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● *Original Contribution*

TESTICULAR SHEAR WAVE ELASTOGRAPHY IN NORMAL AND INFERTILE MEN: A PROSPECTIVE STUDY ON 601 PATIENTS

Laurence Rocher,[*†‡] Aline Criton,[§] Jean-Luc Gennisson,[‡] Vincent Izard,[¶] Sophie Ferlicot,[†‖] Mickael Tanter,[‡] Gerard Benoit,[†] Marie France Bellin,[*†] and Jean-Michel Correas[‡#**]

[*]Department of Adult Diagnostic and Interventional Radiology, Bicetre University Hospital, Le Kremlin Bicêtre, France; [†]Paris South Medical University, Le Kremlin Bicêtre, France; [‡]Institut Langevin, ESPCI Paris, PSL Research University CNRS UMR 7587, INSERM ERL U-979, Paris, France; [§]Supersonic Imagine, Aix en Provence cedex, France; [¶]Department of Urology, Bicêtre University Hospital, Le Kremlin Bicêtre, France; [‖]Department of Pathology, Bicêtre University Hospital, Le Kremlin Bicêtre, France; [#]Department of Adult Radiology, Necker University Hospital, Paris, France; and [**]Paris Descartes University, Paris, France

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Abstract—Our aim in the study described here was to prospectively establish the feasibility of using and reproducibility of testicular shear-wave elastography in the assessment of testicular stiffness in 62 normal patients and 539 infertile men with obstructive azoospermia (OA), non-Klinefelter syndrome non-obstructive azoospermia (non-KS NOA), Klinefelter syndrome NOA (KS NOA), oligoasthenoteratozoospermia (OAT) or a left varicocele. The feasibility rate was 96.9%, with an intra-class correlation coefficient of 0.85 (95% confidence interval: 0.83–0.88). Median stiffness (interquartile range) values were 2.4 kPa (2.0, 2.9), 2.1 kPa (1.8, 2.5), 2.4 kPa (2.0, 2.7), 2.0 kPa (1.7, 2.4), 2.6 kPa (2, 3.2) and 2.2 kPa (1.8, 2.6) for men with a normal testis (n = 108), OAT (n = 689), OA (n = 119), non-KS NOA (n = 183), KS NOA (n = 70) and varicocele (n = 132), respectively. Testicular shear wave elastography is a feasible and reproducible technique. A significant positive association was found between stiffness and testis volume ($p = 0.001$). Testicular stiffness was higher in OA than in non-KS NOA populations ($p = 1.e-10$) and in KS NOA than in NOA populations ($p = 2.0e-8$), but the substantial number of overlapping values limited the clinical impact. (E-mail: laurence.rocher@aphp.fr)

Key Words: **Shear wave elastography, Testis, Male infertility, Varicocele, Klinefelter syndrome.**

INTRODUCTION

Ultrasound imaging remains the gold standard for evaluating scrotal abnormalities and is indicated in many clinical situations including swelling scrotum, pain and infertility. Tissue palpation has always been used by urologists and andrologists to assess scrotal stiffness, but it appears to be a subjective analysis and requires experience. Ultrasound elastography is a novel ultrasound modality that provides information on soft tissue stiffness. Two different approaches are available: strain elastography (SE) and shear wave elastography (SWE). SE relies on small deformations applied by the ultrasound transducer during compression and decompression cycles, and enables semiquantitative measurements such as strain ratios. SWE is a more recent technique that allows quantitative tissue stiffness assessment (in kPa) in a region of interest (ROI). The latter is based on the generation of a shear wave whose velocity is directly linked to tissue stiffness. SWE is increasingly being used to assess liver fibrosis (Ozturker et al. 2016) and improve breast (Au et al. 2015) and thyroid nodule (Xu et al. 2016) characterization. To our knowledge, only a few studies focusing on testicular stiffness have been published. To date, the largest testis studies were performed using the SE technique (Goddi et al. 2012; Grasso et al. 2010). Unfortunately, the lack of reproducibility and quantification with SE limited its development and clinical spread (Aigner et al. 2012). The SWE technique has come into use quite recently, and only a few studies

Address correspondence to: Laurence Rocher, Department of Adult Diagnostic and Interventional Radiology, Bicetre University Hospital, 78 avenue du Général Leclerc, 94275 Le Kremlin Bicêtre, France. E-mail: laurence.rocher@aphp.fr

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have been published. Normal testicular stiffness was evaluated in 66 volunteers ranging from 20 to 86 y in age (Trottmann et al. 2016). Another experimental study using 18 New Zealand White male rabbits investigated stiffness and spermatogenesis after spermatic cord torsion (Zhang et al. 2015).

The primary purpose of this study was to assess both the feasibility and intra-observer reproducibility of testicular SWE. The secondary purpose was to determine tissue stiffness values in normal and infertile men and to evaluate the relationship between testicular volume and stiffness value.

METHODS

Patients

The study was approved by the institutional board, and a signed informed consent form was obtained from each patient (Ethics Committee: Comité de Protection des Personnes—Ile de France VII, Etude prospective sur l'élastographie ultrasonore testiculaire under No. 13-053). This prospective single-center study was performed between April 2014 and November 2015. We enrolled 935 patients referred for ultrasound (US) examination of the testes. Patients were referred for infertility (67%), endocrine disease (9%), pain (8%), testis cancer or nodule follow-up (5%), swelling (4 %) and trauma, as well as for a second opinion in the case of a doubtful mass.

For this study focused on testicular stiffness in normal and infertile men, we did not consider patients with a focal tumor, acute scrotum with spermatic cord torsion, orchitis, followed nodules or very heterogeneous echotexture, and we also excluded infertile patients with testicular compression inside the groin channel (cryptorchidism), extensive microlithiasis, hydrocele and a biopsy within the preceding 3 wk, because we thought that those conditions could modify stiffness. In the infertile population, patients who could not be clearly classified with respect to the mechanism underlying infertility and patients with mixed obstructive azoospermia and non-obstructive azoospermia were also excluded.

Patients were classified in different populations as follows:

- Normal testis: Patients who were referred for a vague pain with normal clinical examination, normal volume and normal echotexture; no US findings of epididymal obstruction; no history of infertility; and no reflux at Valsalva maneuver (VM); and had fathered at least one child. Patients with a history of orchiectomy caused by torsion/infection/tumor were included if they fulfilled the aforementioned criteria.
- Oligoasthenoteratospermia (OAT) according to World Health Organization criteria; obstructive azoospermia if spermatozoa numbered <15 million/mL; asthenoazoospermia in the presence of $<32\%$ progressive motile spermatozoa; and teratozoospermia: Etiologies of the infertility may be multiple.
- Obstructive azoospermia (OA): According to usual criteria (Wosnitzer and Goldstein 2014), normal follicle-stimulating hormone level and testis volume >12 mL. We checked the etiology of the disease. Patients with suspected unilateral obstruction were excluded because in such cases, we could not establish with confidence the mechanism underlying infertility. Testicular biopsies were checked if available.
- Non-obstructive azoospermia (NOA): Normal ejaculated volume and follicle-stimulating hormone level >10 IU/mL (Jungwirth et al. 2012). We also added as a criterion normal findings for the epididymis and vas deferens. We excluded patients with combined obstructive and non-obstructive supposed azoospermia, patients with hypogonadotropic hypogonadism and patients with androgen insensibility. On the basis of the first results, we decided to separate this group into Klinefelter syndrome (KS) NOA and non-KS NOA. Testicular biopsies were checked if available.
- Left varicocele: Patients with OAT and left varicocele clinically palpable from grades 1 to 3 in Dubin's classification (Dubin and Amelar 1970) or non-clinically palpable but with undoubted and prolonged reflux at VM in the supine position in the inguinal channel or other grades according to Sarteschi's classification (Sarteschi et al. 1993).

Ultrasound and shear wave elastography

Ultrasound screening was conducted after palpation by a single radiologist with an Aixplorer US imaging diagnostic system (SuperSonic Imagine, Aix-en-Provence, France) and high-frequency linear transducer (SL15-4, 8-MHz central frequency, SuperSonic Imagine), using conventional B-mode imaging and color Doppler imaging at low pulse repetition frequency (500 Hz). Our standardized report included information on testis volume, echotexture, presence and grade of microlithiasis, description of the epididymis and vas deferens, and presence or absence of varicocele according to Sarteschi's classification. Two perpendicular B-mode images of the testis were acquired to calculate testis volume according to the following formula: volume = length $\times$ width $\times$ depth $\times$ 0.523.

To assess organ stiffness, the SWE mode was used as follows: Ultrasonic radiation pressure, which acts as a shear wave source, is created within tissues by focusing ultrasound for some hundreds of microseconds;