Tolvaptan treatment in an adult Fontan patient with protein-losing enteropathy: a serial $^{23}$Na-MRI investigation

Julia Moosmann, Okan Toka, Peter Linz, Anke Dahlmann, Armin M. Nagel, Mario Schiffer, Michael Uder, Robert Cesnjecar, Sven Dittrich and Christoph Kopp

Abstract

Background: Protein-losing enteropathy (PLE) is a severe complication of the univentricular Fontan circulation and associated with disturbances in salt and water homeostasis. Fontan patients with PLE have a poor prognosis, with increased morbidity and mortality. Due to limited therapeutic strategies, patients are often treated only symptomatically.

Methods: We report our first experience of Tolvaptan (TLV) treatment in a Fontan patient with PLE, severe volume retention and hyponatraemia, refractory to conventional diuretic therapy. In addition to clinical parameters, we monitored drug effects including tissue sodium and volume status via serial $^{23}$Na-magnetic resonance imaging ($^{23}$Na-MRI) and bioimpedance spectroscopy compared with age-matched controls.

Results: $^{23}$Na-MRI identified elevated tissue sodium, which decreased under TLV treatment, as well as volume status, while serum sodium increased and the patient’s symptoms improved. During long-term treatment, we were able to differentiate between sodium and volume status in our patient, suggesting that TLV uncoupled body sodium from water.

Conclusion: TLV in addition to loop diuretics improved clinical symptoms of PLE and lowered tissue sodium overload. Long-term effects should be further evaluated in Fontan patients.

Keywords: Fontan, Tolvaptan, $^{23}$Na-MRI, RAAS, Congenital heart disease

Introduction

The Fontan procedure is a palliative procedure for patients with congenital single-ventricle malformations, diverting blood from the great veins to the pulmonary arteries, bypassing the right ventricle.\(^1\) The Fontan circulation results in a non-pulsatile pulmonary blood flow, elevated central venous pressure and reduced cardiac output.\(^2\) After the Fontan procedure $\sim3$–$15\%$ of all patients develop protein-losing enteropathy (PLE), which is still associated with increased morbidity and an estimated 5-year survival rate of $\sim50\%$.\(^3\)–$^7$ PLE in Fontan patients represents a severe complication with a gradual onset of symptoms including hypoalbuminaemia, hypogammaglobulinaemia, diarrhoea, dystrophy, hyponatraemia and fluid overload with pleural effusions, ascites and peripheral oedema.\(^8\) We do not sufficiently understand the pathophysiological changes leading to PLE in Fontan patients, nor do we have adequate treatment options to improve their state of health and life quality. Patients are usually treated symptomatically with diuretics and steroids; however, the response often remains suboptimal and unsatisfactory. In addition, there are no prospective or controlled data evaluating the impact of chronic diuretic therapy on morbidity and mortality in Fontan patients.
We reasoned that Tolvaptan (TLV), a vasopres- 
sin type-2 receptor antagonist, might be a useful 
adjunctive therapy for these patients. Studies in 
heart failure patients support this viewpoint. TLV 
prohibits the movement of aquaporin 2 into the 
luminal wall of the collecting duct, thus reducing 
the reabsorption of water. TLV has been approved 
for the treatment of hyponatraemia associated 
with congestive heart failure. Studies illustrated 
the efficacy of TLV in heart failure with hypervol-
amia and hyponatraemia, especially during the 
acute phase of cardiac decompensation and in 
patients resistant to conventional diuretic ther-
apy. To monitor the drug effects, we employed 
\( ^{23} \text{Na} \)-magnetic resonance imaging (MRI) – a 
technique that is applied in biomedical research 
applications to quantify tissue sodium (Na\(^{+}\)) concentration. We showed earlier that this 
method is useful in patients with hypertension 
and heart failure by delineating increased tissue 
Na\(^{+}\) content.

**Case presentation**

We present a 22-year-old woman with Fontan 
circulation and PLE with an underlying cardiac 
malformation of pulmonary atresia and an intact 
ventricular septum with a hypoplastic right ven-
tricle. Her surgical history included Blalock-
Taussig-shunt (BT) at the age of 10 days, which 
was converted to a central aortopulmonary-
shunt (AP-shunt) at 17 months, requiring band-
ing of the AP-shunt 8 days later, due to 
overshunting. This was followed by patch 
enlargement of the left pulmonary artery (LPA) 
at the age of 2.5 years, and late bidirectional 
Glenn anastomosis at 9 years. She underwent 
total-cavopulmonary-connection (TCPC) with 
an extra-cardiac conduit at 11 years. After 
Fontan completion, she required interventional 
stent implantation in the LPA; 3 years after 
TCPC she developed symptoms of PLE. Due to 
worsening of her clinical condition, she has been 
hospitalised since the age of 21 for recurring 
pleural effusions, need for intravenous diuretics 
and parenteral nutrition.

PLE was diagnosed using the criteria of the sci-
entific statement of the American Heart 
Association, including elevated faecal alpha-1 
antitrypsin, serum hypoalbuminaemia and symp-
toms of oedema without another identified 
cause.

Patients PLE symptoms included severe diar-
rhoea, hypoalbuminaemia, repeated elevated val-
ues of faecal alpha-1 antitrypsin (>1800 µg/g). 
She presented with peripheral oedema, recurrent 
asites, pleural effusion and abdominal disten-
sion, as well as cachexia and growth failure. The 
patient had received oral budesonide treatment 
for symptom control for years since the first 
symptoms of PLE occurred. She developed severe 
side effects of steroid therapy, including osteopo-
rosis with chronic base and top plate fractures of 
the spine. Therefore, budesonide therapy had 
been weaned. She showed severe immune abnor-
malities with hypogammaglobulinaemia, lympho-
paenia and low T cell count. In the MRI she 
presented with thoracic lymphatic malformations. 
Allupurinol treatment was needed for high uric 
acid >8.5 mg/dl and gout symptoms (Table 1).

Cardiac catheterisation revealed normal pressures 
in the Fontan circulation (Table 1). TLV 
(Samsca®, Otsuka Pharma GmbH, Frankfurt am 
Main, Germany) therapy was started as an indi-
vidual healing attempt based on the patient’s vol-
ume overload and insufficient response to 
high-dose conventional diuretic therapy. TLV 
was started with 25% of the target dose (1.0 mg/ 
kg/day). Increments were based on serum sodium 
concentration. The target dose was achieved on 
day 25 of treatment.

**Control group**

We recruited an age-matched female control 
group at the local university (n = 8). Average age 
was 24.6 ± 2.0 years. Subjects had no history of 
chronic diseases, did not take any regular medica-
tion and blood pressure was in the normal range 
according to European Society of Cardiology/ 
European Society of Hypertension (ESC/ESH) 
guidelines.

\( ^{23} \text{Na} \)-MRI quantification

\(^{23} \text{Na-MRI} \) was performed before TLV treat-
ment, on day 9 (short-term effects), and day 29 
(long-term effects). Tissue Na\(^{+}\) content was 
measured noninvasively with a 3.0 Tesla clinical 
MRI system (Magnetom Verio, Siemens 
Healthcare, Erlangen, Germany) using a \(^{23} \text{Na} \) volume coil (Stark-Contrast, Erlangen, 
Germany) as described previously. Muscle 
and skin sodium were assessed in the left lower
Table 1. \(^{23}\)Na-MRI, laboratory analyses, TLV dosing and concomitant medication.

|                        | First measurement | Second measurement | Third measurement |
|------------------------|-------------------|--------------------|------------------|
| Time according to TLV start (days) | (−26) | 9 | 29 |
| Body weight (kg)       | 52.5             | 51.0              | 52.4             |
| Blood pressure [mmHg] Systolic/diastolic/mean | 106/44/67 | 93/42/58 | 95/42/60 |
| TLV dose (mg)          | 0                | 18.75             | 45               |

\(^{23}\)Na-MRI

|                        | First measurement | Second measurement | Third measurement |
|------------------------|-------------------|--------------------|------------------|
| Muscle sodium (mmol/l) | 24.7              | 22.4              | 21.7             |
| Skin sodium (mmol/l)   | 23.8              | 18.4              | 17.4             |
| BCM overhydration (l)  | 1.0               | 0.1               | 0.5              |
| BCM extracellular water (l) | 11.5         | 10.6              | 10.8             |
| BCM intracellular water (l) | 12.6          | 12.7              | 12.2             |

Laboratory parameters

|                        | First measurement | Second measurement | Third measurement |
|------------------------|-------------------|--------------------|------------------|
| Serum-Na\(^+\) (mmol/l)       | 133               | 131               | 133              |
| Serum-K\(^+\) (mmol/l)        | 3.6               | 3.5               | 3.3              |
| Serum-osmolality (mosm/kg)   | 299               | 296               | 292              |
| Creatinine (mg/dl)          | 0.61              | 0.67              | 0.8              |
| Total-protein (g/l)         | 39                | 46                | 44               |
| Albumin (g/l)               | 21.2              | 27.6              | 22.5             |
| IgG (g/l)                   | 1.3               | 1.9               | 2.3              |
| Aspartate-aminotransferase (U/l) | 24            | 29                | 28               |
| Alanine-aminotransferase (U/l) | 23             | 28                | 23               |
| Gamma-glutamyltransferase (U/l) | 169          | 171               | 116              |
| Renin (pg/ml)               | 9780              | 8350              | 9250             |
| Aldosterone (pg/ml)         | 677.9             | 540.2             | 91.2             |
| Urine-sodium (mol/mol/Kre)  | 18.1              | <detection limit  | 33.8             |
| Fractional sodium excretion (%) | 0.74            | <detection limit  | 1.8              |
| Urine-potassium (mol/mol/Kre) | 36.4            | 51.8              | 80.1             |
| Fractional potassium excretion (%) | 54.53         | 104.63            | 171.67           |
| Urine-osmolality (mosm/kg)  | 311               | 254               | 236              |

Concomitant medication

|                        | First measurement | Second measurement | Third measurement |
|------------------------|-------------------|--------------------|------------------|
| Furosemide (mg/kg/day i.v.) | 5                 | 4                  | 4                |

(Continued)
Table 1. (Continued)

| Drug (mg/kg/day)          | First measurement | Second measurement | Third measurement |
|--------------------------|-------------------|--------------------|-------------------|
| Hydrochlorothiazide      | 1                 | 1                  | 1                 |
| Eplerenone               | 1                 | 1                  | 1                 |
| Sildenafil                | 0.6               | 0.6                | 0.6               |
| Levothyroxine (µg/kg/day)| 2                 | 2                  | 2                 |
| Pantoprazole              | 1.2               | 1.2                | 1.2               |
| Iodide (mg/kg/day)       | 6                 | 6                  | 6                 |
| Methylprednisolone (mg/kg/day) | 0.002          | 0.002              | 0.002             |
| Losartan (mg/kg/day)     | 0.188             | 0.188              | 0.188             |
| Vitamin D (IU/day)       | 1000              | 1000               | 1000              |
| Allopurinol              | 2                 | 2                  | 2                 |
| Heparin (IU/kg/h PTT 60-80 s) | 40                | 40                 | 40                |

Cardiac catheterisation (pressure values mmHg)

| Structure                    | First measurement |
|------------------------------|-------------------|
| Inferior vena cava           | 9/10/10           |
| Superior vena cava           | 10/8/8            |
| Left pulmonary artery        | 12/10/8           |
| Right pulmonary artery       | 12/9/11           |
| Ascending aorta              | 82/39/53          |

Cardiac MRI

| Parameter                     | Value  |
|------------------------------|--------|
| EDV (mL/m²)                  | 111    |
| ESV (mL/m²)                  | 48     |
| Stroke volume (mL/m²)        | 63     |
| Ejection fraction (%)        | 57     |
| Aortic insufficiency (%)     | 5      |
| Mitral insufficiency (%)     | 11     |

BCM, body composition measurement; EDV, end-diastolic volume; ESV, end-systolic volume; IgG, immunoglobulin G; IU, international units; 23Na-MRI, 23Na-magnetic resonance imaging; PTT, partial thromboplastin time; TLV, Tolvaptan.

leg, which was placed on a calibration tube holder to avoid deviation in the Z-axis. Four tubes containing aqueous solutions with 10, 20, 30 and 40 mmol/l NaCl, respectively, served as calibration standards by relating MR-signal intensity to a sodium concentration in a linear trend analysis. To distinguish the anatomical structures of interest, 23H-MRI was conducted with the integrated body coil of the MRI system. Due to the low in-plane resolution (3 × 3 mm²), partial volume effects occur, meaning the Na⁺ skin amount could have been underestimated.
Additionally, $^{23}$Na-MRI shows fast signal decay, which also can lead to underestimated tissue Na$^+$ content measurements.

**Body composition measurements**

A body composition monitor device was used (BCM, Fresenius, Medical Care, Bad Homburg, Germany) to determine volume status. Electrodes were attached to the patient’s hand and foot on the ipsilateral side, and impedance spectroscopy was measured with frequencies ranging from 5 kHz to 1 MHz. While high frequencies pass through the whole body’s water, very low frequencies cannot penetrate cell membranes and thus only pass through the extracellular water (ECW) space. The generated impedance data are applied to calculate total body water (TBW), intracellular water (ICW) and ECW.$^{17}$

**Results**

**Clinical and laboratory parameters**

TLV treatment reduced the patient’s body weight from 52.5 to a minimum on day 5 (48.9 kg). Pleural effusions, ascites, and peripheral oedema regressed. Clinical well-being improved substantially (improved activity level, less abdominal pain, reduced shortness of breath and improved appetite). We were able to reduce the concomitant diuretic therapy on day 12 of TLV treatment (Table 1). As main side effect, the patient described increased thirst and intermittent headache.

Laboratory values including electrolytes, liver and kidney function and urine analysis at each visit (Table 1). Before commencement of TLV treatment, the patient showed a decreased serum sodium concentration of 129 mmol/l, which increased during treatment to a maximum of 135 mmol/l on days 4 and 5 and remained between 130 and 134 mmol/l during the whole treatment period. At the time of $^{23}$Na-MRI measurements, 26 days before, at days 9 and 29 of TVL treatment, only slight differences in serum sodium could be detected (Table 1). Plasma renin activity and aldosterone were both elevated before treatment, aldosterone decreased to normal values, while plasma renin activity remained steady. Liver enzymes did not increase during treatment (Table 1).

**Tissue sodium and fluid status**

The initial image before therapy (−26 days) revealed an increased tissue sodium content in skin (23.8 mmol/l) and muscle (24.7 mmol/l) compared with age-matched female controls (skin 13.3 $\pm$ 2.7, muscle 15.8 $\pm$ 1.6 mmol/l, $n$ = 8, age 24.6 $\pm$ 2.1; Figure 1). The second $^{23}$Na-MRI on day 9, revealed reduced muscle (22.4 mmol/l; reduction of 9.3%) and skin sodium content (18.4 mmol/l; reduction of 22.7%) (Figure 2A, A2). The third $^{23}$Na-MRI on day 29 of treatment revealed the long-term effect on the target TVL dose of 1 mg/kg/day. $^{23}$Na-MRI assessment showed a further decrease in tissue sodium in muscle (21.7 mmol/l) and skin (17.4 mmol/l) (Figure 2A, A3). A total reduction of 12.2% in muscle sodium and 26.9% in skin sodium was detected overall after initiating TLV treatment. Despite a further reduction in tissue sodium in muscle and skin, the extracellular water (overhydration) as measured by BCM and total body weight (52.4 kg) increased slightly in our long-term assessment (Figure 2A, A3).

**Discussion**

This is the first report of additional TLV treatment in a Fontan patient with PLE and severe, persistent fluid retention where conventional diuretic treatment had proven to be insufficient. The
Main finding of this serial $^{23}$Na-MRI investigation was a pronounced accumulation of sodium in muscle and skin, which was mobilised by TLV treatment. While the normalised tissue sodium amount persisted, TLV reduced body water only transiently, illustrating an uncoupling of salt and water homeostasis.

Managing Fontan patients with severe symptoms of PLE remains challenging, and pharmacological strategies are often only symptomatic with limited efficacy over time. TLV has been proposed as a new treatment alternative in biventricular patients with heart failure involving hypervolaemia and hyponatraemia resistant to conventional diuretic therapy. This motivated us to consider TLV as a new therapeutic agent for our Fontan patient with PLE. The intestinal protein loss in Fontan patients results in reduced albumin and total protein and, therefore, reduced oncotic pressure, hyponatraemia and volume overload. In addition, a chronic inflammatory response is thought to be involved in the development and maintenance of PLE symptoms, affecting cell permeability and contributing to protein loss and oedema.

Although the EVEREST study (Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with TLV) failed to demonstrate a survival benefit from TLV treatment in patients suffering from exacerbated chronic heart failure, a sub-analysis showed reduced long-term morbidity and mortality for patients with hyponatraemia. In our patient, who had low sodium level before therapy, TLV alleviated pleural effusions.

Figure 2. $^{23}$Na-MRI of tissue sodium. (A) $^{23}$Na-MRI of the left lower leg for assessment of muscle and skin Na$^+$: before therapy [A1]; and during short-term [A2, day 9] and long-term [A3, day 29] therapy. Four tubes containing 10, 20, 30 and 40 mmol/l of NaCl-standard solution were placed below the lower leg. (B) Anatomic localiser. Graph representing absolute values of tissue Na$^+$ [red, muscle; blue, skin], BCM overhydration [black] and body weight.

BCM, body composition measurement; $^{23}$Na-MRI, $^{23}$Na-magnetic resonance imaging; TLV, Tolvaptan.
and ascites and improved her clinical state of health.

In addition to the clinical improvements, \(^{23}\text{Na-MRI}\) enabled us to visualise sodium accumulation in muscle and skin during treatment. Before TLV treatment, we identified markedly increased tissue sodium levels. Similar findings have been reported in patients with heart failure.\(^{13}\) Despite serum hyponatraemia, Fontan patients seem to be sodium overloaded. \(^{23}\text{Na-MRI}\) identified a gradually decrease in tissue sodium during TLV treatment, which we did not expect, as TLV is supposed to only increase urinary water excretion. However, the anticipated mobilisation of body water was merely transient and not accompanied by a commensurate change in tissue sodium during long-term treatment. The serum sodium analysis in our patient could not have predicted these changes at the tissue level.

We can only speculate how TLV affects overall tissue sodium-water homeostasis in Fontan patients. A direct effect is excluded since aquaporin-2 channels do not exist in skin and muscle. However, the Vasopressin-2 receptor (V\(_2\)R) is expressed not only in the collecting duct, where it promotes water reabsorption, but can also be found in the ascending limb of the Henle’s loop (TAL) in the kidney. Furthermore, antidiuretic hormone (ADH) – the ligand of V\(_2\)R – is known to increase NaCl reabsorption via the NaK2Cl-cotransporter (NKCC2) and additionally by paracellular mechanisms in the TAL.\(^{21,22}\) According to these data, one could assume that TLV increases renal NaCl excretion. A higher urinary sodium excretion has been reported in patients with autosomal dominant kidney disease (ADPKD) receiving TLV therapy, and might explain the tissue sodium mobilisation that we were able to illustrate in our patient.\(^{23}\)

Another explanation could be the observed changes in the renin-angiotensin-aldosterone (RAA) system: aldosterone levels dropped substantially, whereas renin levels fell only temporarily during TVL administration. The aldosterone pathway plays a crucial role in PLE pathogenesis, as blocking it by mineralocorticoid effects of budesonide has the potential to reduce PLE symptoms in some patients.\(^{19}\) Additionally, recent imaging studies suggest lymphatic vessel abnormalities to be associated with the development of PLE and, interestingly, the aldosterone pathway regulates their permeability.\(^{24}\)

Previous investigations reported tissue sodium storage in patients suffering from hyperaldosteronism, which was reversed following specific treatment.\(^{11,25}\) The same aldosterone effect might have caused the pronounced tissue sodium accumulation we observed in our Fontan patient. The effect of TVL on RAAS and particularly aldosterone, might be multifactorial especially in combination with other diuretics (e.g. spironolactone).\(^{26,27}\) The decreased aldosterone level in our patient might represent a favourable TLV mechanism. The current standard treatment of volume restriction and diuretics may even exacerbate this condition by further enhancing RAAS and especially the aldosterone pathway.\(^{27,28}\)

We believe that our results support the rationale of a TLV trial in univentricular patients with hyponatraemia and volume overload due to PLE. Due to the clinical improvements in our patient, we continued TLV therapy beyond this described study period. Importantly, long-term administration of high doses of TLV seem to be safe, as shown in multicentre trials of ADPKD patients receiving TLV treatment for up to 11 years.\(^{29,30}\)

As our report is limited, prospective and controlled studies are needed to clarify TLV effects in Fontan patients with PLE and hyponatraemia, hypoproteinaemia, and treatment resistance, as our case illustrates.

**Conclusion**

\(^{23}\text{Na-MRI}\) and BMC delivered novel insights into the water and sodium homeostasis of a Fontan patients with PLE treated with TLV. TLV lowered tissue Na\(^{+}\) overload and improved clinical wellbeing.

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Authors' contributions
JM and OT had the idea of the study. CK analysed the $^{23}$Na-MRI data. PL performed the $^{23}$Na-MRI measurements. AD performed the laboratory measurements. MS and MU enabled the measurement times and infrastructure. JM and SD and RC analysed and interpreted the patient data. AN established $^{23}$Na-MRI measurement at the University of Erlangen. JM and CK wrote the manuscript, while SD, RC and OT were major contributor in writing. All authors reviewed and approved the final manuscript.

Availability of data and materials
All data generated or analysed during this study are included in this published article.

Conflict of interest statement
The authors declare that there is no conflict of interest.

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Ethics approval and consent to participate
$^{23}$Na-MRI and body composition monitor measurements were approved by our local Ethics Committee (No. 3948) and carried out according to the declaration of Helsinki. Our patient and control group provided written informed consent.

Consent for publication
Patient gave consent for publication.

ORCID iD
Julia Moosmann https://orcid.org/0000-0002-8843-7084

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