Annals of Academy of Romanian Scientists
Online edition *Series: Medical Sciences*
ISSN 2285-4150 *Volume 2, Number 1-2/2011*

Original Article

THE PLACE OF MODERN TECHNOLOGY IN THE ULTRASONOGRAPHIC EVALUATION OF THE PROSTATE AND SEMINAL VESICLES

Victor Cauni[1], Cristian Persu[2]

1) Urologyst, senior researcher, PhD, "Sf. Pantelimon" Medical Center, Department of Urology
2) Urologyst, PhD, "Sf. Pantelimon" Medical Center, Department of Urology

Abstract

Ultrasonography rapidly became an indispensable evaluation tool for many medical specialties, replacing several other procedures in the first line of diagnosis. As time passes by, ultrasonography itself develops continuously, with many new, sophisticated or just spectacular features becoming available from the industry, and requiring validation by medical professionals and the scientific community.

Tridimensional ultrasonography, the Doppler and power angio modules, as well as ultrasonographic contrast agents are not the newest on the market, but the latest to be unanimously recognized as a valuable addition to the technical armamentarium of the physician.

This paper analyzes the main benefits of the use of these modules for the evaluation of the internal genital organs of the male, as well as the limits of each technique.

We conclude that new ultrasonographic methods provide a lot of useful information, making them able to replace more invasive and expensive technologies, but the operator needs to be aware of all possible limits and artifacts that may occur.

Keywords: *ultrasonography, contrast agents, prostate, seminal vesicles*

Rezumat

Ultrasonografia poate reprezenta o metodă de evaluare rapidă pentru anumite specialități, plasându-se alături de alte proceduri, in prima linie de diagnostic. Pe parcurs, ecografia s-a dezvoltat continuu, concomitent cu inovațiile tehnice industriale, ce au fost primite cu succes de comunitățile medicale şi ştiințifice.

Ultrasonografia tridimensională, modulele Doppler sau power angio *sau agenții de contrast pentru ecografie sunt costisitori, dar trebuie să existe ca metode adiționale în arsenalul de investigații al oricărui medic.*

Acest studiu analizează beneficiile utilizării acestor module pentru examinarea organelor genitale interne ale bărbatului şi limitele acestor metode.

[1] **Address for correspondence: Dr. Victor Cauni,** victorcauni@yahoo.com

Concluzionăm că noile metode de ultrasonografie aduc informații utile, fiind considerate tehnologii mai invasive şi expansive, dar utilizatorul trebuie să cunoască limitele şi posibilele artefacte ale acestora.

Cuvinte-cheie: *Ultrasonografia, agenți de contrast, prostată, vezicule seminale*

Introduction

The ultrasound machine reached the medical market a couple of decades ago as a promising device, and developed since then to become an indispensable tool for the modern physician, being often compared, and with good reasons, to a modern stethoscope. Nowadays, urological examination is unconceivable without the use of ultrasonography, and the internal male genital organs are better understood both as morphology but also in pathologic conditions. As any other modern medical tool, the ultrasonography device is in constant evolution, being upgraded with several new modules, built around the use of the Doppler effect: color Doppler, pulsed Doppler and power angio [1]. More recent, the development of tridimensional examination and contrast agents marked a new step forward in the evolution of ultrasonography from basic examination to cutting-edge technology.

Description of the modules

Continuous Doppler. For this mode of examination, the transducer consists of two adjacent piezoelectric components, in which one continuously generates ultrasounds and the other continuously receives echoes. It offers improved visualization for surface blood vessels, but when examining complex vascular flows at different depths, this method does not allow for individual flow evaluation, calculating instead an average feature of all blood flows that are in the range of the transducer - the arithmetic sum of the signals [2].

Pulsed emission Doppler (Doppler pulse). The transducer generates and receives ultrasounds alternatively. If the ultrasounds are emitted in pulses, the device can detect the depth from which each echo is received. The examiner may select the area in which to evaluate the depth of the Doppler signal, an area called "*Doppler sample*". With this technique one can study blood flows in a designated area, and the received signals are not influenced by neighboring blood flows [3].

Color Doppler. For this technique, the two-dimensional ultrasound transducer provides the image, while the software offers elements associated with Doppler analysis. On the two-dimensional ultrasound image one can delineate an area of interest, in which each point is analyzed by pulse Doppler method, being treated as a Doppler sample. The information obtained is color coded; the direction of the blood flow is coded differently depending on its movement toward to the transducer (red) or away from it (blue) [4].

Power Doppler (power Angio). It analyzes the intensity of the Doppler signal, not offering information about the speed or direction of the blood flow. The graphic representation is in grayscale and the color tone varies with the signal strength. It has a much higher sensitivity in tracking the presence of blood flow by detecting slow flow in vessels much smaller. But the high sensitivity of the method is also responsible for its main disadvantage: many artifacts caused by tissue movements. The development of the "Power Angio" module significantly increased the possibility to evaluate the prostatic vascularization, creating the premises of generating a true "vascular map of the prostate" and leading to a better understanding of the vascular anatomy of the gland by "real time" imaging of the vessels [5].

Tridimensional ultrasound (3D). The recent introduction of three-dimensional ultrasound allowed a more precise spatial localization of pathological elements in the gland. Tridimensional reconstruction of the prostate allows a very accurate calculation of the prostatic volume, particularly useful for monitoring changes during the evolution or treatment of a neoplazic disease [6].

Ultrasonographic contrast agents. The best way of highlighting the blood flow inside the prostate is by using contrast agents, a newly developed class of substances. The first generation of ultrasonographic contrast agent (Ecovist) could only be used in cardiology, because the substance could not get in sufficient quantity in the peripheral blood due to the pulmonary filter. The introduction of Levovist, representing a newer generation of agents, led to a significant increase in the sensitivity of Doppler ultrasound for visualization of blood flows inside more organs. Levovist is an agent that increases the ultrasonographic signal strength in the entire pool of blood, having a good safety profile and good tolerance as confirmed by numerous clinical trials [7].

Levovist is less viscous than most radiographic contrast media, it is not toxic, has a neutral pH and is biodegradable. One of the utilities of it is to view the vascular pattern of benign or malignant tumor formations. The galactose microbubbles that compose this agent are stabilized with palmitic acid, thus ensuring the pulmonary passage without the substance being decomposed. This agent remains in circulation for several minutes, providing a better view in the Doppler mode of the entire vascular system. 95% of the microbubbles of Levovist are less than 10μ and 50% of them are less than 3μ, enabling them to safely pass the pulmonary filter.

For prostatic tumors, Levovist helps creating a complete vascular pattern of the prostate, allowing the detection of suspect malignant formations with improved accuracy compared to power Doppler. This is extremely useful for identifying malignant nodules inside a prostatic adenoma.

After the intravenous injection of the agent, the microparticles dissolves rapidly, releasing air bubbles absorbed on their surface. The total amount of air released from 1 g of microparticles is less than 100μL. After being dissolved by blood, the galactose is metabolized in the liver, while palmitic acid has a half-life of 2-4 minutes. The effect of Levovist is reproductible and increases blood echogenity depending on the dose injected, until its complete dissolution in blood. The magnetodynamics of Doppler amplification done by this agent offers an extra of 10 to 20 dB [8].

Today we are witnessing the emergence of a new generation of contrast agents (SonoVue), which promises increased sensitivity and longer half-life [9].

With the increasing life expectancy of male population, came an increased number of people affected by various pathologies of the prostate, benign (prostate adenoma, BPH) or malignant (adenocarcinoma of the prostate). If, in the past, the prostate was revealing to the clinician only through the digital rectal exam (DRE), nowadays, with the introduction of transrectal ultrasound, the evaluation protocol of the seminal vesicle and prostate disorders is revolutionized [10].

McNeal synthesized the concept of zonal anatomy of the prostate, based on its glandular composition. Glandular elements represents two-thirds of the prostate, while the remaining third is represented by stroma and fibromuscular tissue (anteriourly). McNeal describes two separate areas of the prostate: a peripheral and a central area.

The prostate is pyramid shaped, with the apex pointing toward the urogenital diaphragm and the base participating in the formation of a lower bladder wall, around the bladder neck. Anterolaterally, the prostate is covered by the extraperitoneal fascia and posteriorly by the Denonvillier fascia. In the anterolateral side of this fascia there is an important venous plexus the Santorini plexus.

The seminal vesicles are adjacent to the prostate and posterior to the bladder. The ampular zone of the deferent duct is situated anterior and medial to the seminal vesicles, confluating to develop the ejaculator duct [11].

Material and methods

The group we examined was composed of 456 patients with pathology of the prostate and seminal vesicles, prostate biopsy (selected cases) (BPH) - 231 cases

• adenocarcinoma of the prostate - 107 cases
• acute or chronic prostatitis - 83 cases
• spermatocystitis - 35 cases

The age of patients ranged from 23 to 79 years with a variation of the average age depending on the pathology of the prostate. The evaluation protocol of patients with prostate pathology included basic urological tests and some advanced techniques [12]:

• duplex Doppler ultrasonography
• Doppler ultrasound "power Angio"
• Three-dimensional ultrasound (selected cases)
• Vesiculodepherentography (selected cases)
• Doppler sonography with ultrasound contrast agent (selected cases) (figure no 1).

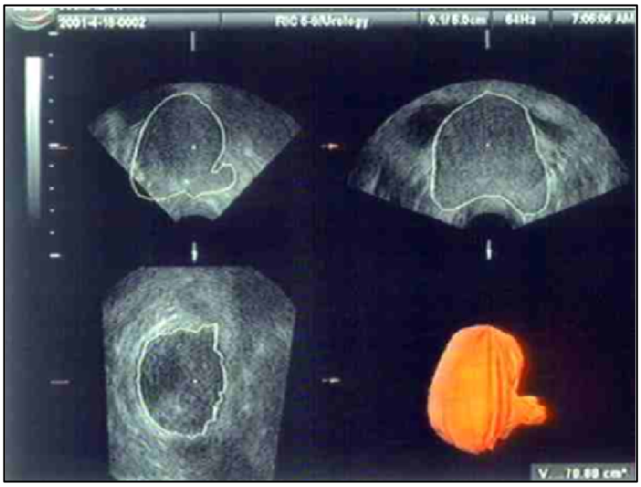


Figure no.1: *Tridimensional reconstruction of the prostate*

Results

Transrectal ultrasound with Doppler module has routinely been used for evaluating patients in this group. Out of a total of 456 patients, after complete evaluation, we selected from 231 patients with prostatic adenoma (BPH). Three-dimensional reconstruction allowed the calculation of the exact volume of the prostate, at the same time making possible spatial visualization of blood vessels. The ecostructure of the gland in patients with BPH was relatively homogeneous, with a regular contour of the prostate. Doppler ultrasound identified a homogenous distribution of blood vessels in the prostate and the injection of ultrasound contrast agent showed homogeneous vascular network, without nodular hyper or hipovascular areas *(table no.1)*.

Table no.1 – Features of BPH compared with a normal prostate

	BPH	**Normal prostate**
Doppler ultrasound	Homogenous vascularization	Homogenous vascularization
IR	0,81 (0,61 – 0,90)	0,69 (0,50 – 0,73)
Prostatic volume	30 - 120 cc	< 20 cc
PSA	0,4 – 8,9 µg/ml	< 3 µg/ml
free PSA	> 23%	> 23%

Three-dimensional ultrasound reconstruction of the gland provides a more accurate assessment of prostate weight, with an error of up to 5% compared with transrectal ultrasound transrectală (10 to 16%) or suprapubic (20% or more).

The variation of resistivity index was proportional to the volume of adenomatous tissue, being larger as the prostate volume was greater *(figure no.2)*.

Figure no.2 – *Tridimensional reconstruction of the prostate showing detailed structure*

In the group of patients with prostatic disease, by pathological examination we selected a total of 107 patients with prostate adenocarcinoma (ADK-P).

Diagnostic correlation of PSA / free PSA – DRE - power Doppler ultrasound. On a study group composed of 338 patients diagnosed with BPH and prostate cancer, the correlation PSA / free PSA with pathology examination was as follows (*table no 2*):

Table no.2 – Correlation between PSA, ultrasonography and the diagnosis of malignancy

PSA	**< 3 µg/ml**								**3 – 10 µg/ml**								**> 10 µg/ml**							
free PSA	**> 21%**				**< 21%**				**> 21%**				**< 21%**				**> 21%**				**< 21%**			
TR	**+**		**-**		**+**		**-**		**+**		**-**		**+**		**-**		**+**		**-**		**+**		**-**	
power Doppler	+	-	+	-	+	-	+	-	+	-	+	-	+	-	+	-	+	-	+	-	+	-	+	-
BPH	-	5	22	169	-	-	2	3	-	-	3	27	-	-	-	-	-	-	-	-	-	-	-	-
Prostate cancer	-	-	-	2	-	-	8	5	-	1	2	-	13	7	1	2	2	1	2	-	39	13	8	1

Power Doppler ultrasound was considered positive (+) if it showed circumscribed vascular changes in nodular areas (hyper or hypovascular). If the nodular lesions showed similar vascularization compared to the adjacent tissue of the prostate, the power Doppler ultrasound was considered negative (-).

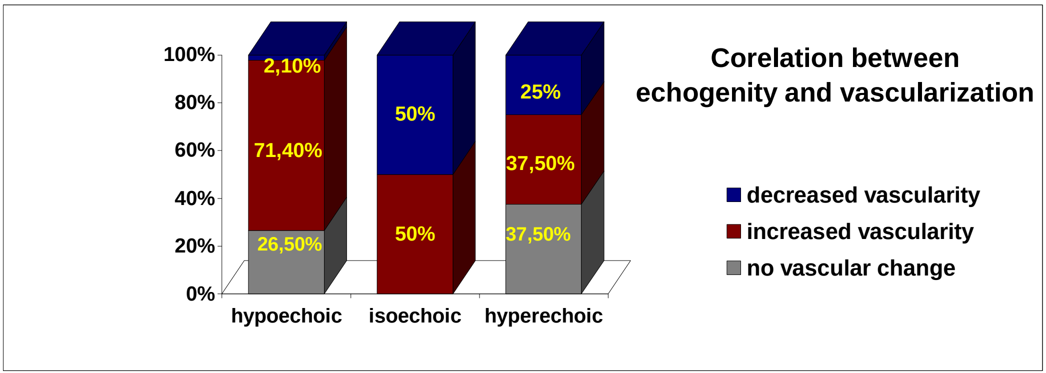
Tridimensional reconstruction of the prostate for prostate cancer may highlight hypoechoic areas alternating with those with hyperechoic structure at the gland surface [13].

Diagnosis correlation of classical ultrasound and power Doppler. In those patients with confirmed prostate cancer, the lesions were detected in the vast majority as hypoechoic nodules, but hyper or isoechoic areas were also identified. The use of the "power Doppler" was intended to evaluate the distribution of blood vessels across the prostate, and with the duplex Doppler module the resistivity index was calculated from the prostate and lesions suspicious of malignity [14].

According to the guidelines, the areas in which changes of topographic vascularity were noticed, were considered as lesions suspicious of malignity, with increased or decreased blood flow in nodular areas [15]. The "power Doppler" module allowed the analysis of the blood vessels in the suspicious areas.

The hypoechoic lesions in patients with prostate cancer were hypervascular in 71.4% of the patients at power Doppler examination while isoechoic lesions presented increased vascularity in only 3 patients (50%). In patients with nodular hyperechoic lesions, 5 patients (37.5%) had focal increased blood flow, whereas 3 patients (25%) had low vascularity in the suspicious malignant nodule *(Graph no.1).*

Graph no.1 – Corelation between echogenity and vascularization



Of the total group of patients with prostate cancer, 63% showed a focal hypervascularization inside the suspected malignant lesion.

Graph no.2 – The blood flow inside the lesion suspected of malignity

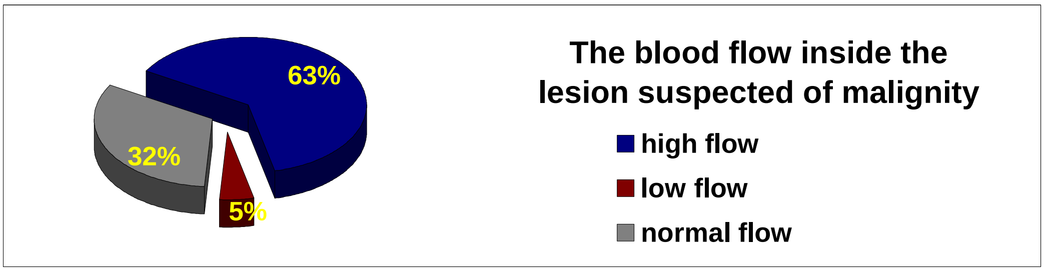


Table no 3 - Correlation between power Doppler and PSA in patients prostate cancer:

	< 3 µg/ml		3 – 10 µg/ml		> 10 µg/ml	
eco power doppler	+	–	+	–	+	–
ADK-P	**5**	**5**	**19**	**10**	**51**	**17**

In patients with confirmed prostate cancer and normal values of the PSA, 5 (50%) had specific signs at "power Angio" ultrasonography (focal changes of vascularization). In patients with PSA between 3 to 10 μg/ml, 18 (64.7%) had changes in vascularity, while those with PSA over 10 μg /ml these changes occurred in 51 patients (75%). On the whole group of patients with prostate cancer (107 patients), vascular changes recorded by the module "Power Doppler" occurred in 75 patients (69.8%).

Use of contrast agent for prostate cancer evaluation.

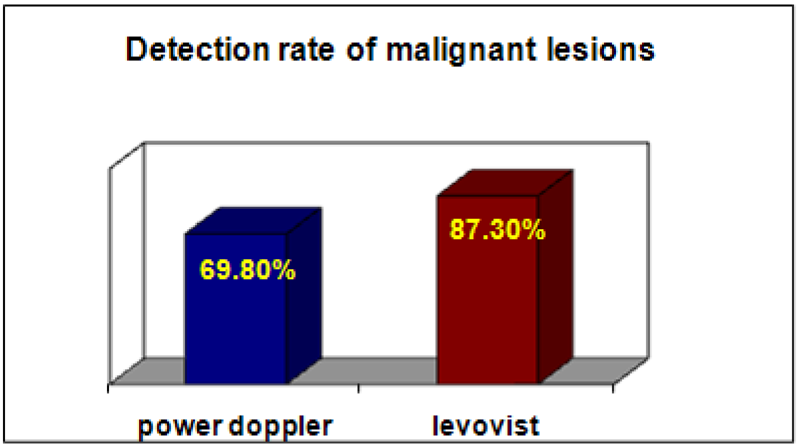
In our group we used a Levovist concentration of 400 μg /ml. After the injection, color Doppler recording is performed for 5 minutes. A few seconds after the injection the prostatic blood flow increases, identifying a network of vessels inaccessible to color Doppler module or the "power Doppler" in the absence of the contrast agent. The group of patients in whom we used ultrasound contrast substance was represented mainly by the 19 patients with prostate without characteristic features at "power Doppler", and other 11 patients with minor changes at Doppler ultrasonography. After the injection of Levovist, those patients that had minor changes to power-Doppler, the increase in blood flow visualization allowed a more accurate evaluation of suspicious malignant areas. The 19 patients with prostate cancer, in which power Doppler examination did not raise the suspicion of malignity, the use of Levovist allowed visualization of neoplazic nodules in 11 cases, increasing the diagnostic accuracy from 69.8% to 87.3%. *(figure no.3 - table no.4).*

Table no.4 – Ultrasonographic features of prostate cancer with contrast agent

Transrectal power ultrasound / **Doppler**	**hyperchoic**		**isoechoic**		**hyperechoic**		**Total**
No ultrasonographical changes at power Doppler	**13**		**3**		**3**		**19**
Levovist	+	-	+	-	+	-	
Total	9	4	1	2	1	2	

Of the 13 patients with hyperechoic nodes with no "power Doppler" signs, after the injection of the contrast agent, 9 of them (69.2%) were found to have significant vascular changes. Of the 6 patients with isoechoic or hyperechoic lesions, two patients did not showed vascular changes even after the injection of Levovist, which increased the detection rate of malignant prostate lesions from 69.8% ("power Doppler") to 87.3% *(graph no.3).*

Graph no.3 – Detection rate of malignant lesions

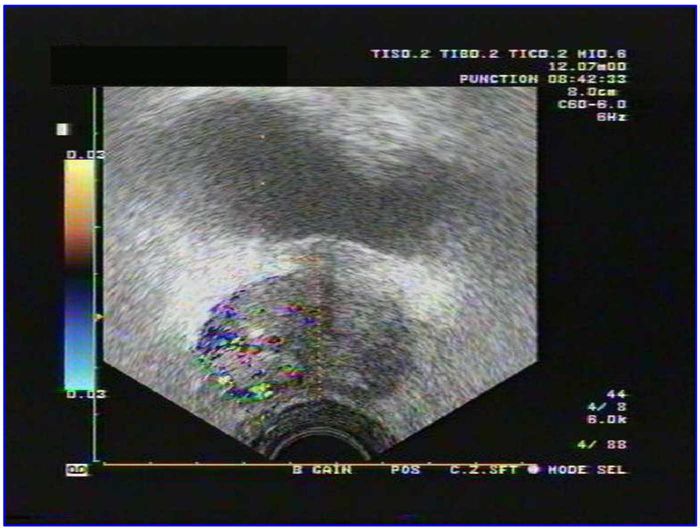


Positive diagnosis of prostate cancer is only possible by pathology examination. Nevertheless, the sampling of bioptic material can sometimes be chalenging, as suspicious nouds can be missed by the needle, especialy in those situations when the echogenity is similar with surrounding tissues [16]. The technique we used was to take 8 biopsy fragments: 3 fragments of the right lobe, other 3 from the left lobe and 1 sample of the prostatic apex. The use of contrast agents allows superior visualization of malignant nodes, and susequently a better targeting during biopsy.

Levovist was used in 22 patients who showed significant changes in blood flow, with high suspicion of malignancy. The control group consisted of the remaining 41 patients with suspected prostate cancer (free PSA, PSA, ultrasound, power Doppler). In this group biopsy was performed in 8 different places. In patients where Levovist highlighted suspicious malignant lesion two biopsy samples where taken only from that area. *(table no 5)*

Table no.5 – Detection rates after biopsy with contrast agent

	8 biopsies	**2 biopsies (Levovist)**
Suspected cancer	41	22
Confirmed cancer	17	16
Percents:	**41.5%**	**72.7%**



In the eight biopsy samples group, prostate cancer was confirmed in 17 (41.5%) cases. In the lot with Levovist, after only two samples of the suspected malignancy node, 16 cases of prostate cancer were confirmed (72.7%) (figure no.4).

Figure no.4 – *Isoechoic node with signs of malignity after contrast agent injection*

After a single prostate biopsy procedure using Levovist, the diagnostic rate of prostate cancer increased from 41.5% to 72.7% in terms of reducing the number of prostate tissue samples from eight to two. As can be observed, the increase was statistically significant at the double biopsies using Levovist compared to the octant biopsies. (17,18,19). The $\chi 2$-test, showed the value $p = 0.000049$. The complication rate was relatively low, in terms of number and their severity. Puncture site pain occurred in almost all patients. It was treated with antalgics. Hematuria was relatively rare, occurring in less than 5% of cases and did not require therapeutic actions. Hemostatic and antibiotics were given. Rectoragia, not requiring treatment, was also noticed in some cases. Urinary infections occurred in less than 10% of cases, in which antibiotics were administered.

Conclusions

Modern ultrasonographic technologies require complex equipment and special training for the medical proffesionals, but the results can often be superior to more invasive and expensive techniques.. Tridimensional ultrasonography offers spectacular images of the prostate and seminal vesicles, allowing at the same time a more accurate evaluation of the volume and structure of the gland.

The Doppler modules are quite operator sensitive and the learning curve are long, but the results add functional information to the examination. The evaluation of the vascular patterns, the possibility to identify the direction of the flow, as well as the advantage of being able to reconstruct the vascular structures inside the prostate are as many steps forward in the evaluation and treatment monitoring of prostatic diseases.

The recent introduction of new generation ultrasonografic contrast agents marks a further development of the technique, allowing to separately identify suspect zones inside a region of homogenous echogenity.

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