range
15	• Right heart catheterization shows resolving vasodilatory shock and predominant cardiogenic shock • Dobutamine continued, IV furosemide infusion started
17	• Dobutamine weaned off with uptitration of hydralazine and spironolactone
26	• Bisoprolol initiated
32	• Ramipril initiated
34	• Discharged with net 25 kg lost on oral heart failure therapy

Table 1 Haemodynamic profile from Swan Ganz catheterization after admission to our cardiac intensive care unit

Time/parameter	Admission	24 h	48 h	72 h	96 h	120 h
Heart rate (b.p.m.)	93	89	87	93	125	129
MAP (mmHg)	65	60	57	60	71	79
Cardiac index (L/min/m^2)	5.7	3.7	4.0	4.4	4.2	1.7
mPAP (mmHg)	36	26	27	25	45	36
PCWP (mmHg)	24	13	11	18	26	23
SVR (dyne/s/cm^5)	297	559	465	464	597	1265
Dobutamine dose (μg/kg/min)	18.7	18.7	18.7	10	10	5
Norepinephrine dose (μg/kg/min)	0.21	0.15	0.08	0.04	OFF	OFF
Mixed venous saturation (%)	73	71	76	76	64	58
Lactate (mmol/L)	1.7	2.4	1.4	1.2	0.9	0.6
Creatinine (μmol/L)	550	518	379	171	95	97

MAP, mean arterial pressure; mPAP, mean pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; SVR, systemic pulmonary resistance.

his respiratory rate was 18 breaths per minute. He was congested on exam (jugular venous pressure noted at 5–6 cm above the sternal angle with the head of the bed at 30° and had 1+ peripheral oedema) and had metabolic evidence of poor perfusion with a lactate of 5.6 mmol/L, a creatinine (Cr) of 125 μmol/L (eGFR 60 mL/min/1.73 m^2), and liver enzyme elevation [alanine transaminase (ALT) 174 IU/L]. Transthoracic echocardiography demonstrated an LVEF of 11% with mild right ventricular dysfunction. He was initiated on an intravenous furosemide infusion.

With ongoing diuresis, by post-admission day (PAD) 8, he developed an AKI with a Cr of 176 μmol/L (eGFR 41 mL/min/1.73 m^2). His liver enzymes remained elevated with ALT 350 μ/L, aspartate transaminase 913 μ/L, and international normalized ratio of 4.4. However, his lactate had normalized to 1.7 mmol/L and he was haemodynamically stable (heart rate 86 b.p.m. and blood pressure 103/66 mmHg), such that he was started on a bisoprolol 2.5 mg PO o.d. and sacubitril/valsartan 24/26 mg PO b.i.d. on PAD 8. Over the next 24 h, he developed progressive shock with a dramatic rise in his Cr from 176 to 476 μmol/L (eGFR 12 mL/min/1.73 m^2) and hypotension necessitating norepinephrine at 0.28 μg/kg/min and dobutamine at 18.7 μg/kg/min. As a result, a request for a transfer to our institution was made.

Upon arrival to our institution the next day (PAD 10), a right heart catheterization was completed for advanced therapies assessment. The trend of these results can be found in *Table 1*. Opening pressures documented a pulmonary capillary wedge pressure of 24 mmHg, cardiac index of 5.7 L/min/m^2, and a systemic vascular resistance of 297 dyne/s/cm^5, whilst on the vasodilators as above. In light of no clear source of sepsis, adrenal insufficiency, fulminant liver failure, or neurogenic cause to explain his haemodynamics, he was diagnosed with vasoplegic shock secondary to the initiation of ARNI. After 96 h (PAD 14) of supportive care with vasopressors and dobutamine, his vasodilatory shock resolved and his Cr normalized to 95 μmol/L (eGFR 84 mL/min/1.73 m^2). On PAD 15, his haemodynamics were more consistent with CS, which was managed with aggressive diuresis, the re-initiation of dobutamine and introduction of oral heart failure (HF) therapy. Dobutamine was weaned off 48 h later. Bisoprolol and ramipril were judiciously added on PAD 26 and 32, respectively. At time of discharge (PAD 34), he was optimized on medical therapy (bisoprolol 3.75 mg PO o.d., ramipril 2.5 mg PO o.d., and spironolactone 25 mg PO o.d.) and was decongested, with a net 25 kg weight loss since admission. His Cr was 148 μmol/L (eGFR 53 mL/min/1.73 m^2) at time of discharge. Seven months post-discharge from hospital, the patient is well (NYHA II) and has not required further HF hospitalization. An attempt was made to re-introduce sacubitril/valsartan as an out-patient, but this was discontinued as he developed hyperkalaemia.

Discussion

With the publication of PARADIGM-HF in 2014, there was much excitement for a novel therapy for patients with HFrEF.[4] Sacubitril/valsartan is one of these novel therapies which is a combination of a neprilysin inhibitor and an angiotensin receptor blocker. As there are many damaging neurohormonal pathways which are activated in HF, neprilysin was found to be an enzyme that acts in concert with well-known HF therapies. Neprilysin is an enzyme that inhibits breakdown of natriuretic peptides, bradykinin and adrenomedullin, which when present, act to retain sodium and cause systemic vasoconstriction.[6–8] PARADIGM-HF found that the introduction of an ARNI in patients with ambulatory symptomatic HFrEF reduces the risk of death and HF hospitalization.[4] Most recently, PIONEER-HF showed that there was a reduction in NT-proBNP levels as early as 1 week post-initiation of sacubitril/valsartan in-hospital after stabilization from ADHF, without an increase in adverse safety events.[5,9] Although this trial allowed enrolment of patients off inotropes for at least 24 h with a systolic blood pressure >100 mmHg prior to randomization, only 66 patients (7.7%) required intravenous inotropes. Additionally, patients with an

eGFR <30 mL/min/1.73 m^2 and known hepatic impairment were excluded. Post-hoc analysis of this trial at the 8-week follow-up time point found sacubitril/valsartan more effective than enalapril in reducing the risk of the composite of cardiovascular death or HF re-hospitalization.[9] Thus far, no clinical trials have examined the role of ARNI in CS.

Our patient had haemodynamic evidence of vasoplegic shock secondary to ARNI initiation in the setting of ongoing evidence of end-organ hypoperfusion from CS. Only one other published case is described in a patient who developed vasoplegic shock necessitating high dose vasopressors and methylene blue post-operatively in the setting of sacubitril/valsartan use prior to orthotopic heart transplantation.[10]

We caution the initiation of an ARNI in patients hospitalized with ADHF who have had CS. In our case, the patient had continued evidence of end-organ hypoperfusion including renal impairment and hepatic injury. Though his Cr was 176 µmol/L (eGFR 41 mL/min/1.73 m^2) at time of medication initiation, which was acceptable for enrolment in PIONEER-HF, it is important to note that the median Cr in this trial was 113 µmol/L. In addition, patients with hepatic impairment were also excluded.[4,9] As the half-life of LQB657 (Sacubitrilat), a metabolite of neprilysin, is 11.5 h in healthy individuals, it is likely that our patient had persistent levels given his prolonged vasodilatory shock (96 h after drug initiation).[11]

Conclusions

Since the use of ARNI has been added to major guidelines for management of chronic HFrEF, we emphasize caution in its introduction while in hospital recovering from CS. To our knowledge, this is the first published case report of profound vasodilatory shock after initiation as an inpatient. More studies are needed to evaluate the efficacy and safety of ARNI initiation after recovery from CS. Until then, we encourage restraint of its use in this subset of HF patients.

Lead author biography

Loai Almazroa was born on 11 February 1990. From 2007 to 2013, he studied Medicine at King Said University, Riyadh where he graduated with first-degree honours. He completed internal medicine residency at University of Toronto and is currently working as a cardiology fellow at University of Toronto. He is interested in cardiac critical care and interventional cardiology.

Supplementary material

Supplementary material is available at *European Heart Journal - Case Reports* online.

Slide sets: A fully edited slide set detailing this case and suitable for local presentation is available online as Supplementary data.

Consent: The author/s confirm that written consent for submission and publication of this case report including image(s) and associated text has been obtained from the patient in line with COPE guidance.

Conflict of interest: The authors whose names are listed immediately below certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

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