2001

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Original Publication Citation

Mevorach, R. A., Cilento, B., Zahorian, S., Badgett, C., Walker, R., Atala, A., . . . Meyer, M. (2001). A noninvasive test for vesico-ureteric reflux in children. *BJU International, 87*(6), 467-472. doi:10.1046/j.1464-410X.2001.00096.

BJU International (2001), **87**, 467–472

A noninvasive test for vesico-ureteric reflux in children

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Objective To report the development and testing of a device for the noninvasive diagnosis of vesico-ureteric reflux (VUR) which avoids the need for urethral catheterization (currently required to reliably determine the presence of VUR), and which thus avoids the anxiety of parents and patients that causes many families to refuse such evaluation.

Patients and methods Fifty-four children (49 girls and five boys, mean age 7.2 years, range 4–14) previously evaluated as having VUR volunteered to participate; no child was symptomatic at the time of the study. Refluxing units were known to be present by voiding cysto-urethrography (within 1 year, mean 7 months) in 45 and absent in 16. The device developed acquires electronically processed acoustic signals from the child during an observed urination. The signals are then analysed 'off-line' to determine the presence or absence of VUR. The initial preparation for the test included: (i) a full bladder [at least $0.80 \times \{(2 + \text{age}) \times 30$ mL$\}$] measured by ultrasonography; and (ii) localization of the pelvi-ureteric junction by ultrasonography to accurately place the device's sensors on the child's back. The children were then positioned at a commode after placing the sensors; the recording was started and continued until voiding occurred. The children were tested with the recording and analysis team unaware of the presence and/or degree of VUR. The first 47 studies were single-kidney examinations and the remaining seven included simultaneous monitoring of both kidneys.

Results Sixty-one renal units were assessed and interpretable signals were obtained from 54 (89%). There were seven episodes of 'system failure' when no interpretable data were obtained. One unit with no VUR had a 'reflux' signal; in four kidneys, spontaneous (two) and postsurgical (two) resolution of reflux was predicted by the testing and subsequently verified by cyclic radionuclide cystography.

Conclusions This noninvasive diagnostic technique detected VUR in 35 of 37 refluxing units and verified no reflux in 16 of 17 units without VUR. Further refinements may allow this technology to be used in all children with suspected VUR.

Keywords acoustic, vesico-ureteric reflux, diagnosis, noninvasive test

Introduction

VUR is one of the most common diagnoses in paediatric urology and has contributed to a substantial portion of renal injury [1–3]. UTI occurs in 4% of children by the age of 12 years and the complete diagnostic evaluation of these children includes a VCUG to assess for the presence of VUR [4]. Additionally, prenatal ultrasonography detects a genitourinary abnormality in 1 : 100 births and most of these are hydronephrosis; VUR can be diagnosed in ≈ 30% of these neonates [5].

In the course of the medical and surgical management of VUR many voiding studies, using either fluoroscopic or nuclear imaging, are routinely undertaken. While generally well tolerated, the invasiveness of this testing can pose an obstacle to follow-up and even be traumatic in certain patients [6]. In response, we developed and preliminarily tested a noninvasive diagnostic acoustic method to detect VUR.

Patients and methods

From 1997 to 1999, 54 children (49 girls and five boys, mean age 7.2 years, range 4–14) with a previous evaluation showing VUR volunteered for the study and were tested using the diagnostic device. There were seven 'system failures' during which no signal file was recorded, leaving 54 renal signals from 50 children available for analysis, comprising 17 units with no and 37 units with VUR. Children were placed at a commode (girls seated and boys standing) once a full bladder $[0.80 \times (2 + \text{age}) \times 30]$ was verified by ultrasonography. Sensors from the VUR data acquisition system (VURDAS) were placed over the PUJ (located by ultrasonography or manually); these

Fig. 1 VUR data acquisition system (VURDAS); the configuration shows two renal sensors, a wetness sensor and acquisition hardware.

automatically recorded acoustic urinary tract signals generated during urination (Fig. 1). The recorded signals were analysed by members of the research team who were unaware of the presence or absence of VUR as assessed by VCUG or radionuclide cystography (RNC) before the study.

The VURDAS system hardware includes three sensors; two electronic stethoscopes (E-Scope, P/N 718–7120, Cardionics Inc. Webster, TX) and a moisture detector. The E-Scope outputs are audio analogue signals and the moisture detector output is a CMOS compatible digital signal of 0.01 V (logical '0') or 4.90 V (logical '1'). The sensors are connected through an interfaced box to a multichannel data-acquisition board in laptop computer. The information is stored and analysed using conventional data acquisition and analysis software.

The test is initiated by first placing the primary sensing elements of the two E-Scopes on the patient's back over the PUJ (using ultrasonographic guidance initially and then placed 1-cm caudal to the costovertebral angle). Next, the primary sensing element of the moisture detector is placed in the urine 'catch container'. The system software allows the user to add a 'header' containing patient information to the file of collected data. Currently, data are analysed separately (off-line) from data collection.

The current software is organized as an administrative section (where patient information is entered and a file name selected) and a data-acquisition section to collect and save the data. The VURDAS accumulates 4 s of data before the trigger (i.e. the onset of urination) is detected; at any time after the 4-s of data has been acquired and the system is triggered, data are collected for an additional 2 s. The 6 s of captured data is then displayed on a graph, which is saved to the appropriate file. The data are acquired continuously, each 4 s of data being saved to a shift register in blocks of 3 s while waiting for the trigger. In this mode, data older than 4 s are discarded and new data saved in memory. When the trigger is detected the shift register terminates and an additional 2.6 s of data are collected. Thus the final data record consists of 6.6 s of data (4 s before urination and 2.6 s afterward). From the user's perspective, once data collection starts the plot flows smoothly across the computer screen until urination is detected. There is no need for any intervention by the operator until the test is finished (although the user has the option of stopping data collection if desired).

To obtain an acoustic spectrogram, the signal is divided into overlapping windowed segments (frames). The short time spectrum is then computed with a fast-Fourier transform for each frame, forming several columns of values of the short-term, time-localized frequency content of the signal. The intensity at each time and frequency is then colour-coded, as shown in Fig. 2, with red areas representing the highest amplitude, yellow the intermediate and blue the lowest. Hence in both spectrograms in Fig. 2 the signals are concentrated at very low frequencies (<200 Hz) for the duration of the record.

The spectrogram function in the software was used to obtain a matrix of frequency intensities so that the frequencies of interest could be easily isolated. As there are major differences at 350–1000 Hz between a 'VUR' record and one showing no VUR, the rows containing the information between those frequencies were captured. The rows were then averaged and plotted, showing peaks in frequency intensity when VUR is present. There are regular intervals of higher frequency acoustic content when VUR is present; as the previous analysis relied upon the magnitude of the signal rather than the frequency content, this new finding could help to eliminate the error that might occur with improper gain settings on the stethoscopes.

Results

Sixty-one renal units were assessed and interpretable signals obtained from 54 (89%); their signal generation in relation to reflux grade, or absence of VUR is shown in Table 1. Reflux signals were characterized by a higher frequency intensity at 400–800 Hz that uniformly began just before micturition. In Fig. 3, the acoustic time signal, spectrogram and frequency intensity from 350 to 1000 Hz are plotted for the left and right kidneys of a patient who had VUR; the differences between signals from VUR or no VUR are apparent, as they occur in the same child at the same time. The results from a child with no VUR in either kidney is shown in Fig. 2; comparing the plots with those in Fig. 3, they closely resemble those from the kidney with no VUR.

One unit without VUR was found to have a 'reflux' signal, giving a positive predictive value of 97%. Two

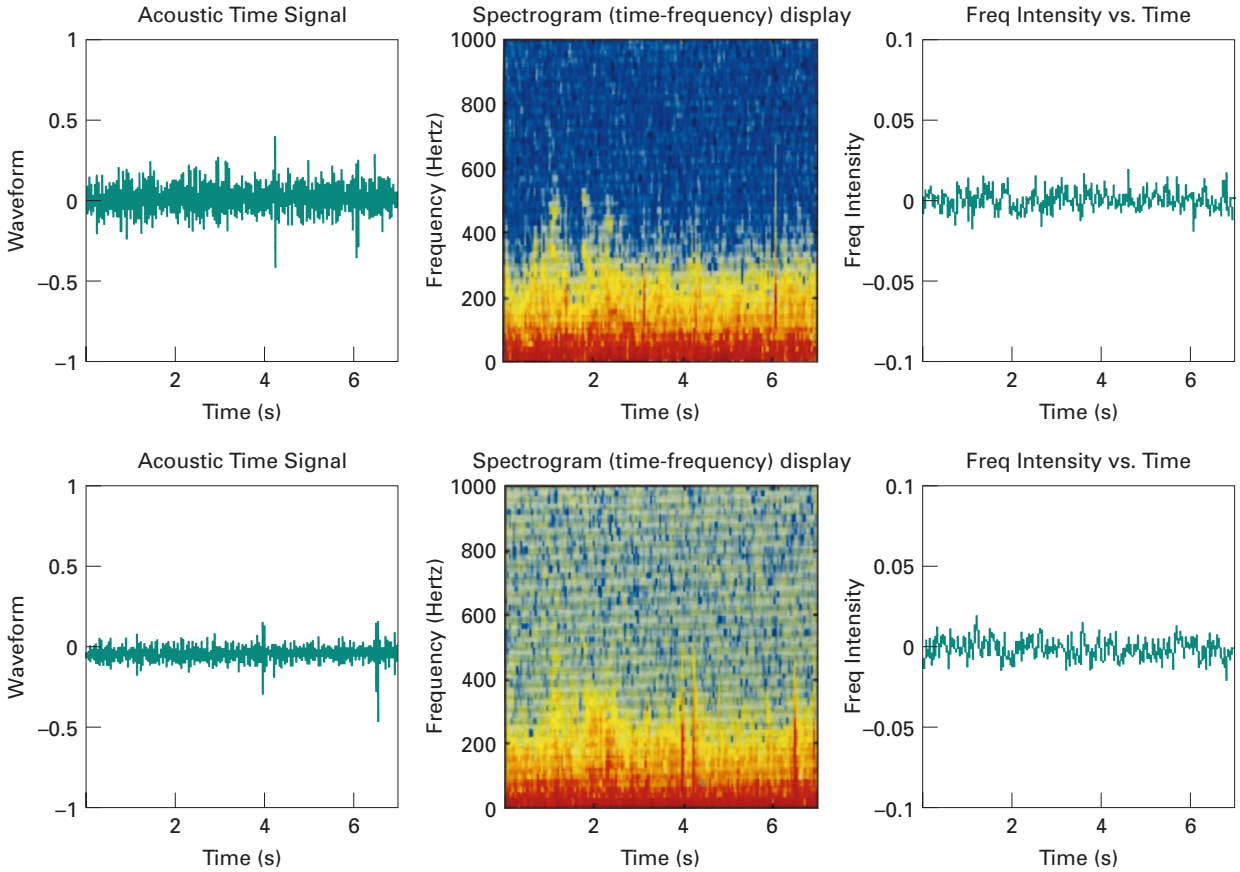

Fig. 2. Signal analysis using spectrograms; the signals from the two kidneys are shown in top and bottom panels. Most of the activity is at ≈ 200 Hz (red represents the highest amplitude, yellow the intermediate and blue the lowest), suggesting no VUR in either kidney.

children with grade 1 reflux generated no detectable reflux signal to the level of the kidney sensor, giving a negative predictive value of 89%. In four kidneys, spontaneous (two) and postoperative (two) resolution of reflux was predicted by the testing and subsequently verified by cyclic radionuclide cystography. No child refused testing and most offered to return if asked.

Discussion

In the 1960s, VCUG was found to complement the information obtained from IVP and became established as an essential step in the proper evaluation of children with UTI and potential VUR [7]. Radionuclide cystography, despite the lack of anatomical detail, subsequently assumed a role in monitoring children with VUR [8,9]. During this period, the definition of VUR and its relation to UTI was determined through a study of anatomy, fluid mechanics, physiology and pathology, but longitudinal human study was limited, partly because of the need for invasive testing [10–17].

The invasive aspect of evaluating reflux remains; advances in digital imaging have decreased radiation exposure, and the use of ultrasonographic contrast material may preclude radiation exposure entirely [18–21]. However, attempts at the noninvasive evaluation of VUR, as with colour flow Doppler ultrasonography, require significant expertise and have lower specificity and sensitivity than VCUG or RNC [22–24].

Although VCUG can be used without causing a medical complication, the emotional effect of this invasive test is apparent in many of our patients in daily practice, and has been reported previously. Indeed, the memory of this testing has been used as a

Table 1 Results of study comparing grade of reflux and signal presence or absence

Reflux grade	*Signal present*	*Signal absent*
1	0	2
2	16	0
3	13	0
4	6	0
None	1*	16
Total	36	18

* Repeat cystogram refused.

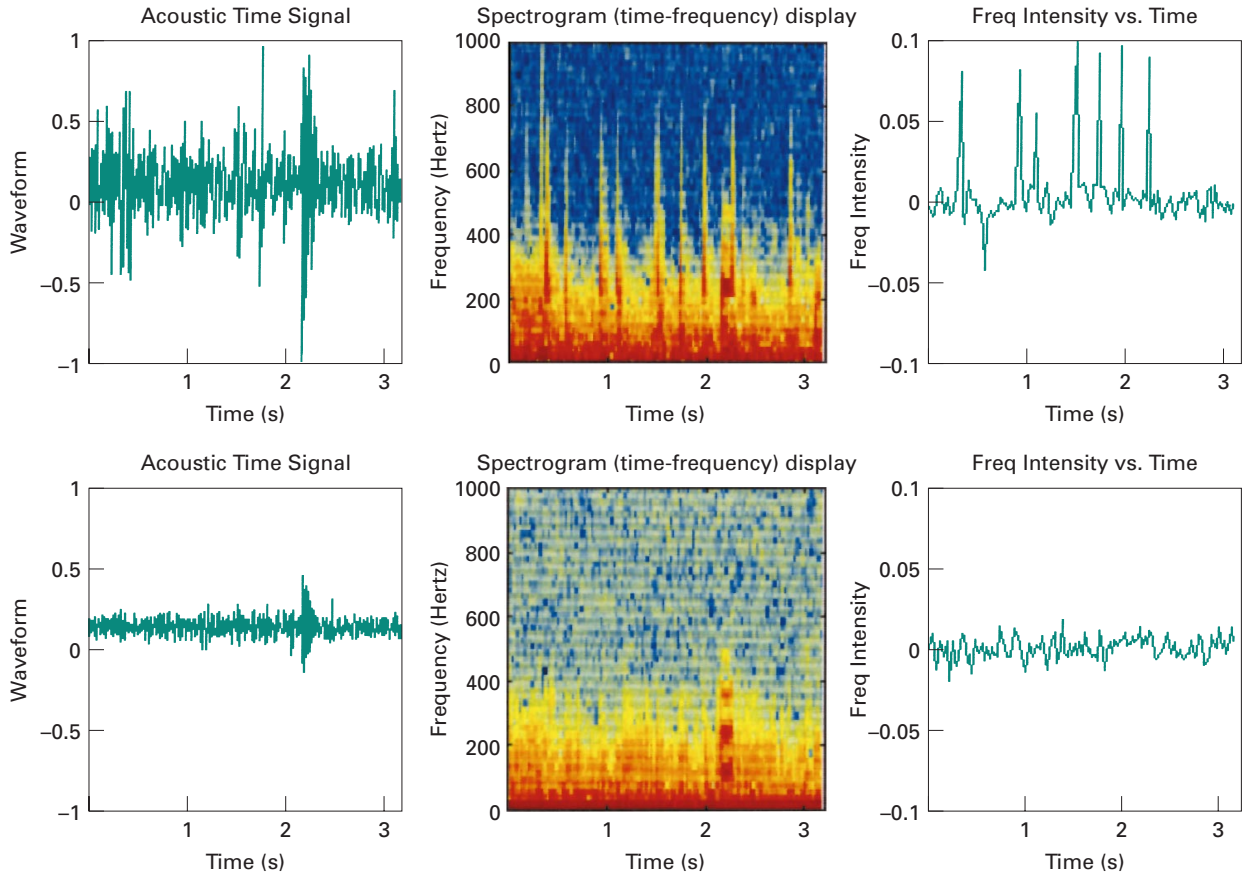

Fig. 3. The two-channel display with spectrogram and frequency intensities of 350–1000 Hz. The VUR signal is on the top row.

benchmark in studies designed to delineate recall variables for childhood psychological trauma and sexual abuse [25].

The preliminary results of the present noninvasive method show an efficacy equal to that of single-fill VCUG, but with no need for catheterization, radiation exposure or skilled technicians. The lack of anatomical delineation certainly precludes the use of VURDAS as a replacement for VCUG, but preliminary results indicate that normal renal/bladder ultrasonography and a normal acoustic study are equivalent in excluding underlying pathology, except for grade 1 VUR. Further, the benign nature of the present procedure may allow a more detailed evaluation of VUR and its management. For example, an important finding during the development of the VURDAS was the relation of the reflux signal to the onset of micturition. From VCUG-based experience, where reflux often occurs only with voiding, the expectation was that a 'reflux signal' would probably occur during urination. However, the initial findings were of a signal onset just before micturition. Given that the moment of maximal pressure within the refluxing bladder, as outlined by Sillen [26], often occurs before passing urine (because there is an element of dyssynergia) this finding is consistent with bladder physiology. This deviation from expectation that was based upon 'VCUG experience' was the first important indication that not only could reflux be detected from acoustic signals, but also that the detection of passive reflux would provide new information.

Many questions about the clinical behaviour of VUR remain unanswered. The influence of hydration and position upon the grade or presence of VUR remain undetermined. Long-term data on the resolution of VUR with medical and surgical treatment (at >2 years of follow-up) have not been pursued, largely because current testing is invasive [27–29]. The behaviour of patients with VUR, whether repaired surgically or not at the time of pregnancy, is also incompletely understood [30,31]. With improvements in the VURDAS, these questions may be pursued.

The advent of routine prenatal ultrasonography has identified a new group of patients with VUR. Disregarding the question of the overall clinical pertinence, none would dispute that some neonates with hydronephrosis will be spared renal scarring from UTI and VUR through early detection and prophylactic antibiotics. Perhaps noninvasive diagnostics, minimally invasive and medical therapy, and a noninvasive follow-up will provide the

tools to prospectively study the natural history of managing VUR and thereby improve the care of these children.

Invasive testing should remain the gold standard as long as it provides diagnostic information unattainable noninvasively [32]. The present noninvasive technique might be applicable to all children undergoing an evaluation for VUR. Enhancements in signal analysis may provide not only greater ease of use in any setting, but also serve as a tool for the improved prospective evaluation of VUR and its management.

Acknowledgements

Carin Davis, Patrick Hayes, Mike Lamberty, and Karl Wojcik, William Hart, William Groves, Arthur Whittaker, of the Department of Electrical and Computer Engineering at Old Dominion University for substantial contributions to this work.

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