Experimental study with Doppler ultrasound in partial chronic obstructive uropathy

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Abstract

Introduction: This study has aimed to assess the hemodynamic parameters, Renal Resistive Index (RI), Peak Systolic Velocity (PSV), End-Diastolic Velocity (EDV) and Blood Flow of the Renal Artery (FR) by Doppler ultrasound for diagnosis and monitoring postsurgical partial chronic obstructive uropathy.

Material and methods: Fifty pigs were used. The experiment was divided into three phases. Phase I consisted of a duplex-Doppler evaluation of the both kidneys to determine the parameters under study. The ratio of each index is calculated as the difference between the value of study kidney and the contralateral. After, a fluoroscopic examination was performed by compressive cystography, excretory urography and retrograde ureteropyelography. Finally, a model of partial right ureteral obstruction was created. After six weeks of the obstructive model, Phase II was begun with the diagnosis of the uropathy, by means of the aforementioned diagnostic methods and the endourological treatment was completed. Phase III is a follow-up performed at 6 months of treatment using the same methods as in the previous phases.

Results: Of the parameters studied, the EDV and its ratio showed greater sensitivity and specificity as a diagnostic marker of obstructive uropathy. In the postoperative monitoring, it was observed that the RI and the EDV returned to baseline levels, with the baseline values.

Conclusions: The ΔEDV and its ratio are the parameters that show the greater efficacy for the diagnosis of chronic partial obstructive uropathy; however, it is insufficient to avoid conventional diagnostic techniques. All the parameters, mainly the EDV, have proven useful as complementary tests for monitoring after endourologic resolution of obstructive uropathy.

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PALABRAS CLAVE
Doppler;
Uropatía;
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Estudio experimental con Ecografía Doppler en uropatía obstructiva parcial crónica

Resumen

Objetivo: La valoración de los parámetros hemodinámicos índice de resistencia renal (RI), velocidad pico sistólica (PSV), velocidad mínima diastólica (EDV) y flujo de la arteria renal (FR) mediante ecografía Doppler para el diagnóstico y monitorización posquirúrgica de la uropatía obstructiva parcial crónica.

Material y métodos: Se emplean 50 animales de la especie porcina. El estudio se divide en 3 fases. La fase I consta de la valoración ecográfica dúplex-Doppler de ambos riñones, determinando los parámetros objeto de estudio. La razón de cada índice se calcula como la diferencia entre el valor del riñón en estudio y su contralateral. El examen termina con la realización de cistografía de compresión, urografía excretora y ureteropielografía retrógrafa. Seguidamente, se procede a la creación de un modelo de obstrucción parcial del uréter derecho. Transcurridas 6 semanas, comienza la fase II mediante la realización de las pruebas descritas anteriormente y posterior resolución endourológica de la obstrucción. La fase III consiste en un seguimiento a los 6 meses del tratamiento mediante las pruebas realizadas en las fases previas.

Resultados: De los parámetros estudiados la EDV y su ratio son los que mayor sensibilidad y especificidad muestran como marcador diagnóstico de uropatía obstructiva. En el seguimiento posquirúrgico se observa cómo el RI y principalmente la EDV retornan a los valores basales.

Conclusiones: La EDV es el parámetro que mayor eficacia muestra para el diagnóstico de uropatía obstructiva parcial crónica; pero esta es insuficiente para relegar las técnicas de diagnóstico convencionales. Todos los parámetros, principalmente la EDV, han mostrado ser útiles como pruebas complementarias de monitorización y pronóstico tras la resolución endourológica de la uropatía obstructiva.

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Introduction

The management of obstructive uropathy of the upper urinary tract is often controversial. The techniques used for the characterization of obstructive lesions are radiological and invasive, and they do not offer acceptable sensitivity for the diagnosis of renal injury. Therefore, it is essential to develop new tests to make up for the limitations that traditional methods report. In this sense, some authors defend the combination of blood markers and imaging techniques, of which, Doppler ultrasound is shown as a non-invasive alternative, painless, easily available, and relatively easy to learn and perform.

In recent decades, we have tried to correlate the increase in intrarenal pressure occurred after obstructive uropathy with increased RI, a hemodynamic parameter measured by Doppler ultrasound. Currently, there is a general agreement about the usefulness of the RI as an additional proof of the diagnosis of complete and acute obstructive uropathy. However, the behavior of this parameter in the presence of a partial or chronic obstructive uropathy is not well established, primarily due to the lack of homogeneous experimental studies which consider the factors that interfere with the hemodynamic parameters and the fact that clinical series exclude cases of mild obstructions or chronic course.

Moreover, the increasing use of Doppler ultrasound in urology has led to the use of other markers, such as PSV, EDV, or FR, some of them not studied so far in obstructive uropathy.

Thus, the need to assess the performance of the RI arises in the presence of a partial chronic obstructive uropathy, through a homogeneous experimental study, eliminating the controllable factors that interfere with the hemodynamic parameters, as well as studying the usefulness of new markers, which could be more reliable than the RI in the presence of a partial ureteral obstruction.

Therefore, the objective of this work is to study the behavior and evolution of the variables RI, PSV, EDV, and FR in a chronic partial obstruction, and to evaluate their possible clinical use in the diagnosis of the condition and subsequent monitoring of the renal recovery after the endourological resolution of the uropathy.

Material and methods

We used 50 healthy sows, weighing between 30 and 40 kg. The study was approved by the ethics committee for animal experimentation, fulfilling the European legislation on animal protection used for experimentation and other scientific purposes.

After the mandatory period of adaptation and quarantine, the study begins. The experimental approach is divided into 3 phases. In each of these, the animals receive identical anesthetic protocol, intraoperative analgesia being administered always after ultrasonographic and fluoroscopic testing, avoiding possible interferences with the study.

Phase I. Baseline study and creation of a model of partial obstructive uropathy

The study begins with an examination of the animal’s health status through ultrasonography of the right and left upper
urinary tract, which consists of a previous mode B exploration to determine the degree of hydronephrosis according to the Society of Fetal Urology\textsuperscript{10}, followed by a duplex Doppler examination, to assess intrarenal vascularity and calculate the hemodynamic parameters under study: RI, PSV, EDV, and FR. RI, PSV, and EDV determination is performed on the arciform arteries; while that of the FR is performed on the renal artery. The measurement of these parameters is performed when the Doppler register detects 5 identical waves, repeating each determination three times. Next, we calculate the ratio of each parameter, using the difference in value in the ipsilateral kidney and its contralateral one. Consecutively, we complete the exploration of the urinary tract by compression cystography, excretory urography, and retrograde ureteropyelography.

Those animals showing abnormalities in the tests performed will be excluded from the study. Determinations of serum urea and creatinine, as well as ultrasound and fluoroscopic tests will be repeated with the same protocol at the beginning of each phase of the study.

After animal evaluation, we proceed, by means of laparoscopic approach, to the creation of a model of partial obstruction in the right lumbar ureter, consisting in a ligation thereof with Safil Quick\textsuperscript{a} 3/0 (polyglycolic acid), after intraureteral tutoring with a 5 Fr catheter which prevents the obstruction from being complete.\textsuperscript{11}

**Phase II. Diagnosis and treatment of the ureteral obstruction**

After 6 weeks of the creation of the model of stenosis, enough time for the degradation of the suture and the creation of a real stenosis,\textsuperscript{12} we proceed to the diagnosis of partial obstructive uropathy and the assessment of the right and left renal collecting system, by means of the same laboratory, ultrasound, and fluoroscopic tests described in phase I.

Then, all the animals receive identical endourologic treatment, through retrograde endoureterotomy with diathermy device and subsequent placement of a double-pigtail ureteral catheter, which is cystoscopically removed after 3 weeks.

**Phase III or follow-up phase**

Phase III is developed within 6 months of the endourologic treatment of the obstructive lesion, this final stage consisting in a study of the right and left renal collecting system by means of the techniques used in the previous phases of the study.

**Statistical analysis**

The RI, PSV, EDV, and FR variables, as well as their ratios have been defined by the average ± standard error in each of the phases of the study.

The evolution of such parameters is analyzed by means of a multivariate analysis, repeated measures ANOVA, whereas the comparison between groups 2 to 2, in each of the phases, was performed using the $t$-test. The level of significance in all cases is $p < 0.05$.

The evaluation of the parameters as a diagnostic technique, as well as the determination of the optimal cut-off points, was obtained by using ROC curves. For the statistical analysis we used the SPSS 17.0 for Windows; SPP, Chicago, IL, U.S.A.

**Results**

In phase I, no animal showed signs of alteration in the upper urinary tract, where 0 was the degree of hydronephrosis observed in all the cases. Table 1 shows the baseline values of the parameters studied. In phase II, all the kidneys suffering from the model of ureteral obstruction showed nephrostographic and fluoroscopic evidence of partial ureteral obstruction, with grades I (8%), II (72%), and III (20%) hydronephrosis. Fig. 1 shows the evolution of the different parameters during the study; while Table 2 shows the values of the ratios in each phase. By means of the ROC analysis, we determined in the obstructive phase that the RI, EDV, and, to a greater extent, their ratios are the only parameters with an area under the curve above 0.5 and which, therefore, have efficacy as a diagnostic test of obstructive uropathy (Fig. 2 and Table 3).

In phase III, the animals were distributed according to the success or failure of the treatment, considering the condition of success as those cases in which the signs of hydronephrosis resolved and there was no evidence of stenosis in the tests, while in the failure group, those who continued with hydronephrosis and those who developed renal atrophy were included (Fig. 3). The comparison of both groups revealed statistically significant differences (SSD) for the EDV ($p = 0.012$) and the FR ($p = 0.003$) (Fig. 1). In addition, we compared the group of animals that in phase III developed renal parenchymal atrophy with the group in

<table>
<thead>
<tr>
<th>Phase</th>
<th>$\Delta$RI</th>
<th>$\Delta$PSV</th>
<th>$\Delta$EDV</th>
<th>$\Delta$FR</th>
</tr>
</thead>
<tbody>
<tr>
<td>FI</td>
<td>0.055 ± 0.012</td>
<td>1.86 ± 8.80</td>
<td>0.4 ± 1.23</td>
<td>3.5 ± 10.94</td>
</tr>
<tr>
<td>FII</td>
<td>0.066 ± 0.016</td>
<td>1.88 ± 11.52</td>
<td>2.84 ± 1.25</td>
<td>9.35 ± 11.55</td>
</tr>
<tr>
<td>FIII</td>
<td>0.035 ± 0.018</td>
<td>1.75 ± 10.92</td>
<td>1.4 ± 1.6</td>
<td>0.7 ± 16.68</td>
</tr>
</tbody>
</table>

**Table 2** Ratio of the parameters studied in each of the phases of the study.
which there was not this process, showing SSD only for EDV in phase II ($p = 0.022$).

Discussion

The management of patients with obstructive uropathy is often controversial, particularly with regard to the choice between conservative or surgical treatment and determination of the optimal timing of surgery. Furthermore, the techniques used for the assessment of these conditions are invasive or radiological, their use in children, pregnant women, or people allergic to contrast media being discouraged. Currently, numerous research studies evaluate less aggressive methods, such as blood or urine markers and hemodynamic parameters measured by Doppler ultrasound, with the aim of establishing a differential diagnosis and establishing a pre- and postsurgical monitoring of the patient, which helps guide the management and provide an accurate prognosis.

Figure 1  The fractions of the figure show the RI parameter values (A), EDV (B), PSV (C), and FR (D); for the ipsilateral kidney (orange line) and the contralateral kidney (blue line); determined in each of the phases of the study (phase I, phase II, and phase III), having divided phase III of both kidneys into 2 groups: successful resolution group (solid line) and unsuccessful resolution (dotted line). The SSD within each kidney are set with different letters, capital letters for the ipsilateral kidney, and lower case letters for the contralateral one. The SSD in phase III between the group of successful resolution and unsuccessful resolution within each of the kidneys are marked with *.

Figure 2  ROC curves for evaluating the parameters studied (A) and their ratios (B) as diagnostic markers of obstructive uropathy. In the tables, the area under the curve of each of the indexes is reflected.
In this sense, the RI has been extensively studied in recent decades, as a Doppler parameter able to distinguish between obstructive and non-obstructive etiology of the hydronephrosis; in spite of this, there is no general consensus about its usefulness, especially when it comes to partial obstructions or extended in time.

Unlike other works, where the RI obtains values greater than 0.7 in the presence of ureteral obstructions, in the present study, a slight increase is shown, without reporting significant differences with regard to the baseline values. Thus, we agree with Fung et al., Brkljacic et al., and Opdenakker et al. about asserting that both the partial nature and chronicity of the process are factors that may elucidate the poor response that the RI experiments. Despite this, it is important to point out, although very discreetly, all the studied parameters showed the expected changes according to the pathophysiology of the ureteral obstruction.

In the spectral Doppler wave of the arcuate arteries, the increase in the RI corresponds to a more marked reduction of the diastolic component with respect to the systolic increase. Therefore, it is likely that the hemodynamic changes occurring in the presence of an obstructive uropathy are reflected in the EDV to a greater extent than in the PSV, as evidenced in phase II of our study.

Indeed, the efficiency shown by this parameter to establish the diagnosis of obstructive uropathy is superior to that of the PSV and even the RI itself. The PSV reveals very subtle variations and it is, therefore, not very useful for the assessment of obstructive diseases. This finding contradicts the results published by Pope et al., who claim that the PSV is more sensitive than the RI for the detection of the obstructive processes.

In clinical practice, when the RI does not prove indicative of an obstructive process, determining the ratio significantly improves the reliability of the test, because it interrelates the effects that the obstruction causes on the affected kidney, and the compensatory response of the contralateral kidney. Our results support this theory, since the diagnostic potency shown by all the parameters considerably improves when calculating the ratio.

Of all the variables studied, the ΔEDV and EDV are those which show greater efficacy to establish the diagnosis of obstructive uropathy. However, the reported sensitivity and specificity are too low to relegate conventional diagnostic techniques, which can be applied as additional evidence of assessment.

According to our knowledge, there is no work relating the EDV to ureteral obstructions; however, some authors consider it the best ultrasound marker of vascular disorders of the renal parenchyma, as increase of intraparenchymal resistance or peripheral vasoconstriction, events that occur during the obstructive uropathy. In addition, the works by Pearce et al. reveal a strong correlation between the EDV and the loss of excretory renal function.

Consequently, we cannot discern whether the etiology of the decrease in the EDV in phase II of the study lies in the obstructive process itself or in the renal parenchymal damage associated with this. However, it has been shown how the EDV in the obstructive phase is significantly lower in the group of animals that develop long-term renal atrophy compared with those that do not. This observation could mean that the changes in the EDV are a reflection of the events occurred at the level of the renal parenchyma in the presence of a chronic partial obstructive process, such as the introduction of interstitial infiltrate of profibrotic and proapoptotic agents, precursors of renal atrophy. In fact, it has been shown that the deposit of apoptotic bodies occurs between the first and third week post-obstruction, which may be reversible or not depending on factors within-subject and the time at which treatment is effected. Therefore, we agree with Pearce et al. to say that this parameter is more sensitive than the PSV or the RI to detect renal parenchymal abnormalities. Furthermore, the fact that the EDV is able to predict which individuals will develop long-term renal atrophy is an interesting finding, which shows the EDV as a prognostic marker, with future clinical applications in the treatment of patients with obstructive uropathy. Recently, Ba et al. have also pointed the usefulness of this index as a predictor of renal damage in transplanted patients.

As for the final objective of the study, the usefulness of Doppler in postsurgical renal monitoring, both the EDV and the RI have proven to be good parameters of follow-up, because it has been shown how in phase III of the present study both variables return to the baseline values in those individuals with satisfactory resolution of the obstructive process, the EDV also being significantly lower in the group in which the treatment was not successful, with values close to those reported in the obstructive phase. Therefore, these findings confirm the observations of Shokeir et al. for the use of Doppler ultrasound in the postoperative follow-up of the patients, thus avoiding the use of radiological and invasive tests.
Further applications derived from the usefulness of the EDV for detecting changes at the level of the renal parenchyma can be:

- The determination of the optimal surgical time in patients with ureteropelvic junction obstruction, preventing radiological and invasive techniques and making it possible to opt for conservative treatment or nephrectomy in adults with irreversible parenchymal damage that will evolve into renal atrophy.\(^1\),\(^2\),\(^7\)
- Monitoring of the patients after surgery to predict which cases could develop long-term nephropathy, in order to establish a preventive treatment.\(^2\),\(^7\),\(^8\)

In order to validate these claims and to establish a cut-off point for the EDV, we need further studies that correlate the histological alterations, the loss of function, and the changes in the EDV that occur during an obstructive process. These studies would also evaluate these applications in other fields of urology like renal transplantation.\(^3\)

After analyzing our results, we can conclude that Doppler ultrasound is a technique that reflects the hemodynamic changes occurring during a chronic partial obstructive process, a fact scarcely described nowadays, all of the studied parameters being useful as complementary tests for pre-and postoperative monitoring of obstructive uropathy, especially the EDV and the RI. However, none of the indexes evaluated revealed good reliability as a diagnostic marker per se, the \(\Delta\)EDV being the most effective. Finally, the changes in the EDV evoke the possible use of this variable as a prognostic parameter of renal parenchymal damage in the presence of obstructive lesions, further studies being needed to apply this variable in the management of obstructive uropathy.

Conflict of interest

The authors declare that they have no conflict of interest.

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