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Renal hemodynamics in dogs with experimental hydronephrosis treated with transarterial embolization of renal artery

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Abstract : This study was performed to evaluate the renal hemodynamics using color Doppler ultrasonography in dogs with unilateral experimental hydronephrosis treated with transarterial embolization of the renal artery (TAE-RA). Experimental hydronephrosis was induced by ligation of unilateral ureter in 12 dogs. The mean resistive index (RI) value of kidney was significantly increased at 4, 9, 17 days after ligation of ureter. Unilateral hydronephrosis was established in 12 dogs at 17 days after ligation of ureter. Renal artery embolization was performed using selective catheterization in the hydronephrotic kidney of seven dogs and EKG, SpO_2, body temperature, pulse, and respiratory rate were within normal ranges during procedures. There were no dogs expired after TAE-RA and no side effects associated with regurgitation of iohexol-ethanol solution. In color Doppler ultrasonographic findings, there was no blood flow into the embolized kidneys treated by TAE-RA, however, blood flow signal was found in hydronephrotic kidney not treated by TAE-RA. No significant difference of RI value was found in contralateral normal kidney of dogs treated with TAE-RA compared to that of normal kidney in normal control group. It is concluded that TAE-RA does not affect the hemodynamics of contralateral normal kidney in dogs with experimental hydronephrosis and color Doppler ultrasonography is simple and non-invasive modality for the monitoring of the revascularization of the renal artery after TAE-RA.

Key words : dog, hydronephrosis, color Doppler ultrasonography, renal artery embolization, resistive index

Introduction

Hydronephrosis refers to dilation of the pelvis of the kidney from obstructed urine flow. Specific data on incidence of obstructive uropathy are not available for dogs, but cases are relatively commonly observed. The causes of obstructive uropathy in dogs include urethral uroliths, neoplasia, trauma, ectopic ureter and so on. Signs of obstructive uropathy vary considerably, depending on several factors including anatomic site of the primary lesion, degree of urine outflow impairment, duration of disease, and presence of secondary infection. Azotemia and uremia may be the prominent findings if urine outflow from both kidneys is obstructed. Unilateral ureteral obstruction may remain asymptomatic and may be detected only when hydronephrosis results in a marked increase in kidney size. However, acute ureteral obstruction may lead to intense pain[1].

Patients with a poor general medical condition may also be treated with less invasive therapy, sparing them the additional morbidity associated with an operative procedure. TAE-RA was initially described in an experimental canine model with the intent of developing a therapeutic technique for treating neoplasia. This technique has been developed into an accepted method of treating advanced or unresectable renal cell carcinoma of human with persistent bleeding, pain or manifestations of the paraneoplastic syndrome[2].

The occlusive effects of embolic materials in TAE-RA have been evaluated mostly by follow-up arteriograms clinically as well as experimentally[2,3,4,5]. Color Doppler ultrasonography enables physicians to evaluate the treatment response to nonsurgical interventions for the vascular and neoplastic diseases of human. For example, color Doppler sonography can effectively evaluate the patency of transjugular intrahepatic portosystemic shunts and the viability of hepatocellular carcinoma treated by percutaneous ethanol injection by observing inflow of

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blood to target organ[6,7]. Also color Doppler ultrasonography is considered to be the best technique for the follow-up examination of human renal artery aneurysm because it can be performed non-invasively and repeatedly at the patient's bedside[8]. Although a role for the selective angiograms remains in the evaluation of TAE-RA, ultrasonography and CT scan have emerged as alternative primary screening tools. However, the recanalization after TAE-RA with iohexol-ethanol solution for the treatment of canine unilateral hydronephrosis using color Doppler ultrasonography and enhanced CT has not been performed, yet.

The purposes of this study was performed to evaluate the renal hemodynamics using color Doppler ultrasonography in dogs with unilateral experimental hydronephrosis treated with transarterial embolization of the renal artery.

Materials and Methods

Experimental animals

Twelve mongrel dogs, ranging 2 to 4 years old, with body weight ranging from 3 to 10 kg were used. The dogs were housed in indoor cages and diet (Jerony, Che-il Jedang) and water were supplied *ad libitum*. Experimental animals were used without distinction of sex.

Experimental unilateral hydronephrosis

Twelve dogs were anesthetized with 10 mg/kg of ketamine HCl (Ketalar®, Yu-han Yanghang Co. Ltd., Seoul, Korea) by intramuscular injection and maintained with isoflurane (Aerane®, Choongwae medical Co. Ltd., Seoul, Korea).

During surgery, SpO_2 probe was applied to dog's tongue and SpO_2 was monitored and lead II of EKG, rectal temperature were monitored with anesthesia monitoring system (Vet-Ox™ plus 4700, U. S. A). The mid-abdomen was shaved and the animal was fastened to an operating table. The surgical area was scrubbed with povidone-iodine solution then draped in a sterile fashion. Under sterile conditions, a 7 cm midline incision was made around the umbilicus. A segment of the unilateral ureter was located and freed by blunt dissection so as not to damage any of the associated vascular structures. Then, the proximal part of the unilateral ureter was ligated with 2-0 black-silk in two places adjacent to renal pelvis. Carprofen was administered before extubation to all dogs and was repeated at 4 to 6-hour intervals during the next 12 hours. After 17th days after ligation of the unilateral ureter, hydronephrosis was confirmed.

Renal artery embolization

Dogs with unilateral hydronephrosis were anesthetized with 10 mg/kg of ketamine HCl (Ketalar®, Yu-han Yanghang Co. Ltd., Seoul, Korea) by intramuscular injection and maintained with isoflurane (Aerane®, Choongwae medical Co. Ltd., Seoul, Korea). During procedure, SpO_2 probe was applied to dog's tongue and SpO_2 was monitored and lead II of EKG, rectal temperature were monitored with anesthesia monitoring system (Vet-Ox™ plus 4700, USA). Under aseptic conditions, a stab incision was made on the inguinal region where pulsation was detected and a femoral artery was bluntly isolated. The distal portion of the artery was ligated while tension was applied to the proximal artery with 4-0 silk. The artery between the silk placement sites was punctured and an introducing sheath was introduced into the femoral artery. Then, the catheter (Fas-tracker® 18, length : 150 cm, outer diameter : 2.5F, Target therapeutics Inc., Fremont, CA, USA) and the 'J' shaped guide wire (Seeker® - 16 Flexible guide wire, length : 175 cm, diameter : 0.016 inch, Target therapeutics Inc., Fremont, CA, USA) were introduced through the introducing sheath. Under fluoroscopy (Dong-a X-ray R/F TV System, Seoul, Korea), the catheter with guide wire was selectively introduced into ipsilateral artery of hydronephrosis. Iohexol (Optiray® 320, Mallinckrodt Medical, Inc., St. Louis, MO, USA) was used as the contrast agent. One thousand mgI/kg of contrast agent was used as a maximum dosage for selection of renal artery. During procedures, 0.5 m*l* of saline was administered to flush the remnant contrast agent in the catheter after every injection of contrast agent.

Ethanol mixture (iohexol : pure ethanol = 1 : 1) was injected through the catheter in 7 dogs with unilateral hydronephrosis and saline was injected in 5 dogs with unilateral hydronephrosis. During renal artery embolization, to avoid the regurgitaion of embolic material into abdominal aorta, slow infusion (approximate 1 m*l*/min) was made under fluoroscopy. Then, the catheter was retrieved and the femoral artery was ligated with 4-0 silk.

Ultrasonography and color Doppler ultrasonography

Ultrasonography and color Doppler ultrasonography

were performed using a Toshiba SSA-260A machine with a 7 MHz electronic sector probe at 0, 4, 9 and 17 days after surgery and 0, 1, 3, 5, 10, 30, 60, and 90 days after renal artery embolization. Both kidneys of experimental group (hydronephrosis + TAE-RA) and control group (hydronephrosis) were examined. A normal control group was consisted of thirty-seven healthy dogs and the RI values from this group were used as reference range. When selecting subjects for the control group, a great care was taken in order to exclude any renal, past renal and urologic disease. The age was ranging 1 to 8 years in normal control dogs. The same Doppler settings (pulse repetition frequency of 6000 Hz, medium gain setting, wall filtering of 100 Hz, and low to medium color Doppler flow setting) were utilized to minimize technical errors.

After shaving the right and left flank area, color Doppler ultrasonography was performed initially to identify the interlobar or the arcuate artery for subsequent spectral Doppler analysis. Once a particular vessel was localized, interrogated using the Doppler gate to obtain a spectral waveform and thus quantitative information. The RI was determined by : RI = (PSV - EDV)/PSV, where PSV was peak systolic velocity, and EDV was end diastolic velocity. The RI was calculated for each vessel as an average value obtained from three similar-appearing Doppler waveforms to reduce the effects of physiologic variation.

Statistical analysis

Statistical analysis was performed using the SPSS statistical computer program. According to property of sample, one-way ANOVA and paired t-test were applied to data analysis.

Results

Experimental hydronephrosis

The RI values of interlobar artery or arcuate artery of obstructed kidney are 0.77±0.03 (4 days), 0.79± 0.05 (9 days), and 0.80±0.05 (17 days), respectively and they are significantly increased ($p<0.005$, one-way ANOVA, Fig 1). The fasting serum levels for BUN, creatinine, calcium, phosphorus, and ALT level remained within the normal range for 17 days after unilateral obstruction. All of the animals were in good general conditions throughout the study.

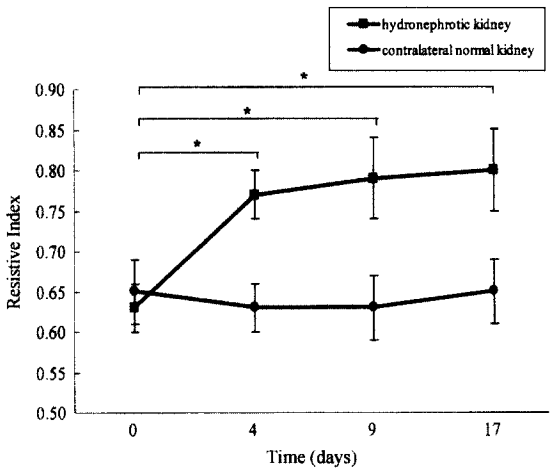

Fig 1. Resistive index of kidney with unilateral hydronephrosis. The RI values of interlobar artery or arcuate artery of obstructed kidney are significantly increased ($p<0.005$) at 4 days, 9 days, 17 days after unilateral ureter obstruction (one-way ANOVA).
* : $p < 0.005$

Image analysis of color Doppler ultrasonography

All 7 dogs underwent successful complete obstruction of the renal artery, as demonstrated by the absence of blood flow to the embolized kidneys on color Doppler ultrasonography throughout the observation period. However, blood flow signals were detected at the thinned renal cortex of the hydronephrotic kidney in 5 dogs not treated by TAE-RA throughout the observation period (Fig 2).

Resistive index of contralateral normal kidney after TAE-RA

The mean RI value of interlobar artery or arcuate artery of kidney are summarized in Fig 3. The mean RI value of normal control group was 0.65±0.05. The mean RI value of contralateral normal kidney in experimental group was not significantly different from normal control group throughout the observation period. The mean RI value of contralateral normal kidney in control group was not significantly different from that of contralateral normal kidney in experimental group ($p<0.05$) except 1 day and 7 days after TAE-RA (one-way ANOVA). Also, the mean RI value of contralateral normal kidney in control group was not significantly different from that of normal control group except 3,

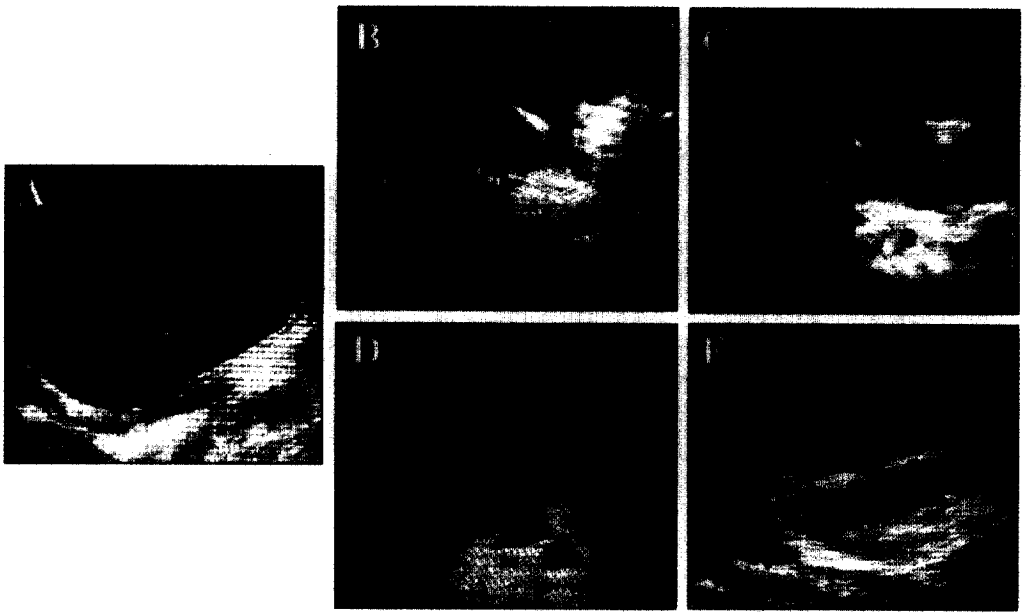

Fig 2. Color Doppler ultrasonographic findings after TAE-RA. There is a blood flow signal in thinned renal cortex of hydronephrotic kidney not treated by TAE-RA 14 days (B) and 60 days (C) after TAE-RA, however, color Doppler ultrasonogram 14 days (D) and 60 days (E) after TAE-RA shows no color signal in the kidney contrary to normal kidney (A), confirming the complete ablation of the embolized kidney (black arrow : color signal of aorta).

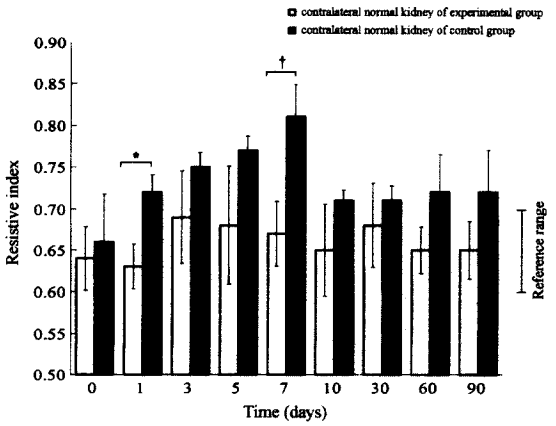

Fig 3. Resistive index of kidney treated by TAE-RA. The mean RI values of contralateral normal kidney in experimental group was not significantly different from normal control group throughout the observation period (paired t-test). The RI values of contralateral normal kidney in control group was not significantly different from that of contralateral normal kidney in experimental group except 1 day ($p<0.05$) and 7 day ($p<0.005$) after TAE-RA(one-way ANOVA). Also, the RI values of contralateral normal kidney in control group was not significantly different from that of normal control group except 3, 5, 7 day (paired t-test).
* : $p < 0.05$, † : $p < 0.005$

5, 7 days after TAE-RA ($p<0.05$).

Discussion

Most animal studies have described that at the late phase of obstruction renal vascular resistance markedly rises and RI elevation will be expected. Platt *et al.* (1989, 1993)[9] according to his series based on 229 human kidney, mentions that 0.70 is a resonable cutoff value for RI in a kidney with a dilated system suggestive of obstruction. We obtained similar findings with an RI value of 0.65 ± 0.05 in 74 nonobstructed healthy kidney and 0.80 ± 0.05 in obstructed kidney at 17 days after ligation of the ureter. We have not performed a gold standard technique such as the Whitaker test in order to confirm the obstruction of thc ureter and hydronephrosis.

Transarterial embolization of renal artery is accepted in the ablation of diseased kidney in human patients. It includes the Gianturco steel coil, gelfoam, Ivalon particles, polyvinyl alcohol, autologous clot, detachable balloon catheters. Also, there have been many experimental studies done about the embolization of kidneys in dogs with various embolic materials[3,4,5,10,11,12,13]. One of the techniques available for permanent vascular occlusion

seems to be the use of the Gianturco stainless steel coil[10,13,14].

Chen *et al.* (1993)[15] observed no difference in the RI values in kidneys without obstruction among the human patients with obstructive uropathy and normal controls. In this study, the mean RI value of contralateral normal kidney in control group was not significantly different from that of contralateral normal kidney in experimental group ($p<0.05$) except 1 day and 7 days after TAE-RA.

Also, the mean RI value of contralateral normal kidney in dogs treated by TAE-RA after hydronephrosis was not significantly different from normal control group throughout the observation period. The fact that the normal contralateral kidneys in control group and in experimental group had no elevated RI suggested that the hemodynamic changes in obstructed kidneys are local intrarenal rather than systemic events as suggested by Ichikawa and Brenner (1979)[16] in an animal study and Chen *et al.* (1993)[15] in human clinical study. Also, it is implied that TAE-RA after hydronephrosis did not alter the hemodynamics of contralateral normal kidney.

For nonsurgical interventional treatments, a precise follow-up evaluation is needed. Follow-up studies of non-functioning hydronephrosis in human patients treated with TAE-RA using absolute ethanol were performed periodically by enhanced CT and found that marked shrinkage of hydronephrosis without any enhancement of the parenchyma[17]. In case of traumatic renal hypertension secondary to unilateral hydronephrosis in human patients treated TAE-RA using Gianturco-Wallace coil, revascularization were evaluated with abdominal aortogram and selective left renal arteriogram and they demonstrated the total occlusion of the left renal artery distal to the coils[18].

Also, digital subtraction of angiograpy was employed to evaluate the TAE-RA with alcohol for proteinuria in patients with end-stage renal disease[19]. In our study, color Doppler ultrasonography was performed after TAE-RA for follow-up examination of TAE-RA and observed the obstruction and shrinkage of embolized kidney. However, although enhanced CT and selective angiogram are useful for evaluation of the configuration of the kidney and the revascularization of the embolized kidney, enhanced CT requires general anesthesia and injection of iodinated contrast medium and selective angiogram is an invasive procedure that requires a percutaneous puncture of the femoral artery. The ability of MR to depict the shrinked embolized kidney appears to parallel that of CT and ultrasonography, although no accuracy levels have been established. Despite this, it seems that because the differentiation of revascularization is not possible in MR scanning, MR will not serve a primary function in the evaluation of TAE-RA after hydronephrosis of dogs. Shonai *et al.* (2000)[8] performed the percutaneous transarterial embolization for treatment of renal artery aneurysm in human patients and the therapeutic effects and the vascular change were evaluated quite precisely without any contrast material by color Doppler ultrasonography. Color Doppler ultrasonography can evaluate the treatment response to nonsurgical interventions for the vascular diseases.

In our study, the embolized kidney was evaluated using color Doppler ultrasonography and no blood flow signals in the embolized kidney in 7 dogs treated by TAE-RA were detected without general anesthesia and no use of contrast medium In summary, we believe that color Doppler ultrasonography is the simple and non-invasive technique for the follow-up examination of hydronephrosis treated by TAE-RA using iohexol-ethanol solution.

Conclusion

The study was performed to evaluate the renal hemodynamics using color Doppler ultrasonography in dogs with unilateral experimental hydronephrosis treated with transarterial embolization of the renal artery.

The mean RI value of contralateral normal kidney in experimental group was not significantly different from that of normal control group throughout the observation period. Also, the mean RI value of contralateral normal kidney in experimental group was not significantly different from that of contralateral normal kidney in control group except 1, 7 days after TAE-RA. Therefore, TAE-RA in the dogs with unilateral hydronephrosis did not affect the resistive index of contralateral normal kidney.

Color Doppler ultrasonography were available for the detection of revascularization of renal artery after TAE-RA in dogs with hydronephrosis. Also, color Doppler ultrasonography was a simple and non-invasive modality for the detection of the revascularization of the renal artery after TAE-RA in dogs with hydronephrosis.

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신장동맥색전술을 실시한 개의 실험적 수신증의 혈동학

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(2001년 8월 28일 게재승인)

국문초록 : 개에서 실험적으로 편측성 신수종증을 유발한 후, 이오헥솔-에탄올 용액을 신장동맥내로 주입하여 신수종증이 유발된 신장으로의 혈류를 차단하는 신동맥 색전술을 실시한 후, 컬러 도플러 초음파상을 이용하여 색전술이 실시된 신수종증의 신장과 반대편 정상신장을 평가하고자 본 실험을 실시하였다. 수뇨관 결찰 후, 유발 전에 비하여 혈관저항지수가 4일, 9일, 17일째에 유의적으로 증가하였으며, BUN, creatinine, ALT, calcium, phosphorus는 변화하지 않았다. 이를 통하여 12두의 개에서 요관 결찰 17일째에 편측성 수신증이 유발되었음을 확인할 수 있었다. 신장동맥 색전술은 7두의 신수종증이 유발된 신장측의 신장동맥에 대퇴동맥을 통하여 선택적으로 카테터를 삽입한 후 이오헥솔-에탄올 용액을 주입하였으며, 시술 중 심전도, 산소포화도, 체온, 맥박, 호흡수는 모두 정상범위에 있었다. 신장동맥 색전술 후 사망한 개체는 없었으며, 색전물질의 유출로 인한 부작용도 관찰할 수 없었다. 색전술 실시 후 시행한 칼라도플러 초음파 검사에서는 7두 모두에서 실험 전 기간에 걸쳐 색전된 신장에서 혈관신호를 관찰할 수 없었으나, 색전술을 실시하지 않은 5두에서는 신장내에서 혈관신호를 관찰할 수 있었다. 그리고 색전술을 실시한 7두의 정상신장의 평균 혈관저항지수는 정상견의 혈관저항지수와 유의적인 차이가 없음을 확인할 수 있었다. 칼러 도플러 초음파 검사법은 개의 수신증에 실시한 신장동맥 색전술 후의 신장동맥의 재맥관화를 평가할 수 있는 간편하며, 비침습적인 검사법으로 사료된다.

핵심어 : 개, 수신증, 칼라 도플러 초음파, 신장동맥 색전술, 혈관저항지수