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Doppler Applications In Azoospermia :A Prospective Study

Mohammed K. Magzoub* Abdulla Gabir** Suzan Omer*** Abdelraheem Adam****
** MOH, Department of family Medicine and Primary Healthcare; Wad Medani Gezira,; Sudan*
***Prof; Director and Senior Consultant Radiologist ; Royal care Hospital; Khartoum; Sudan*
****Assistant Professor. National Institute of cancer; University of Gezira; Sudan*
Assistant Professor. University of Gezira; Sudan, MD Dermatology SMBS
Correspondence Information: Dr. Mohammed Khalid

Abstract:
Introduction*: Infertility affects up to 15 per cent of couples. A male factor is solely responsible in about 20 per cent of infertile couples and contributory in 30–40 per cent of cases. Azoospermia is found in 15–20 per cent of the infertile male population, and in 10 per cent the sperm density is below 1 million/ml.*
Objective*: To determine the role of Color Doppler Ultra-Sonography Resistive Index (RI) measurement of the testicular artery as a predictor values in the diagnosis & categorization of azoospermia.*
Materials and Methods*: This is a prospective study conducted in a period from March 2016 – March 2017, Wad Medani, Aljazeera, Sudan & includes 75 subjects, ratio 1:4, 15 with normal sperm (Normospermic) and the remaining with pathological sperm count (azoospermia or zero sperm), proved by semen analysis three months apart, referred by consultant Dermatovenerologist & Andrologist.*
Testicular echogenicity, texture, volume, colour perfusion & testicular artery RI at rete testes in two groups were calculated and data was analyzed statistically by SPSS software.
Results*: Waveform with a high flow in diastole, low downstream vessel impedance showed low RI of 0.52±0.08, (applicable for Normospermic and OA) in contrast, waveforms with a little diastole flow, or reversed flow showed high RI 0.72±0.04 (applicable for NOA.)*
Conclusion*: The study concludes that RI values of the testicular artery can be used as a simple, safe, rapid predictor value and non-invasive tool for evaluation &categorizations of azoospermia*
Keywords*: Doppler US, PSV, EDV, RI, OA, NOA & SPSS.*

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I. Introduction

Infertility affects up to 15 per cent of couples. A male factor is solely responsible in about 20 per cent of infertile couples and contributory in 30–40 per cent of cases. Azoospermia is found in 15–20 per cent of the infertile male population, and in 10 per cent the sperm density is below 1 million/ml. Male infertility can be classified into three major groups: non-obstructive infertility (60 per cent): inadequate sperm production by the testes, obstructive infertility (38 per cent): normal sperm production, but there is a blockage in the genital tract, coital infertility (2 per cent): normal sperm production and patent genital tract; however, infertility is secondary to sexual dysfunction, which impairs intromission or ejaculation (1).

The **aim** of our study was to assess the role of Doppler applications in azoospermia using the testicular volume, colour perfusion, peak systolic velocity (PSV), end-diastolic velocity (EDV) together with the resistive index (RI) of testicular arteries in two group's subjects were calculated and data was analyzed statistically by SPSS software. and their usefulness as a quick, easy, non-invasive imaging technique in differentiation of the types of azoospermia, in this study the actual RI ±SD of the testicular artery at rete testes in relation to the testicular volume and perfusion will be calculated so as to be used in assessment categorization of the types of azoospermia proved by semen analysis.

II. Materials and Methods

Ultrasonography: There are two methods of estimating circulatory haemodynamics **a**) Direct measurement of the volume of blood flow **b**) Indirect estimation of flow velocity using waveform analysis
Samples: This is a prospective study conducted in a period from March 2016 – March 2017, Wad Medani, Aljazeera, Sudan & includes 75 subjects, ratio 1:4, 15 with normal sperm (Normospermic) and the remaining with pathological sperm count (azoospermia or zero sperm), proved by semen analysis three months apart, referred by consultant Dermatovenerologist & Andrologist.
Machine: Doppler performed by Chison QBit9 with high multi-frequency flat linear transducer. Color Doppler

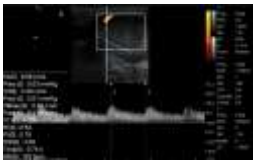
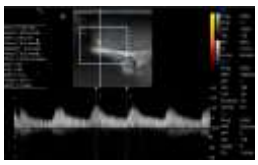
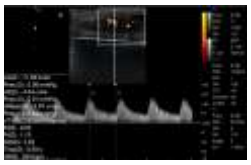
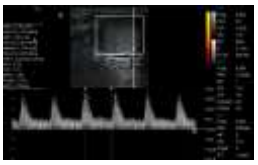
imaging was performed in all cases to investigate extratesticular vascularization and testicular perfusion, with parameters optimized to display low flow velocities (low wall filter [100 kHz], low pulse repetition frequency [1–2 Hz], and 70%–90% color gain output settings). We add power Doppler imaging in cases of azoospermia to supplement conventional color Doppler imaging. The main theoretical advantages of power Doppler imaging are a higher sensitivity to low blood flow and the fact that the signal is independent of the Doppler angle. The main disadvantage is its susceptibility to movement, which can be a significant drawback in un-cooperative subjects. According to some authors, addition of power Doppler imaging to scrotal imaging increases the sensitivity for detection of blood flow, but this is not the opinion of others. In my research study, it has good results in azoospermic subjects.

Ultrasound technique: Scrotal US performed with the patient in the supine position, frog leg position, the scrotum supported by a towel placed between the thighs & penis resting on the abdomen. A large amount of warm ultrasonic gel was used to minimize pressure on the scrotal skin, reassurance & analgesia if necessary.
The use of ultrasonography is to image testes echogenicity & texture. Testicular size was determined by measuring the anteroposterior diameter on comparable transverse images of the left and right sides so as to calculi the testicular volume with the machine using the formula for an ellipsoid: $V = L \times W \times H \times 0.52$, where V = volume, L= length, W = width, and H = height, the testicular volume is approximately 20 - 25ml. Pulsed-wave Doppler imaging of the testicular artery performed, spectrum was obtained, RI (Resistivity Index), Doppler indices PSV, EDV were calculated by the machine and recorded for upper pole artery in both testicles for each patient expressed in cm/second.
Problems: In the Sudan the percentage of infertility is 10% and in some Sudan areas it was up to 15%, peoples feels shame to expose their genitalia for any medical purposes rather than in acute cases such as trauma, epididymitis, orchitis and acute torsions and all mentioned are listed in an exclusive criteria and that was due to their Islamic believes,

Exclusion criteria: Epididymitis, epididymal indurations, testicular mass, orchitis, trauma, torsion, congenital absence of Vasa differentia,
Hydrocele, Spermatocele, varicocele, hernia and ambiguous genetalia.
Importance of the study: In this study I am going to apply Doppler imaging technique to the testicular artery so as to be used as a first non-invasive an easy screening method of examinations for candidate males whom are going to marry especially in Muslim countries, because one of the main factor for marriage is to increase the human population rate; Also peoples in Muslim countries are very poor cost for infertility treatment is very high and will be not affordable by majority. Good news now for all infertile men, researchers at Munster University in Germany, has developed in vitro culture conditions using a three-dimensional agar culture system which induces mouse testicular germ cells to reach the final stages of spermatogenesis, including spermatozoa generation. If reproduced in humans, this could potentially enable infertile men to father children with their own sperm.
Ethical approval: study was approved by ethical committee ministry of health, Aljazeera, Sudan

III. Results

In the study 75 total subjects were studied, 15 are Normospermic and 60 are pathological (azoospermic), waveform with a high flow in diastole, low downstream vessel impedance found with Normospermic and obstructive azoospermic subjects & showed RI of 0.63±0.08. Those subdivided according to the testicular volume, so RI of 0.52 ±0.00 found with subjects having a testicular volume of ≤10cc while RI of 0.64±0.02 found with subjects having a testicular volume of >10cc. (i.e.: RI directly proportion with testicular volume) subjects also were classified according to the testicular perfusion, those of ≤ 10cc volume and normal perfusion have an RI of 0.52 ±0.00 and those of >10cc volume and normal perfusion have RI 0.61 ±0.07. (i.e.: RI directly proportion with testicular perfusion). Subjects of ≤10cc volume and diminished perfusion not observed, while those of >10cc volume and diminished perfusion have RI 0.72 ±0.04,
In contrast, waveforms with a little diastole flow, or reversed flow with high RI of 0.68 ±0.11 found with non-obstructive azoospermic subjects, those subdivided according to the testicular volume, so RI of 0.69 ±0.02 found with subjects having a testicular volume of ≤10cc while RI of 0.66±0.02 found with pathological subjects having a testicular volume of >10cc. (i.e.: RI inversely proportion with testicular volume) Subjects of ≤10cc volume and normal perfusion have RI of 0.61±0.06, while those of >10cc volume and normal perfusion have RI 0.57 ±0.04, (i.e.: RI inversely proportion with testicular perfusion). Azoospermic subjects of ≤10cc volume and diminished perfusion have RI of 0.76±0.09 while those of >10cc volume and diminished perfusion have RI 0.76 ±0.02, (i.e.: in azoospermic testes with diminished perfusion volume doesn't play any role)

IV. Discussions

Our study has correlate between testicular artery RI, testicular perfusion and testicular volume in 75 total subjects, normal to pathological ratio is 1:4, 15 subjects with normal (Normospermic) sperm count and 60 subjects with pathological (zero sperm) sperm count. Different studies done on the testicular artery RI regarding Normospermic, others studied testicular perfusion as an index for spermatogenesis,

Vicari E, Calogero AE. (2) Stated that patients with obstructive azoospermia have the testicular parenchyma architecture and function preserved, those patients are able to produce spermatozoa and only face problems with sperm transport. Ezeh UIO, Moore HDM, Cooke ID. (3) Concludes that PSV and RI could be used as indicators of spermatogenesis.

In our study testicular volume and EDV has significant P value (0.001 & 0.001) respectively. Jee WH, Choe JK, Byun JY, Shinn KS, Hwang TK. (4) worked on the Resistive index of the intrascrotal artery in scrotal inflammatory disease. Acta Radiol 1997; 38:1026-30 and their study showed a clear differentiation of OA from NOA using PSV and RI. No patients with NOA had a PSV > 4.5 cm/sec or RI > 0.95. No patients with OA had PSV <11.5 cm/sec or RI < 0.93. Thus we conclude that recording the PSV & RI is an easy, convenient and valuable method for differentiating OA from NOA. Moreover, measuring PSV & RI is inexpensive and quick' as scrotal echo-Doppler scanning is routine for infertility.

In our study we have stated that: Men with NOA had a significantly higher EDV than the others, probably because of a high resistance to blood flow by the testicular parenchyma, in which connective tissue is more abundant than in other patients and we have found that EDV has significant P value (0.006).

Roberto Gandini, Danial Konda, Carlo Andrea Reala (5) have concludes in their study that low sperm count with a testicular volume, PSV, RI, EDV within the normal range may indicate MAGI, thus avoiding more invasive procedures. These findings agree with Biagiotti et al 2002 (6) and Vicari & Calogero 2001 (7).

The results of our study disagree with Roberto in azoospermic and agreed with him in normospermic. In the present study patients with OA had PSV and RI values similar to those of the controls, but significantly higher than in men with unexplained infertility or NOA. This goes in agreement with Souza et al 2005 who reported that obstructive azoospermia is compatible with normal testicular micro-vascularization. These results are consistent with previous reports (8, 9, 10) and indicate that PSV and RI may be useful for distinguishing the two forms of azoospermia. On the contrary EDV and testicular volume are not useful for differentiation of OA from NOA as already noted by other authors (6,10) and our study showed significant P(0.001 & 0.0061) for volume & EDV respectively and disagreed with Souza et al 2005 (6) and reports (8, 9, 10)

Does testicular volume reflect spermatogenic pattern in men with azoospermia? Kupat Holim Mehuhedet Unit, Shaare Zedek Medical Center, Jerusalem (10) study, concluded that testicular volume cannot be used as a predictive parameter, neither for the presence of spermatozoa nor for the cytological pattern of the testes of azoospermic infertile men.

Our study disagree with Kupat (11) and stated that: testicular volume has significant P values (0.001) in both types volume (<14cc volume & ≥14cc volume), so low RI values were found with low volume Normospermic and high volume azoospermic while high RI values were found with high volume Normospermic and low volume azoospermic.

Our study agreed with the study result by Takihara H, Cosentino MJ, Sakatoku J, Cockett AT (12) that concluded the size of the testis bears a direct correlation with testicular function and, thus, it can be helpful to assess rapidly andrological status during the initial physical examination, also our study agreed with an article first published online: 21 NOV 2008 British Journal of Urology Volume 64, Issue 6, that done on testicular size in infertile men and relationship to characteristics of semen and Hormonal Blood Levels (13) the study results are, the lowest mean sperm counts and lowest mean motility percentages were found in patients with bilateral testicular atrophy, significant correlation was found between testicular volume and spermatogenesis and testicular volume is considered to be a reliable indicator of testicular function, testicular volume may be confusing in assessment and categorization of the disease, so testicles, which produce a normal amount of sperm, may be small and those which produce no sperm (which have maturation arrest) may often be large. The same is true for ultrasonography of the epididymus; large epididymus do not imply OA, as similarly a normal epididymus does not always indicate NOA (11)

In our study the RI values were found directly proportion in two subjects groups regarding volume in normospermic, while inversely proportion in two subjects groups regarding volume in azoospermic, some authors use diagnostic testicular biopsy to distinguish OA from NOA; and our study used RI values in differentiating

between the two types of azoospermia.
International Urology and Nephrology (14) study showed that no correlations were found between serum LH and testosterone levels and testicular volume. Department of Urology, Dokkyo University School of Medicine, Mibu, Tochigi, and JAPAN (15) have applied Doppler ultrasound in assessment of testicular volume in relation to spermatogenesis and found that: Patients with a testicular volume of less than 10mL were azoospermic, while volumes of less than 20 mL were associated with severe Oligozoospermia. Department of Ultrasound, Shanghai Institute of Andrology (16), Have stated that Testicular volume was significantly larger for obstructive (median, 16.0 mL) than for nonobstructive (median, 8.6 ml) azoospermia. They have concluded that scrotal US and transrectal US are effective imaging modalities for distinguishing obstructive from nonobstructive azoospermia and can provide meaningful diagnostic information for determining the etiologic classification of obstructive azoospermia.
In our study we have found that azoospermic subjects with large volume have low RI with significant P value (0.001) in both conditions of normal testicular perfusion and diminished perfusion.
In the study by Gahzy (17) he found that RI could be used as an indicator for spermatogenesis. Gumbsch (18) study used color coded duplex ultrasound to examine the testes of 42 dogs which were normal on clinical examinations and defined normative value of testicular blood flow using RI. Tarhan (19) also examined the effect of unilateral testicular torsion on the blood flow of contra-lateral testes including RI measurement in experimental study on 14 dogs and concluded that unilateral testicular torsion does not decrease contra-lateral testicular blood flow as shown by CDUS and the study done by lefort (20) concluded that elevated RI is suggestive for ischemia to testes. University of Padova, Padova, Italy (21) stated that: The analysis of intratesticular vessels per organ was quantified using a semi quantitative score: category 0, no vessels visible; category 1, between one and three intratesticular vessels visible; and category 2, more than three vessels visible, accordingly in our study we have classified our subjects into two groups one with normal colour perfusion and the other with diminished colour perfusion,
With normal perfusion our study found that testicular volume, PSV and EDV have significant P values (0.001, 0.025 and 0.006 respectively) while with diminished perfusion only the testicular volume has significant P (0.001), also in our study azoospermic were classified according to the testicular volume & perfusion.
Clinica Medica 3, University of Padova (21) Has results of study demonstrate that colour and power Doppler Sonography represent promising methods for the assessment of patients affected by azoospermia allowing us to discriminate obstructive azoospermia (normal vessel distribution) from non-obstructive azoospermia (reduced or absent testicular vessels), although they cannot be extrapolated to all non-obstructive azoospermic subjects, suggest that the presence of blood vessels, especially in peripheral regions, may indicate the possible presence of residual spermatogenic areas.
Furthermore In our study, we have defined specific RI values for normospermic and azoospermic and we have found that two groups volume normospermic and azoospermic of <10.0cc & ≥10.0cc volume with normal perfusion has low RI values 0.52 and 0.61and that was applicable for normospermic and OA respectively,

V. Conclusions

Significant correlations were found between testicular volume, colour perfusion, RI values in both subjects (normospermic and azoospermic), testicular volume and EDV are considered to be reliable indicator of testicular function.
In normospermic subjects of (low) volume (≤10.0cc) and diminished perfusion RI values were not recorded and of no role.
In low volume normospermic normal perfusion testes the study showed RI value of 0.52±0.00
In both normospermic and azoospermic subjects RI directly proportional to the testicular volume.
Normal perfusion normospermic with high testicle volume (>10.0cc) and azoospermic with low testicular volume (≤10.0cc) were found in the study have the same (relative high) RI value of 0.61±0.07.

Azoospermic subjects with diminished perfusion regardless to the volume in the study showed high RI value of 0.76±0.07, so that can be applicable for **non-obstructive** type.
Azoospermic subjects with normal perfusion regardless to the volume in the study showed RI value of 0.57±0.04 and that can be applicable for **obstructive type**, i.e. while assessing azoospermic patient testicular perfusion is very important.

Vl. Recommendations:

Subjects with low RI values are applicable for normospermic & obstructive type azoospermia and recommended for further differentiation study in correlation with male fertility hormones.
Subjects with high RI values are applicable for nonobstructive type azoospermia.
Further studies with concentration and volume were recommended.
High resolution ultrasound machines with high colour sensitivity recommended in all fertility clinics.

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