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Vesicoureteral Reflux Imaged in an Animal Model Using EIT

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Abstract - A preclinical study was conducted in July 2021 to detect Vesicoureteral Reflux (VUR) non-invasively using Electrical Impedance Tomography (EIT). VUR involves the backflow of urine from the bladder to the ureters or kidneys and diagnosed predominantly in the paediatric population from birth to 5 years of age. To recreate VUR in three healthy pigs, stents were positioned at the junction between the bladder and ureters – the Ureterovesical Junctions (UVJ). A Foley catheter was introduced into the bladder via the urethra and used to inject solution mimicking the properties of urine. The stents opened the UVJ to allow urine to more freely travel from the bladder into the ureters and the kidneys during bladder infusion. The simulated VUR was confirmed using fluoroscopic imaging. VUR is a long-term condition, whereas this stenting procedure resulted in acute kidney reflux. VUR achieved using this method was approximately Grade II-III (2-3). The refluxed solution was detectable through regional conductivity changes reconstructed from EIT measurements and localised to the correct kidney. Conductivity changes were observable in 73% of cycles without motion (8 of 11) and 44% of cycles with motion (4 of 9).

Keywords: Vesicoureteral Reflux (VUR); animal model; kidney; bladder.

1. Introduction

Vesicoureteral Reflux (VUR) is an anatomical and/or functional disorder causing backflow of urine from the bladder to the kidneys (Figure 1). With a prevalence of 1.8% in the paediatric population, the condition occurs in 30-40% of children who present with Urinary Tract Infections (UTIs) (Sargent 2000, Hoberman *et al.* 2003). It is the most common urinary tract abnormality in babies and children up to five years of age (Snow *et al.* 2010). VUR has potentially serious consequences such as renal scarring and renal parenchymal damage secondary to increased risk of recurrent febrile urinary tract infections (UTIs). VUR associated nephropathy can lead to hypertension and end stage renal disease (Mattoo 2002). There are five grades of VUR ranked based on the severity of urine backflow and dilation of the ureters and kidneys. VUR often resolves over time, but in certain cases requires surgical intervention.

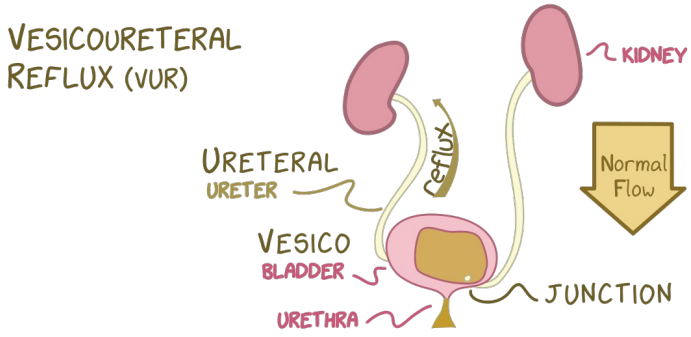

Figure 1. The kidneys are protected by the lower ribs, near the spine, at the back of the abdominal wall. The kidneys are in the retroperitoneal space, separated from the visceral organs (stomach, liver, intestines, and colon) by a thin layer of the peritoneum. The right kidney is typically lower than the left due to the placement of the liver. Normally, urine flows from the kidneys to the bladder through the ureters (3-4 mm dia. and 9-21 cm long in children 1-7 years of age), assisted by smooth muscle peristalsis along the lower third of the ureters. The ureters enter on the underside of the bladder.

The gold standard method used to detect VUR is the Voiding Cystourethrogram (VCUG) and involves radiation exposure, catheterisation and observed voiding. Guidelines recommend that ultrasound be performed on patients with signs of VUR, and if the ultrasound shows concerning features such as uretral dilation or hydronephrosis, a VCUG is recommended. However, ultrasound is not sufficiently sensitive to detect VUR (sensitivity is 0.44 with a 95% CI of 0.34 to 0.54) (Shaikh et al. 2016). More recently, contrast-enhanced Voiding Urosonography (ceVUS) has started to gain popularity in place of the VCUG procedure in the USA (ceVUS has been widely used in Europe for some time). A ceVUS will avoid radiation exposure but still requires catheterisation. A VCUG uses fluoroscopy to observe the introduction of radiocontrast into the bladder through a catheter (Figure 2). VUR is detected when the contrast agent moves from the bladder into the ureters or kidneys. In the most severe VUR (Grade V), the contrast agent fills and dilates the ureters and the kidneys.

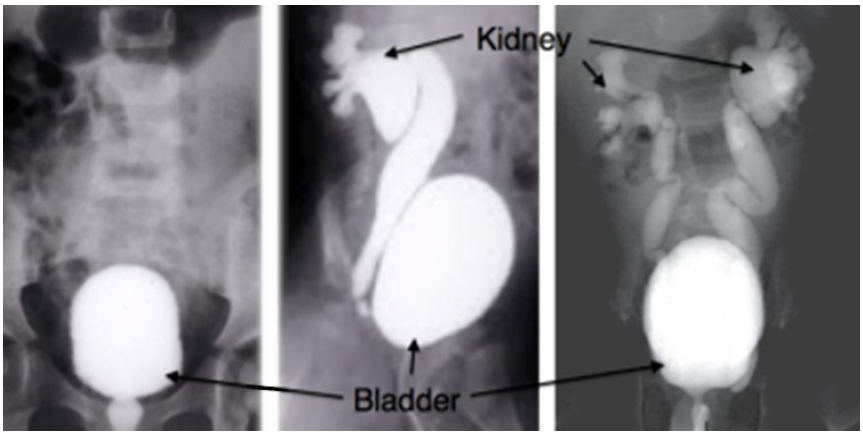

Figure 2. X-ray images of contrast agent in a patient (*left*) with no VUR (full bladder), and (*middle and right*) with severe Grade V VUR (side and front views, respectively; bladder, ureters and kidneys filled).

The VCUG procedure is traumatising and painful for the child, and it is stressful for parents, medical imaging staff and physicians. Specific risks associated with the VCUG are catheter associated UTIs, bladder spasm, painful urination post-procedure, and contrast agent allergic reaction. Behaviours consistent with post-traumatic stress disorder have been observed in young children after a VCUG, such as repetitive play, difficulty communicating, sudden changes in behaviour, and a newfound fear of health care settings (Stashinko *et al.* 1998). There is a clinical need for a non-invasive VUR detection method without radiation exposure and trauma.

A pre-clinical trial using a 32-electrode EIT system and inertial measurement units (IMU) was conducted in July 2021 on three pigs. Ethics approval for the animal study was granted by the Government of Cantabria, Spain (GAN/55/2013, reference PI-06-21, NIF: 72034697P). The key features distinguishing this data from previous pre-clinical VUR experiments by Kite Medical (Dunne *et al.* 2019) are:

- Stenting of the ureters, rather than severing them, thereby including bladder filling effects in the data. A stent was positioned between the ureters and bladder, where previously a catheter directly infused solution into the ureters.
- Intentional movement of the animal during data collection. Six IMUs (accelerometer, gyroscope, magnetometer) were used to directly measure the movement and to quantify the amount of movement at the skin surface around the kidney where electrodes were most densely placed.
- New EIT hardware and software.
- Electrode positions optimised to detect VUR and to isolate nuisance conductivity parameters (Aggrawal *et al.* 2021) in a 3D arrangement where previously a 2D ring of electrodes was used.

This paper reports briefly on this new animal model of VUR, the analysis of these results, and addresses the primary question “Does it work?”, concluding with the overall outcome and next steps.

2. Method

For three pigs, the following procedure was completed:

1. The animal was anaesthetised and ventilated. Either one or both UVJs were stented. Placement of the stent was confirmed with CT or fluoroscopy.
2. Sensors were applied and calibrated.
3. Up to 32 cycles of catheterised filling and draining the bladder were completed while capturing measurements. For the first and last cycles, x-ray contrast agent and fluoroscopy were used to confirm VUR. Otherwise, saline was used with conductivity values that similar to urine. On alternating cycles, movement was modelled by manipulating the pig’s left leg. Each stage of a cycle (empty, filling, filled, draining, back to empty again) was 30 to 90 seconds. Data was recorded continuously throughout the experiment.

The experiment was conducted in July 2021 at Hospital virtual Valdecilla (HvV) in Santander, Spain. In these experiments, up to 32 cycles per pig were possible. To accelerate the experiment, the data was collected continuously

across all cycles for each pig.

Movement results in noise in the signal that can be challenging to overcome. The intention was to produce a steady movement artefact. Initial movement was a gentle circular rotation of the leg: foot approximately circling a 15 cm diameter region at 3 Hz with movement largely restricted to the area around the left thigh. By halfway through the first pig, the movement had transitioned to using the pig's lower leg (fibula and tibia) to lever the hip (still at approximately 2 Hz) causing the hip to lift off the table and the whole surface of the pig to shake at higher harmonics of the movement frequency.

Data was analysed by constructing models of the initial shape for each pig using photogrammetry. The stimulus and measurement sequences were designed specifically for our 3D electrode arrangement to localise conductivity changes in both kidneys, (Aggrawal *et al.* 2021). The model was meshed; then simulations of current density were used to iteratively refine the mesh density based on the element-wise sensitivity computed from the Jacobian (Figure 3).

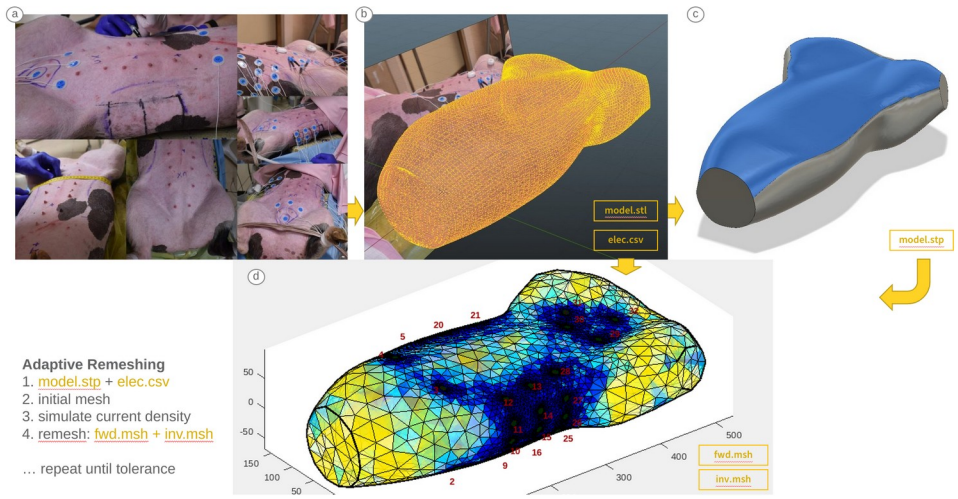

Figure 3. (a) Photos were acquired from many angles, (b) a model was constructed from the photos using 3D modelling software, (c) the 3D model was converted to a set of smooth surfaces so that the model vertices did not define the mesh density, (d) the smooth 3D model was meshed with electrodes. The electrode coordinates were acquired from the photos and mapped to the 3D model-space.

The EIT data was used to reconstruct conductivity change in 3D. Blocks of data were filtered over time to compare empty to full bladder states. The dynamics of a transition from empty to full and back to the empty state were observed, both with and without movement. The IMU data was used to (a) corroborate when movement was happening and to quantify the movement of the leg and around the electrodes, and (b) to confirm the breathing signal in the EIT data.

3. Results

The bilateral and unilateral stent cases presented distinct patterns in the conductivity reconstructions. The unilateral case was clearly identifiable with increases in conductivity (red region) on the left side of the pig, matching the location of the stent. The region of conductivity change is clearly associated with the location of the kidney. For the bilateral case, the conductivity increase is shared between right and left side. The situation is identifiable with or without motion (Figure 4, Figure 5).

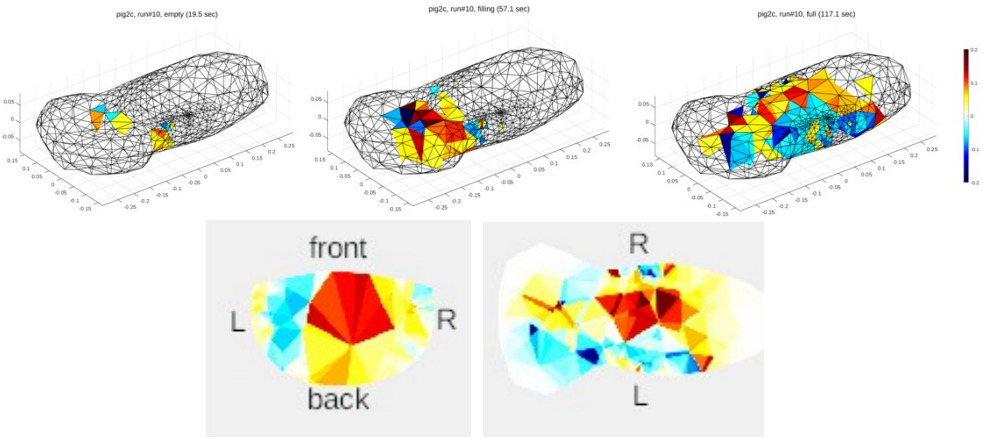

Figure 4. (*above*) Bilateral filling (pig A) from empty, filling (bladder changes), to full state (kidney changes); no motion; (*below*) A cross-sectional view in x, y, and z-axes in the full state, illustrating bilateral changes in conductivity near the kidneys.

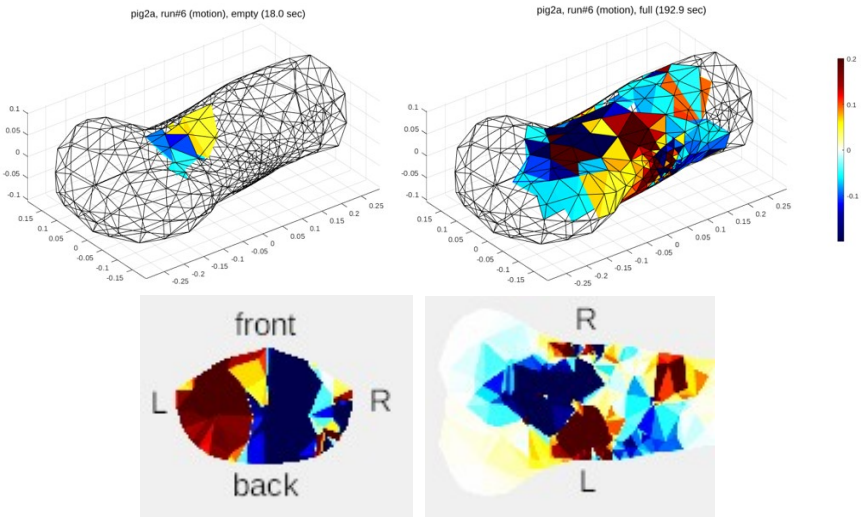

Figure 5. (*above*) Unilateral filling (pig B, left-side stent) from empty to full state bladder state (left-kidney changes); with motion; (*below*) A cross-sectional view (x- and z-axes; full state), clearly illustrates unilateral changes in conductivity for the left kidney.

4. Discussion

In the study, we recreated approximately Grade II to III VUR. The acute VUR condition induced by a stent means that stretching of the ureters into a tortuous expanded tube, associated with chronic Grade IV or V VUR, was not possible. A porcine model was the most appropriate animal model to simulate VUR because physiological characteristics and the dielectric properties of the porcine kidney are similar to that of humans (Paltiel *et al.* 2000).

Multiple photographs were acquired to build a 3D model of each pig. Use of a camera or video in a human clinical trial is problematic from a privacy perspective. Developing high quality initial models is important for 3D EIT reconstructions. CT and MRI data for developing Statistical Shape Models of the lower abdomen in both pigs and humans is under-represented in the available data sets we have examined. CT/MRI data are expensive to acquire. Many of the promising data sets did not include the exterior of the body: most renal and bladder CT/MRI use a narrow field of view to focus on specific organs. Therefore, fast methods for acquiring patient-specific models are important.

Improved 3D EIT reconstructions using IMU data to track movement is a promising avenue for further work.

5. Conclusions

The available evidence suggests that VUR is detectable, independent of breathing, and in many cases independent of aggressive, repetitive movement of the lower limbs. Changes in induced unilateral and bilateral VUR were correctly localised. This data provides further evidence of the potential for EIT to identify VUR in a non-invasive and radiation-free manner.

In the cases where conductivity changes were not detected, the key issues were measurement noise due to either movement (typical bioimpedance/electrode movement effects) or intermittent instrument noise. Instrument noise must be addressed going forward. Further algorithm development will help to mitigate residual movement effects.

Acknowledgments

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