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.
**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). 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 m²]. 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**

| 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 |

**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
his respiratory rate was 18 breaths per minute. He was con-
gested 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-i-
peripheral oedema) and had metabolic evidence of poor perfu-
sion with a lactate of 5.6 mmol/L, a creatinine (Cr) of 125 μmol/L
(eGFR 60 mL/min/1.73 m²), and liver enzyme elevation [alanine
transaminase (ALT) 174 IU/L]. Transthoracic echocardiography
demonstrated an LVEF of 11% with mild right ventricular dys-
function. 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 m²). His liver enzymes remained elevated with ALT 350
μmol/L, aspartate transaminase (ALT) 174 IU/L. Transthoracic echocardiography
demonstrated an LVEF of 11% with mild right ventricular dys-
function. He was initiated on an intravenous furosemide infusion.

Upon arrival to our institution the next day (PAD 10), a right
heart catheterization was completed for advanced therapies as-
essment. The trend of these results can be found in Table 1.

| 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/m²) | 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/cm²)   | 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.

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 en-
zyme 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.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 m² 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. 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. As the half-life of LQ8657 (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).

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 m²) 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. As the half-life of LQ8657 (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).

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 Saud 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 hono- raria; 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.

References

1. Ezekowitz JA, O’Meara E, McDonald MA, Abrams H, Chan M, Ducharme A et al. 2017 comprehensive update of the Canadian Cardiovascular Society guidelines for the management of heart failure. Can J Cardiol 2017;33: 1342–1433.
2. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS et al.; ESC Scientific Document Group. 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 Heart J 2016;37:2129–2200.
3. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Colvin MM et al. 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA Guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. Circulation 2017;136:e137–e161.
4. 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.
5. Velazquez EJ, Morrow DA, DeVore AD, Duffy CI, Ambrosy AP, McCague K et al.; PIONEER-HF Investigators. Angiotensin-neprilysin inhibition versus enalapril in heart failure. N Engl J Med 2019;380:539–548.
6. Cataliotti A, Tonne JM, Bellavia D, Martin FL, Oehler EA, Harders GE et al. Long-term cardiac pro-B-type natriuretic peptide gene delivery prevents the development of hypertensive heart disease in spontaneously hypertensive rats. Circulation 2011;123:1297–1305.
7. Tonduangu D, Hittinger L, Ghaleh B, Le Corvoisier P, Sambin L, Champagne S et al. Chronic infusion of bradykinin delays the progression of heart failure and preserves vascular endothelium-mediated vasodilation in conscious dogs. Circulation 2004;109:111–119.
8. Nakamura R, Kato J, Kitamura K, Onitsuka H, Imamura T, Cao Y et al. Adrenomedullin administration immediately after myocardial infarctionamelio- rates progression of heart failure in rats. Circulation 2004;110:426–431.
9. Morrow DA, Velazquez EJ, DeVore AD, Desai AS, Duffy CI, Ambrosy AP et al. Clinical outcomes in patients with acute decompensated heart failure randomly assigned to sacubitril/valsartan or enalapril in the PIONEER-HF trial. Circulation 2019;139:2285–2288.
10. Almulfah A, Mielniczuk LM, Zinoviev R, Moeller A, Davies RA, Stadnick E et al. Profound vasoplegia during sacubitril/valsartan treatment after heart transplanta- tion. Can J Cardiol 2018;34:343.e5–343.e7.
11. Product Monograph including patient medication information for EntrestoTM. Novartis Pharmaceutical Canada Inc.; 2017. http://www.ask.novartispharma.ca/download.htm?res=entresto_scrip_e.pdf&resTitleId=1137 (27 January 2020).