

# Renal elasticity quantification by acoustic radiation force impulse in children born preterm: preliminary results

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## Abstract

An emerging hypothesis from the recent literature describes how specific adverse factors related to growth retardation and low birth weight might influence renal development during fetal life and the insurgence of relevant pathologies in adulthood.

Preterm births and related perinatal events can affect the mechanical proprieties of kidneys in childhood.

We retrieved the laboratory medical records of 3 children born preterm, all in good condition, and investigated the elastic properties of their kidneys using the acoustic radiation force impulse (ARFI) technique. Shear wave velocity (SWV) obtained by the ARFI technique depends on the elasticity of a parenchymatous tissue.

Medical records of case patient 1 showed a shorter right kidney (5<sup>th</sup> percentile), a greater protein/creatinine ratio and higher  $\alpha$ 1-microglobulin in the urine spot if compared with controls. Patients 2 and 3 had unremarkable laboratory results. Moreover, compared with the same results of healthy full-term normal children obtained from a previous study of ours, we observed higher SWV values (m/s) for the left kidney in patients 1 and 3; patient 2 had lower SWV values in both kidneys.

The altered SWV values, measured in these children born preterm, may be correlated with a possible underlying renal pathology (for instance, disruption of the renal histology). Altered SWV values are generally observed also in 2 out of 3 children with a history of normal laboratory markers of renal function. Further studies are needed on larger cohorts of patients.

## Keywords

Acoustic radiation force impulse, chronic kidney disease, prematurity, shear wave velocity.

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## Introduction

Acoustic radiation force impulse (ARFI) is a recently established ultrasound (US)-based diagnostic technique that allows physicians to obtain a measure of the elastic properties of an organ. Shear wave velocity (SWV) obtained by the ARFI technique depends on the elasticity of a parenchymatous tissue: the stiffer a tissue is, the faster the shear waves spread through it.

An emerging hypothesis from the recent literature [1-3] described how specific adverse factors related to growth retardation and low birth weight (LBW) might influence renal development during fetal life. However, LBW and premature birth have been associated with focal segmental glomerulosclerosis development [4]. Moreover, LBW and prematurity are the most consistent clinical surrogates for a low nephron number and are associated with increased risk of hypertension, proteinuria and kidney disease later in life [5].

To date, few studies [6-8] have focused on the ARFI technique applied to native kidneys in childhood. Among these, no studies have been designed to evaluate kidneys of children born preterm. We hypothesize that a disruption of the renal histology, consequential to preterm birth and various perinatal events, can affect the mechanical properties of the kidneys of these children. The aim of the present study was to investigate the elastic properties of the kidneys in 3 children born preterm.

## Methods

We reviewed the medical records of 3 children born preterm. In particular, we reviewed the serum level of creatinine, nitrogen and cystatin-C, spot urinary creatinine and protein excretion and

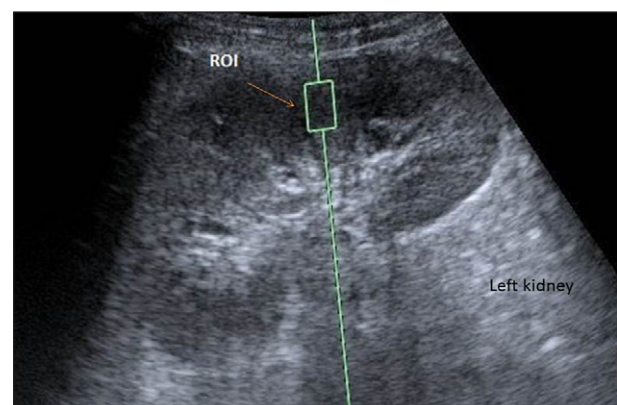
urinary  $\alpha$ 1-microglobulin, all assessed by standard laboratory methods. Estimated glomerular filtration rate (eGFR) was recalculated using the formula according to Schwartz et al. [9]. Conventional US results were also reviewed and compared with standard charts for age [10].

We recalled the 3 children for a conventional US follow-up and to measure the SWV using the ARFI technique.

All ultrasounds were done by a single qualified technician using a convex probe (frequency 4 MHz) on an ACUSON S2000™ system (Siemens, Erlanger, Germany). All three patients were evaluated soon after micturition, in the supine position with a subcostal approach, during breath-holding. The ultrasound system was equipped with a quantitative implementation of the ARFI technology (Virtual Touch™ Tissue Quantification [Siemens, Erlanger, Germany]) expressing the SWV value as m/s (Fig. 1). A mean of three different measurements obtained at the upper, middle and lower third of the parenchymal kidney resulted in the final SWV value for each kidney [7]. The average of the SWV values obtained for the right and left kidneys was considered as the mean SWV value for the subject under consideration. Reference values of SWV were considered  $3.13 \pm 0.09$  m/s (min 3.00 – max 3.30 m/s), of 16 patients aged 9-16 years [7].

## Results

We retrieved the medical records regarding clinical history, laboratory results and US findings of the 3 pre-school children involved in our study (Tab. 1). Case patient 1 showed a reduced right renal length (5<sup>th</sup> percentile), a high protein/creatinine



**Figure 1.** The region of interest (ROI) of the acoustic radiation force impulse (ARFI) technique applied on the left kidney of case number 3.

ratio and high  $\alpha$ 1-microglobulin in the urine spot. Patients 2 and 3 had unremarkable laboratory results.

At follow-up (**Tab. 2**), conventional US confirmed that patient 1 had reduced right renal length (< 5<sup>th</sup> percentile). A DMSA scintigraphic evaluation was performed but did not confirm this finding (46%). At the same time, the eGFR was normal (93.5 ml/min per 1.73 m<sup>2</sup>). The other two patients had normal renal length. Using the ARFI technique, we observed higher values for the left kidney in patients 1 and 3; patient 2 had low SWV values for both kidneys, compared with healthy full-term normal children [7].

## Discussion

The mechanical properties of the kidney, such as stiffness and deformity, depend on various conditions that alter its histology, mainly the amount of fibrosis in the renal interstitium that may compromise kidney function, and which may result in tubular atrophy and organ failure. Our results showed that the 3 children born preterm showed renal SWV values different from those of full-term children counterparts [7]. Although renal function was normal in 2 of the children, and slightly altered in 1 child, they all may have an underlying renal histology that affected both stiffness and deformity properties.

Two studies reported the ARFI technique applied to kidneys in pediatric age. Lee et al. published the

renal SWV values of 202 healthy children. Slight differences were reported between the right ( $2.19 \pm 0.03$  m/s) and left ( $2.33 \pm 0.03$  m/s) kidneys. However, they showed that SWV measures increased progressively most notably in children under 5 years old [6]. Their renal SWV values were lower than those found by Bruno et al. for healthy children [7]. Also, between the two studies there were different renal regions of interest (ROI) involved in the ARFI measures: the first study [6] included in the calculation both cortex and medulla, the second study considered only the outer renal cortex, excluding the medulla and calyceal system [7]. Bruno et al. investigated the ARFI technique applied to childhood renal pathology. Mean SWV values of renal parenchyma in 28 children with chronic kidney disease (CKD) from malformative uropathies (vesico-ureteral reflux [VUR] and posterior urethral valves [PUVs]) were higher ( $5.70 \pm 1.71$  m/s) than those of 16 normal controls and followed the sequence: secondary high-grade VUR (PUVs) > primary high-grade VUR > “healthy” controlateral kidney of the high-grade VUR > healthy subjects [7].

Studies on adults with native kidney diseases showed discordant results. Guo et al. [11], in 64 adult patients, showed a progressive reduction of SWV values as CKD stages increased. Stages were assigned according to serum markers of renal function. On the contrary, Cui et al. reported that mean SWV values of subcapsular parenchyma of kidneys with different percentages of renal fibrosis (assessed by renal biopsy) were higher than those

**Table 1.** Medical records regarding laboratory results and renal conventional ultrasound (US) performed in infancy on 3 children born preterm.

Case number	Demographic information			Laboratory results				Right kidney		Left kidney	
	Age (years)	Gestational age (weeks)	Birth weight (g)	Glomerular filtration rate (ml/min)	Protein/creatinine ratio	$\alpha$ 1-microglobulin (mg/L)	Cystatin-C (mg/L)	Length (cm)	Thickness (mm)	Length (cm)	Thickness (mm)
1	4.9	24	550	98	0.24	6.7	0.69	6.1 ↓	10.5	6.9	10
2	4.3	32	1,500	113	0.2	0	0.57	7.2	8.3	7.3	13
3	5.5	29	1,330	93	0.19	0	0.69	7.9	8.0	8.4	10

**Table 2.** Conventional renal ultrasound (US) and shear waves velocity (SWV) values, obtained by the acoustic radiation force impulse (ARFI) technique, of 3 children born preterm.

Case number	Age (years)	Right kidney			Left kidney			Mean SWV (m/s)
		Length (cm)	Thickness (mm)	SWV (m/s)	Length (cm)	Thickness (mm)	SWV (m/s)	
1	10.5	6.8 ↓↓ (8.2) <sup>a</sup>	14	3.27 =	8.5 (9.0) <sup>a</sup>	12	4 ↑↑	3.64 ↑
2	10	8.0	12	1.32 ↓↓	8.0	13	2.2 ↓	1.76 ↓
3	10.9	9.0	12	3.08 =	8.8	14	4.89 ↑↑	3.99 ↑

<sup>a</sup>Estimated renal length by DMSA scintigraphy.

of non-fibrotic kidneys [12]. Wang et al. reported for 45 adult patients with CKD, mainly IgA nephropathy, variable mean SWV values of the renal cortex between kidneys with increased grades of renal fibrosis [13].

The studies reviewed above are not fully comparable with the present study, not only because of the different pathology under investigation but also because of the technical procedures used, as discussed by Bruno et al. [7]. In particular, conditions that can modify renal elasticity can be related to the structure of the kidneys, a complex architecture created by glomeruli, tubuli and stromal components; to urinary pressure and vascular changes; and to the degree of manual compression exerted on the transducer by the operator. To limit such variability, it is helpful to orient the ROI with its main axis lying as parallel as possible to the main axis of pyramids with a subcostal approach in patients lying supine while holding their breath in order to obtain uniform results thereby reducing the effect of anisotropy. However, the ROIs must be in the outer cortex, as in the present study. In such location the percentage of collecting cavities is limited, minimizing the possible effect of calyceal pressure on the SWV values obtained.

In conclusion, altered SWV values have been observed in 2 out of 3 children with a history of normal laboratory markers of renal function. The altered SWV values measured in our study children, born preterm, may be correlated with a possible underlying renal pathology (i.e., modification or disruption of the renal histology). Although lack of standardization make actually difficult to obtain results comparable with those of other investigations, further studies are needed on larger cohorts of children born preterm to clarify this paradox.

## Abbreviations

ARFI: acoustic radiation force impulse

CKD: chronic kidney disease

eGFR: estimated glomerular filtration rate

LBW: low birth weight

PUVs: posterior urethral valves

ROI: region of interest

SWV: shear wave velocity

US: ultrasound

VUR: vesico-ureteral reflux

## Declaration of interest

The Authors declare that there is no conflict of interest. Funding: none.

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