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Research Article

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Evaluation of the Pre-Renal Azotemia and Acute Tubular Necrosis in Puppies by Doppler Ultrasonography

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Abstract

Background and aim: The diagnosis of pre-renal azotemia from acute tubular necrosis (ATN) is very important in order to choose the appropriate treatment method. Considering that urinary diagnostic indices are usually not very reliable due to the use of crystalloids and diuretics, a fast and accurate diagnostic method can significantly help the treatment of these patients. This study was designed and implemented in order to investigate the diagnostic value of Doppler ultrasound in differentiating pre-renal azotemia from ATN.

Materials and Methods: Fourteen puppies of different breeds that did not receive any fluids and were referred to the specialized small animal clinic of the Faculty of Veterinary Medicine of the Islamic Azad University, Urmia Branch due to oliguria or anuria were evaluated. In the first 24 hours after admission and in the recovery phase of acute kidney failure, ultrasound was performed and resistance index (RI) was measured in them. Based on history, clinical course and laboratory findings, acute renal failure (ARF) was divided into two categories: pre-renal azotemia and ATN, and appropriate treatment were given.

Results: The sensitivity and specificity of the resistance index (RI) in differentiating these two conditions were calculated. At the RI cutoff point of 0.75, the sensitivity and specificity of ultrasound were calculated as 92.1% and 86.5%, respectively.

Conclusion: According to the obtained results, Doppler ultrasound can be helpful in differentiating pre-renal azotemia from ATN in puppies. At the cutoff point equal to 0.75, RI has the highest diagnostic accuracy.

Keywords: *Doppler ultrasound, Pre-renal azotemia, Acute tubular necrosis, Puppies*

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Introduction

Acute kidney failure is a sudden and almost complete decrease in kidney function. In which, during a period of several hours to several days, the amount of glomerular filtration rate (GFR) decreases and at the same time the amount of urea and creatinine increases. Kidney failure is usually caused by renal blood circulation failure and glomerular or tubular dysfunction. Research has shown that acute tubular necrosis (ATN) is the most common cause of acute renal failure (ARF). Acute tubular necrosis is the destruction of tubular epithelial cells as a result of reduced kidney blood circulation or direct damage caused by nephrotoxic substances. Nephrotoxic substances such as antibiotics, gentamicin, heavy metals, chemicals, etc. are not suitable for the nephron and disturb the function of the nephron. Although in the advanced stages of kidney failure, the death rate even reaches 60-70%, but timely treatment causes recovery and usually does not leave any complications. The cause of ATN is divided into three categories: 1- With a pre-kidney origin, disorders of this group cause a decrease in kidney blood flow, such as: blood pressure (the most common cause), bleeding, shock, cardiac causes (heart failure and cardiac tamponade), diarrhea and dehydration. 2- With the after the kidney origin, they include the disorders that do not allow the produced urine to leave the kidney (ureter, bladder and urethra). This category of factors includes: obstruction in the urinary tract (pelvis, ureter, bladder or urethra) due to kidney stones, tumor and benign hypertrophy of the prostate, and swelling and inflammation in the urinary tract caused by injuries. 3- With the origin inside the kidney, which includes changes in the kidney parenchyma tissue caused by diseases or drugs and nephrotoxic substances, and in 35-40% of cases, the cause of ARF is caused by this category. Factors that have an intra-renal origin can include the following: Glomerulonephritis, pyelonephritis, diabetes, nephrotoxic drugs, myoglobinuria, hemoglobinuria (caused by blood incompatibility, hemolytic anemia and hemolytic uremic syndrome) (Ross, 2011; Cole *et al.,* 2020; Davis *et al.,* 2022).

Azotemia occurs when kidneys are damaged by disease or trauma. This condition may develop when kidneys are no longer able to get rid of enough nitrogenous waste. Azotemia is usually diagnosed using urine and blood tests. The main cause of azotemia is loss of kidney function. However, different types of azotemia, which may result from or be part of kidney failure, have different causes: old age, heart failure, complications of diabetes, dehydration, kidney damage, severe burns, loss of blood volume, surgeries. There are three types of azotemia: 1- Prerenal azotemia occurs when not enough fluid passes through the kidneys. This low fluid flow causes a high concentration of serum creatinine and urea. 2- Intrinsic azotemia usually occurs from infection or disease. The most common cause of intrinsic azotemia is ATN. 3-Postrenal azotemia: urinary tract obstruction causes post renal azotemia. Post renal azotemia can occur simultaneously with pre renal azotemia. This type of azotemia may have different treatments, causes and results. However, each can lead to acute kidney injury and failure if not treated or diagnosed early. (Defauw *et al.,* 2018; GU *et al.,* 2020)

Kidney length measurement has a special place in the diagnosis and treatment of kidney diseases. In patients with azotemia, first of all, it should be determined whether the kidney failure is acute or chronic. In cases where kidney function is recently and suddenly disturbed, physical examination and laboratory findings do not help much to differentiate between the two. The main symptom of chronic kidney failure is the reduction of the size of the kidneys, which, with timely diagnosis and treatment, can be prevented from progressing to the kidney, and ESRD (End Stage Renal Disease) (Kasper *et al.,* 2015). In various diseases, the kidney size becomes smaller or larger than normal. So far, sonography has been a good method for measuring kidney size because it is accurate and it is a low-cost, non-invasive method that is available at the same time (Armstrong *et al.,* 1990; Sutton, 2003).

Proffer a reliable and quick diagnostic method for differentiating pre-renal azotemia from ATN in puppies is important for several reasons. Firstly, dehydration is common in puppies and they are more prone to kidney failure due to dehydration than older dogs, and secondly, urinary diagnostic indices include fractional excretion of sodium (FENa) and urine to plasma osmolality due to consumption. Crystalloids and diuretics do not have the necessary diagnostic accuracy before referral to the hospital. In addition, when the patient is completely anuresis, these indicators will not be usable. Few studies have

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been conducted to investigate the diagnostic value of Doppler ultrasound in pre-renal azotemia and ATN (Abildgaard *et al.,* 1997; Gao *et al.,* 2019) and the resistance index (RI) is the most efficient parameter that has been proposed for this purpose. But different cut-off points have been proposed in different studies. In addition, the studied populations in these studies were mature dogs, while the renal blood flow indices in puppies are different from mature dogs (Quaia *et al.,* 2018). This study was designed and implemented to investigate the diagnostic value of Doppler ultrasound in differentiating pre-renal azotemia from ATN and finding a cutoff point for RI in puppies.

Materials and Methods

The study sample was 14 puppies from different breeds (8 male and 6 female) with acute kidney failure, which were referred to the small animal's clinic of the Faculty of Veterinary Medicine, Islamic Azad University in Urmia. All puppies had acute oliguria or anuria and their previous kidney tests were normal. The mean±SD of age of puppies was 5.85±2.53 months (1- 9 month-old). The working procedure was as follows: a patient who came to the clinic with clinical symptoms related to kidney complaints, based on the suspicion of the veterinarian for pre-renal or renal azotemia, without any intervention (receiving fluid and fluid therapy) in the first 24hour, it was hospitalized and referred to the radiology department for Doppler ultrasound. According to the clinical condition and laboratory findings, the patients were treated appropriately. In the recovery phase of acute kidney failure (urine volume Cc/Kg/hr <1), Doppler ultrasound was performed again. The diagnosis of pre-renal azotemia was made based on history, clinical course and laboratory findings (Table 1).

Ultrasound was performed by a veterinary radiologist and sonographer with a GE Voluson 730 Pro device (GE Kretz, Zipf, Austria) and a 8-12 MHz linear probe (linear trapezoid array 3D Transducer). Along with Doppler ultrasound, standard ultrasound was also performed (Figure 1, 2 and 3) to rule out the presence of morphological disorders such as hydronephrosis or accumulations around the kidney that lead to increased renal vascular resistance. Following biopsy with a thin needle by ultrasound, pathological sections were also prepared (Figure 4). The rank index (RI) in each patient was calculated from the following formula: (p-q)/p.

P was the maximum speed of systolic blood flow and q was the speed of blood flow at the end of diastole. RI in each patient was considered as the average RI in both kidneys.

Statistical methods

The data were analyzed with SPSS software (version 21) and one-way ANOVA test, by Tukey's post hoc test. The results of the study were presented as mean ± standard deviation. The P values less than 0.05 were considered as statistically significant.

Results

The mean and standard deviation of RI in patients with ATN was 0.85±0.33 and in the pre-renal azotemia group was 0.80±0.39 and there was a significant difference between the two groups ($P<0.05$). Mean and the standard error of the reduction of RI after treatment in the ATN group was 0.27±0.22. And in the pre-renal azotemia group was 0.05±0.01 ($P<0.05$). The sensitivity and specificity of ultrasound at the cutoff point RI=0.75 in differentiating pre-renal azotemia from acute tubule necrosis were 92.1% and 86.5%, respectively.

Variable	reference range	Anuria and Oliguria Dogs (n=14)
Urea (mg/dL)	19.8-58.9	159.21 ± 6.33
Creatinine (mg/dL)	0.6–1.4	6.9 ± 0.87
Potassium (mEq/L)	3.4–4.4	5.6 ± 0.89
Phosphorus (mg/dL	2.5–6.5	14.0 ± 1.64
Calcium (mg/dL)	8.7-11.8	11.9 ± 0.43
Sodium (mEq/L)	137-149	168.71 ± 5.80
Chloride (mEq/L)	99-110	113.21 ± 3.01
Urine Specific Gravity	1.035-1.045	1.035 ± 0.017

Table 1. Urine and blood analysis of poppies referred to the Faculty of Veterinary Medicine of the Islamic Azad University, Urmia Branch.Data are expressed as mean ± standard deviation.

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Figure 1. Sagittal sonogram of the left kidney in a 9-month-old mixed-breed male puppy. The length of the kidney is 20.5 mm, and the echogenicity of the cortical and central part of the kidney is obviously increased.

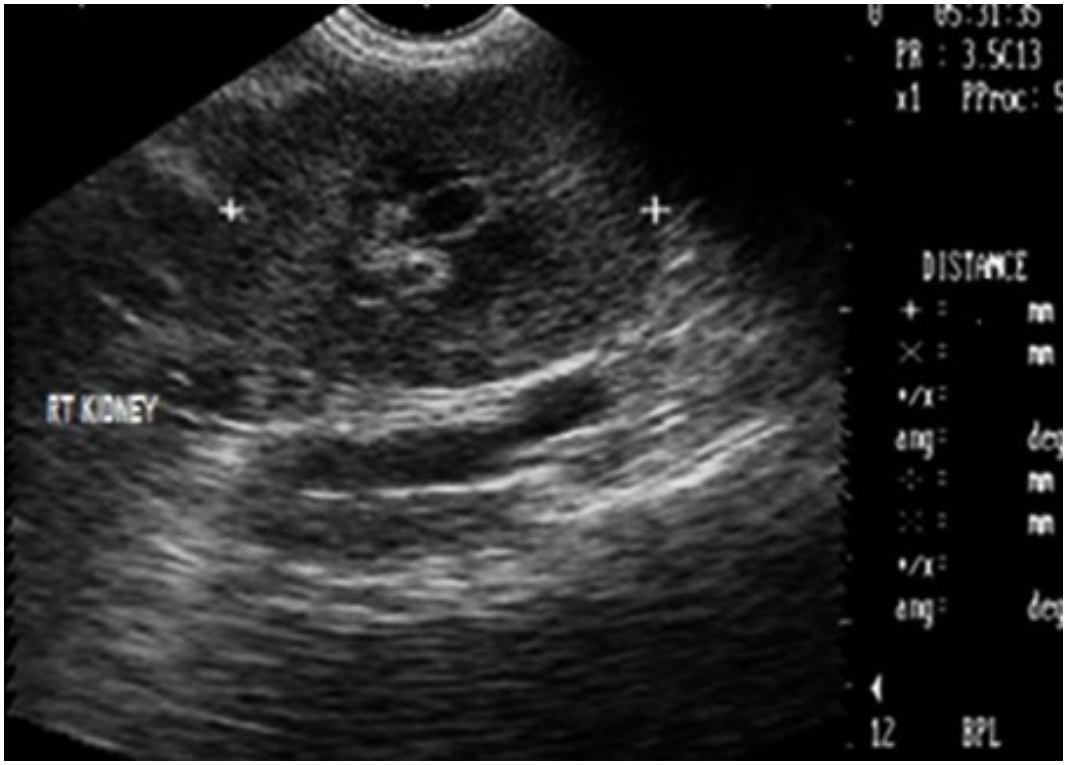

Figure 2. Transverse sonogram of the enlarged right kidney in an 8-month-old mixed-breed male puppy. The width of the kidney is 10.5 mm and the cortex of the kidney is hyperecho.

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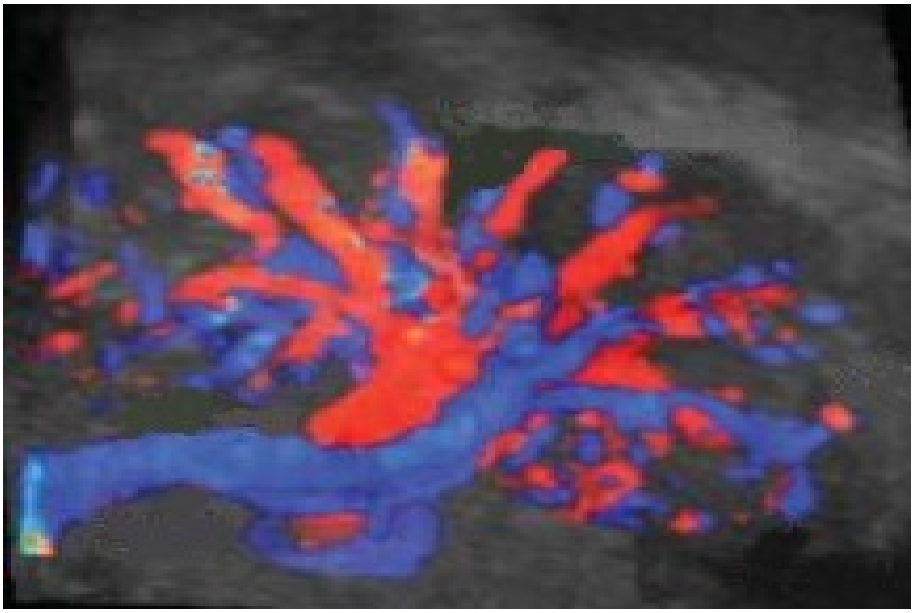

Figure 3. Color Doppler image of renal and interlobar arteries and veins in puppy's kidney using 0.6 (kHz) for the pre-renal azotemia [Note that the arterial flow is away from the transducer (blue colored) while venous flow is toward the transducer (red colored)].

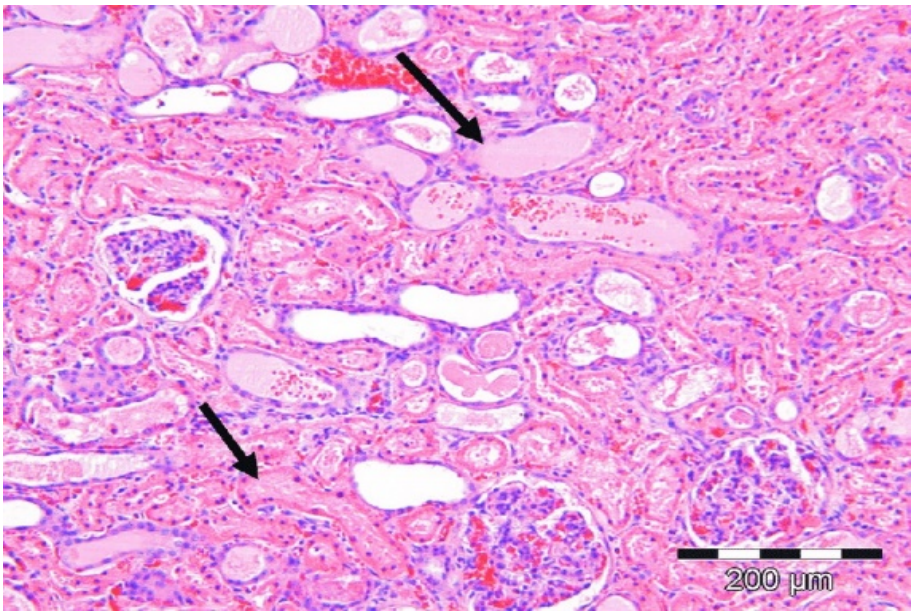

Figure 4. Acute tubular necrosis. Protein casts (arrows) within necrotic tubular epithelial cells in a kidney.

Discussion

Pre-renal azotemia and ATN are the main causes of acute kidney failure. Differentiating these two conditions is very important for choosing the true treatment. Acute kidney failure can be seen in puppies, and all clinical conditions associated with hypo-volemia, hypoxia, and hypotension can lead to kidney failure, the most common of which are ischemia, perinatal anoxia, and septicemia (Camacho *et al.,* 2021). Acute kidney failure is an acute decrease in glomerular filtration, which causes the accumulation of water and additional compounds in the body. Although there are many definitions for acute kidney failure; the best definition in puppies, is an increase in plasma creatinine level due to the growth of the puppy and the change in glomerular filtration rate. Several factors are used to diagnose the causes of acute pre- renal failure, including the

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animal's hydration status, the ratio of urea to creatinine, etc. Considering that invasive diagnostic procedures such as kidney biopsy are not acceptable in acute conditions of these patients, and on the other hand, urine diagnostic indices are not very reliable due to the previous use of crystalloids and diuretics in these patients. Therefore finding a non-invasive, accessible and reliable diagnosis method is necessary (Guess & Grauer, 2017).

Several studies have evaluated and confirmed the efficiency of Doppler ultrasound in the investigation of acute kidney transplant rejection (Huber *et al.,* 2003; Mailloux *et al.,* 1994; Parfrey *et al.,* 1989; Pickering, 1991; Reid *et al.,* 1980). Few studies have also evaluated the role of Doppler ultrasound in differentiating ATN from pre-renal azotemia (Abildgaard *et al.,* 1997; Arger *et al.,* 1999; Tanaka *et al.,* 2019; Gao *et al.,* 2019; Quaia, 2018). These studies show that Doppler ultrasound can be used as an acceptable diagnostic tool in differentiating these two conditions, but two issues need further investigation. First, these studies did not propose a single cut-off point for RI, and second, most of these studies were conducted in mature dogs, while RI varies according to age (Quaia et al., 2018). The results of this study show that Doppler ultrasound has high sensitivity and specificity in differentiating ATN from pre-renal azotemia. The sensitivity and specificity obtained in this study are higher than the values reported in previous studies in adults (Rivolta *et al.,* 1999; Sehgal *et al.,* 2001), which may indicate the diagnostic accuracy of RI is higher in puppies. In previous studies, the reduction of RI after treatment in affected patients was reported from 0.10 to 0.15 and in pre-renal azotemia from 0.01 to 0.02, which is lower than the values obtained in this study (Reid *et al.,* 1980; Rivolta *et al.,* 1999; Sehgal *et al.,* 2001). This difference may be due to the reversibility of renal circulation disorders in puppies compared to adult dogs. There is a Different cause of ATN in puppies and mature dogs that may be effective in this matter (the most common causes of ATN in mature dogs are drug poisoning and in in puppies are intravascular volume reduction).

Conclusion

This study shows that Doppler ultrasound can be used as an acceptable diagnostic method in differentiating pre-renal azotemia from ATN necrosis. The cutoff point equal to 0.75 has the highest diagnostic value for this purpose.

Acknowledgment

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Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this article.

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ارزیابی ازوتمی پیش کلیوی و نکروز حاد توبولار در توله سگ ها با استفاده از اولتراسونوگرافی داپلر

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چکیده

زمینه و هدف: تشخیص ازوتمی پیش کلیوی از نکروز حاد توبولار (ATN) به منظور انتخاب روش درمانی مناسب اهمیت زیادی دارد. با توجه به این که اندکس های تشخیصی ادراری معمولا به دلیل استفاده قبلی از کریستالوییدها و دیورتیک ها چندان قابل اعتماد نیستند، یک روش تشخیصی سریع و دقیق می تواند به درمان این بیماران کمک قابل ملاحظه‌ای کند. این مطالعه به منظور بررسی ارزش تشخیصی سونوگرافی داپلر در افتراق ازوتمی پیش کلیوی از ATN طراحی و اجرا شد.

مواد و روش‌ها: چهارده توله سگ از نژادهای مختلف که هیچ گونه مایعی دریافت نکرده بودند و به علت الیگوری یا آنوری به کلینیک تخصصی دام های کوچک دانشکده دامپزشکی دانشگاه آزاد اسلامی واحد ارومیه ارجاع شده بودند مورد ارزیابی قرار گرفتند. در ۲۴ ساعت اول پس از پذیرش و در فاز بهبود نارسایی حاد کلیه سونوگرافی شدند و اندکس مقاومت (RI) در آن ها اندازه گیری شد. براساس شرح حال، سیر بالینی و یافته‌های آزمایشگاهی، نارسایی حاد کلیه (ARF) به دو دسته ازوتمی پیش کلیوی و ATN تقسیم شد و درمان مناسب صورت گرفت.

یافته‌ها: حساسیت و ویژگی RI در افتراق این دو حالت محاسبه گردید. در نقطه قطع RI برابر ۰/۷۵، حساسیت و ویژگی سونوگرافی به ترتیب ۹۲/۱ درصد و ۸۶/۵ درصد محاسبه شد.

نتیجه گیری: با توجه به نتایج به دست آمده سونوگرافی داپلر در افتراق ازوتمی پیش کلیوی از ATN در توله سگ ها می‌تواند کمک کننده باشد. در نقطه قطع برابر ۰/۷۵، RI بیشترین دقت تشخیصی را دارد.

واژه‌های کلیدی: *سونوگرافی داپلر، ازوتمی پیش کلیوی، نکروز حاد توبولار، توله سگ ها*

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