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Citation	泌尿器科紀要 (1996), 42(9): 655-661
Issue Date	1996-09
URL	http://hdl.handle.net/2433/115807
Right	
Type	Departmental Bulletin Paper
Textversion	publisher

SERIAL CHANGES IN PROXIMAL URETHRAL FUNCTION AFTER TRANSURETHRAL BALLOON LASER HYPERTHERMIA OF THE PROSTATE (TUBAL-H) IN A CANINE MODEL

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We performed transurethral balloon laser hyperthermia of the prostate (TUBAL-H) in 6 mongrel dogs. To evaluate the changes in proximal urethral function after TUBAL-H, the urethral cross sectional area (CSA, cm²) and urethral pressure (Pu, cmH₂O) were measured using a balloon probe that allows their simultaneous measurement, and the urethral compliance (Comp, cm³/cmH₂O) was calculated from these parameters and serially evaluated. In addition, the changes in Pu, CSA and Comp after administration of an α -adrenoceptor antagonist were evaluated before and 16 weeks after TUBAL-H.

Before TUBAL-H, the mean Comp was 0.013, and the mean maximum CSA (MCSA) was 0.66. Eight weeks after TUBAL-H, the mean Comp was 0.038, and the mean MCSA was 1.39, showing a significant increase ($p < 0.01$). Sixteen weeks, after TUBAL-H, the mean Comp was 0.026, and the mean MCSA was 1.21, being lower than those at 8 weeks after TUBAL-H, but significantly higher than those before TUBAL-H ($p < 0.05$).

After administration of the α -adrenoceptor antagonist, phentolamine (1 mg/kg), before TUBAL-H, the mean Comp significantly increased to 0.046 ($p < 0.05$), and the mean MCSA to 1.40 ($p < 0.01$). The mean Comp was significantly increased to 0.033 ($p < 0.05$), by phentolamine administration 16 weeks after TUBAL-H, but no other changes were observed.

After TUBAL-H, urethral elasticity increased, and this increase persisted for 4 months. The responses of Comp and MCSA to α -adrenoceptor antagonist administration before and 16 weeks after TUBAL-H suggested that part of the effects of TUBAL-H is due to damage to α -adrenoceptors.

(Acta Urol. Jpn. 42 : 655-661, 1996)

Key words: Balloon laser hyperthermia, Proximal urethral function, Canine model

INTRODUCTION

Recently, medication¹⁾, laser ablation (VLAP)²⁾, hyperthermia³⁾, and thermotherapy⁴⁾ have attracted attention as less invasive treatment methods for benign prostatic hypertrophy (BPH). Hyperthermia has been reported to be effective⁵⁾, and its action mechanism has been suggested to be damage to α -adrenoceptors⁶⁾

We have been studying the effects of transurethral balloon laser therapy (TUBAL)⁷⁻¹⁰⁾ In this study, we evaluated the serial changes in proximal urethral function after transurethral balloon laser hyperthermia of the prostate (TUBAL-H) to clarify the action mechanism of the treatment.

MATERIALS AND METHODS

Animal model

Six male mongrel dogs each weighing 9-15 kg (median, 11.5 kg) were used. The median prostate volume was 8.0 cc (3.3-12.4 cc). Perineal urethrostomy was performed before treatment in all dogs. All dogs were handled according to the Institute's Guide lines for the Care and Use of Laboratory Animals.

Anesthesia

All procedure were performed under the following anesthesia. Anesthesia was induced with sodium pentobarbital (25 mg/kg) and atropine sulfate (0.05 mg/kg). Mask anesthesia was performed under spontaneous respiration. The nitrogen monoxide: oxygen ratio was 1 : 1 (1.5-2.0 l/min each). The halothane (Zeneca Co. Ltd., England) concentration was 2.0% during induction of anesthesia and 1.5% during maintenance.

TUBAL-H

The PROSTALASETM system used for this experiment consisted of CL50FS, which generates Nd: YAG laser, and CATM, which is a computer-assisted temperature monitor system. This system was described in our previous study⁷⁾ The balloon was perfused and cooled with water at 10°C. After the tissue temperature 5 mm deep from the mid-prostatic urethral mucosa (T5) reached 45°C at an output of 30 W, TUBAL-H was performed for 30 minutes. The urethral surface temperature (Ts) was maintained at 40° or less during treatment.

Measurement of proximal urethral function

Fig. 1 shows the probe that measured proximal urethral function. This probe was equipped with a 2

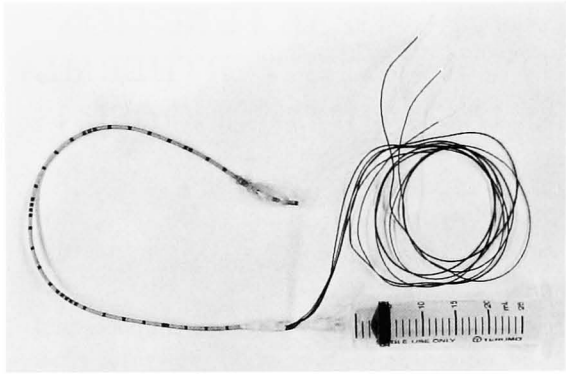


Fig. 1. Balloon probe for measuring urethral function.

cm balloon near its tip that contained two pairs of generating and detecting electrodes connected to an impedance plethysmograph amplifier (Nihon Kodens Co., Ltd., Tokyo, Japan) that measures CSA using the field gradient principle^{11,12} CSA was calculated by $CSA = CSA_p + \sigma L / Z_0$ (CSA_p : cross sectional area of the probe = 0.032 cm², σ : resistant ratio = 65 Ω cm, L: distance of detecting electrodes = 0.5 cm, Z_0 : impedance, Ω). There was a good correlation between CSA' (caliper measured) and CSA: $CSA' = 0.78 \times CSA + 0.0458$, $r = 0.996$ (Fig. 2). All values given below were obtained by the calculation (CSA'). It was also equipped with a pressure transducer connected to an amplifier (Nihon Kodens Co. Ltd., Tokyo, Japan) that measured urethral pressure simultaneously. The balloon was made of latex condom (Yamanouchi Pharmaceutical Co. Ltd., Tokyo, Japan) and its intrinsic pressure (Pbi) was lower than that of the original Harada's balloon¹² so that changes in the pressure could be measured more exactly. The actual urethral pressure (Pu) is the

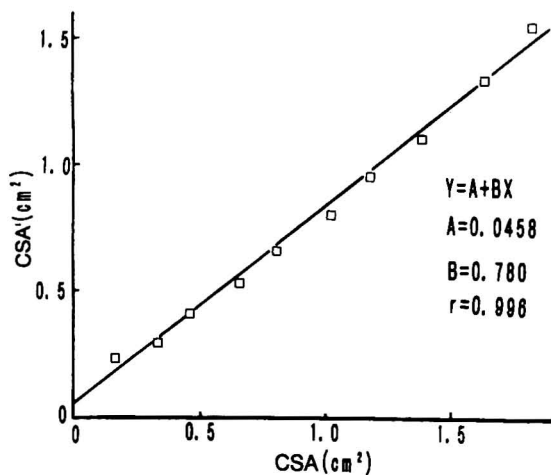


Fig. 2. Correlation between CSA' and CSA. CSA': cross sectional area measured by caliper (cm²), CSA: cross sectional area measured by balloon probe (cm²).

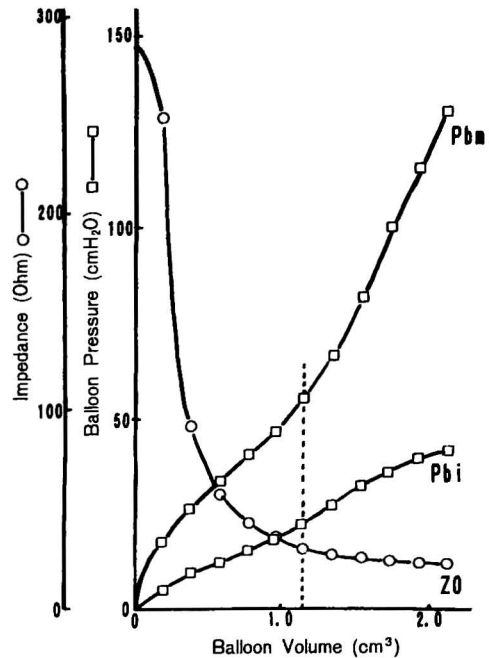


Fig. 3. Chart of urethral function measurement. Pbm: measured balloon pressure (cmH₂O), Pbi: intrinsic pressure (cmH₂O), Z0: impedance (ohm).

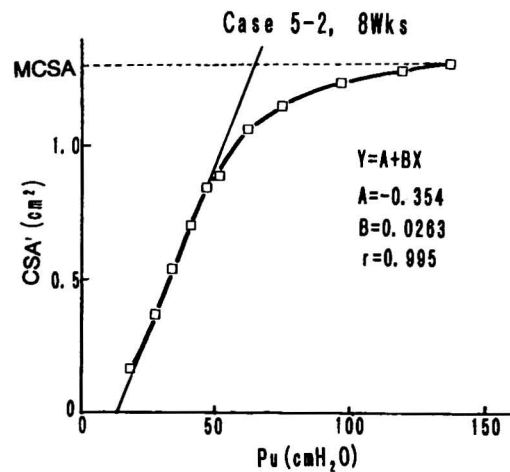


Fig. 4. Plot between CSA' and Pu. Pu: urethral pressure (cmH₂O), M-CSA: maximum cross sectional area (cm²).

difference between the measured balloon pressure (Pbm) in the prostatic urethra and Pbi (Fig. 3). Then, CSA' and Pu were plotted (Fig. 4). The main slope of the graph was constructed into a straight line determined by the regression equation of $Y = B + AX$. Assuming that the urethral length is a unit length, i.e., $dV = 1 \text{ cm} \times dCSA$ ($dv = \text{volume change}$, $dCSA = \text{change in the CSA}$), then Comp was represented as $Comp = dV/dP = 1 \times dCSA/dP$ (cm³/cmH₂O, $dP = \text{pressure change}$), and by the constant value "A" in the regression equation. The maximum CSA (M-CSA) was determined by the point where CSA' reached a plateau.

Actual measurements were performed as follows (Fig. 5). When the depth of anesthesia reached a

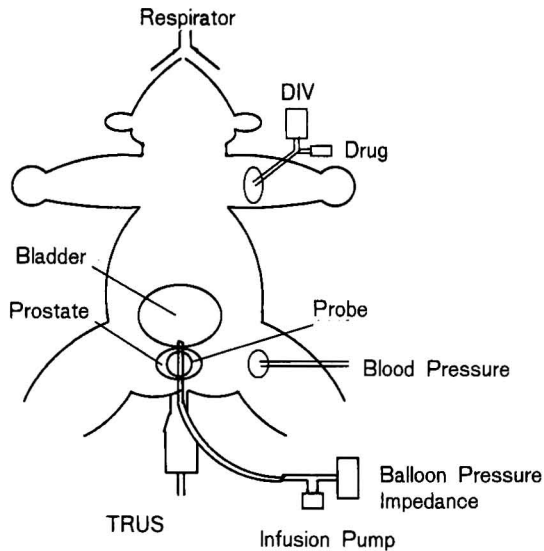


Fig. 5. Schema of the measurement of urethral function induced by administration of α -adrenoceptor antagonist. TRUS: transrectal ultrasonography.

constant level about 20 minutes after induction of anesthesia, the dogs were placed in the supine position. After stools in the rectum were completely removed, the balloon probe introducer (14 Fr, 15 cm long) was inserted into the bladder, and urine was adequately withdrawn. Under transrectal ultrasound (TURS) guidance, the balloon probe was inserted through this introducer to the prostatic urethra, and the introducer was removed. Air in the probe was adequately removed by physiological saline, and the probe was connected to an infusion pump for physiological saline and a pressure transducer. Physiological saline was infused at a rate of 0.39 ml/min using the infusion pump, and Z0 and Pbm were measured at 30-second intervals. This plot is shown in Fig. 3. The measurement was terminated 5–6 minutes after the initiation of measurement when Z0 became constant, i.e., MCSA was observed. The reproducibility of this measurement under the same conditions was within 15% for

Comp and MCSA.

Changes in these parameters after drug administration were evaluated by the following procedure. Phentolamine (1 mg/kg) was infused as a bolus intravenously. The femoral arterial pressure began to decrease immediately after the infusion and reached a constant level after about 4 minutes, when measurement was performed¹³⁾ (Fig. 6).

Measurement was performed before as well as 4, 8, 12, and 16 weeks after TUBAL-H in all dogs, and at 1-week intervals from immediately after TUBAL-H until after 11 weeks in dogs in which this was possible. In addition, changes after drug administration were evaluated before and 16 weeks after TUBAL-H.

Values were statistically analyzed using paired t-test, and p values less than 0.05 were considered to indicate significant differences.

RESULTS

Changes in the prostate volume

The median prostate volume was 8.0 cc (3.3–12.4 cc) before TUBAL-H, increased to 10.8 cc (6.8–16.3) immediately after TUBAL-H, but decreased to 7.0 cc (2.9–14.8) 16 weeks after TUBAL-H.

Serial changes in Comp

The changes in Comp ($\text{cm}^3/\text{cmH}_2\text{O}$) in all dogs are shown in Fig. 7. Comp was 0.013 ± 0.015 before TUBAL-H, slightly decreased immediately after TUBAL-H, but began to increase 1 week after TUBAL-H, reaching the maximum of 0.043 ± 0.020 4 weeks after TUBAL-H ($P < 0.05$). Comp slightly decreased thereafter, being 0.038 ± 0.013 8 weeks after TUBAL-H ($p < 0.01$), and continuously decreased, reaching 0.029 ± 0.014 12 weeks after TUBAL-H ($p < 0.05$). Comp 16 weeks after TUBAL-H was 0.026 ± 0.0085 , showing a further decrease, but was still significantly higher than that before TUBAL-H ($p < 0.05$).

Serial changes in MCSA

The changes in MCSA (cm^2) in all dogs are shown in Fig. 8. MCSA was 0.66 ± 0.27 before TUBAL-H,

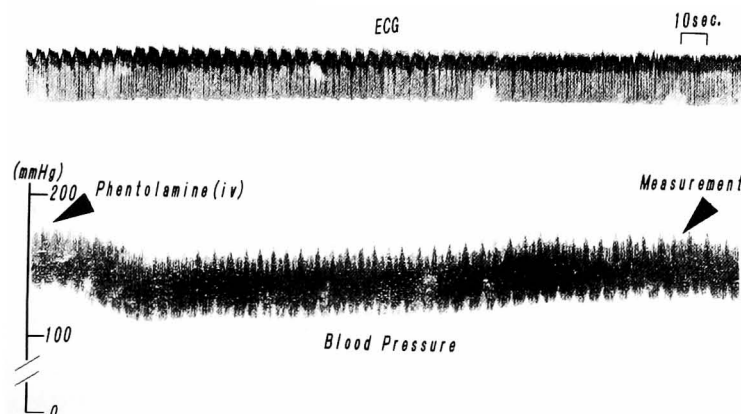


Fig. 6. Chart of the femoral arterial pressure after administration of α -adrenoceptor antagonist.

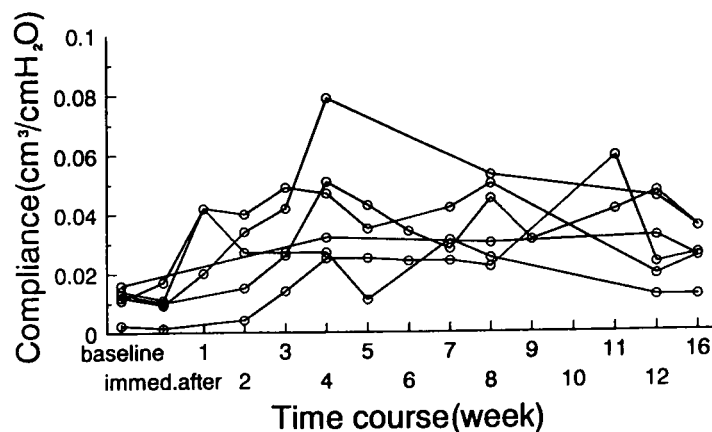


Fig. 7. Serial change of compliance after TUBAL-H. baseline: 0.013 ± 0.015 $\text{cm}^3/\text{cmH}_2\text{O}$, 8 weeks: 0.038 ± 0.013 ($p < 0.01$), 12 weeks: 0.029 ± 0.014 ($p < 0.05$), 16 weeks: 0.026 ± 0.0085 ($p < 0.05$).

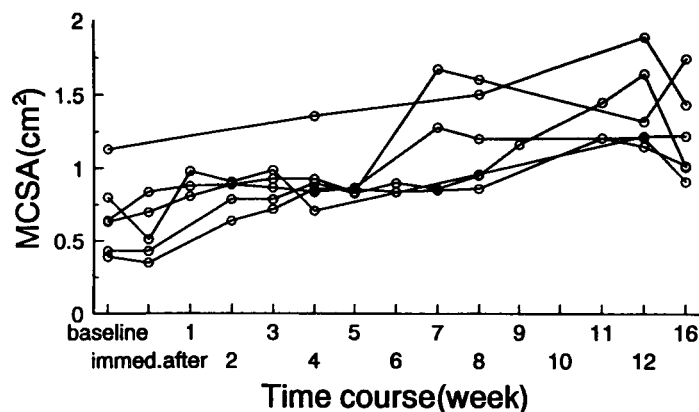


Fig. 8. Serial change of maximum cross sectional area (MCSA) after TUBAL-H. baseline: 0.66 ± 0.27 cm^2 , 8 weeks: 1.18 ± 0.31 ($p < 0.01$), 12 weeks: 1.39 ± 0.29 ($p < 0.01$), 16 weeks: 1.21 ± 0.32 ($p < 0.01$).

Table 1. Change of urethral functional parameters after administration of α -adrenoceptor antagonist at before treatment

	Closure pressure (cmH ₂ O)	Compliance (cm ³ /cmH ₂ O)	Cross sectional area (cm ²)
Baseline	15.4	0.013	0.66
	14.3	0.015	0.27
Phentolamine	11.0	0.046*	1.40**
	6.3	0.029	0.25

upper: Mean lower: SD *· $p < 0.05$ **· $p < 0.01$

Table 2. Change of urethral functional parameters after administration of α -adrenoceptor antagonist at 16 wks post treatment

	Closure pressure (cmH ₂ O)	Compliance (cm ³ /cmH ₂ O)	Cross sectional area (cm ²)
Baseline	17.5	0.0260	1.21
	2.8	0.0085	0.32
Phentolamine	13.0	0.0330*	1.30
	6.2	0.0100	0.26

upper: Mean lower: SD*: $p < 0.05$

slightly decreased immediately after TUBAL-H, but began to increase 1 week after TUBAL-H and was 0.93 ± 0.22 4 weeks after TUBAL-H ($p < 0.05$). MCSA further increased thereafter to 1.18 ± 0.31

8 weeks after TUBAL-H and to the maximum of 1.39 ± 0.29 12 weeks after TUBAL-H. MCSA 16 weeks after TUBAL-H was 1.21 ± 0.32 , showing a slight decrease, but was still significantly higher than that

before TUBAL-H ($p < 0.01$).

Changes in Comp after administration of an α -adrenoceptor antagonist

Table 1 shows the changes in Comp and MCSA caused by phentolamine administration before TUBAL-H. Comp and MCSA significantly increased after drug administration ($p < 0.05$, $p < 0.01$ respectively).

Sixteen weeks after TUBAL-H, Comp significantly increased after phentolamine administration ($p < 0.05$). MCSA also increased after drug administration, but not significantly (Table 2).

DISCUSSION

Several studies have shown that hyperthermia improves symptoms of BPH^{3,5)}. The action mechanism has been suggested to be damage to α -adrenoceptors⁶⁾. However, in these studies, hyperthermia was performed using a radiofrequency waves (RF). There are no studies on the effects of hyperthermia using a laser. We previously evaluated the temperature distribution in the prostatic tissue during TUBAL in dogs⁷⁾ and examined the interstitial temperature appropriate for hyperthermia (42–45°C) under the conditions used in the present study. This temperature distribution showed a convex pattern with a peak (45°C) at a depth of 6 mm from the urethral mucosa. A similar study on interstitial temperature after hyperthermia using RF showed a gentle temperature distribution (4°C per 1 cm) with a peak (45°C) in the urethral mucosa¹⁴⁾. Since the effects of these differences in heat distribution and the heat source, remain unknown, we examined the effects and action mechanism of TUBAL-H.

To clarify the action mechanism of TUBAL-H, we noted the changes in proximal urethral function and evaluated this with the following devices. In dogs, Pu decreases to an extremely low value with deep anesthesia, resulting in a decrease in reproducibility. Therefore, to maintain a slightly shallow constant depth of anesthesia, we used mask anesthesia. In addition, a balloon was used to measure Pu since Breslin et al.¹⁵⁾ and Shapiro et al.¹⁶⁾ reported measurement of Pu in dogs by an improved method using a balloon for the measurement of esophageal pressure. However, instead of direct comparison of Pu, Comp was calculated and compared. For this, we used a balloon probe based on the field gradient principle developed by Colstrup et al.¹¹⁾ and Harada et al.¹²⁾. The Pbi obtained using the original balloon developed by Harada et al., was so high that Pu could not reflect subtle changes in pressure. Therefore, we reduced Pi using the tip of a condom as the balloon surface material. As a result, Pi decreased considerably, allowing accurate measurement of Pu. In addition, since perineal urethrostomy was performed, a thicker catheter (9 Fr) than Harada's

original balloon could be inserted, increasing the accuracy of measurement. The balloon probe could be accurately placed in the prostatic urethra under the guidance of TRUS. With these devices, we accurately evaluated proximal urethral function with high reproducibility.

Comp ($\text{cm}^3/\text{cmH}_2\text{O}$) was 0.013, and MCSA (cm^2) was 0.66 before TUBAL-H but significantly increased to 0.038 and 1.39, respectively, 8 weeks after TUBAL-H ($p < 0.01$). Sixteen weeks after TUBAL-H, both Comp and MCSA were slightly decreased (0.026 and 1.21, respectively) but still significantly higher than those before TUBAL-H ($p < 0.05$). These findings suggest that the flexibility of the prostatic urethra increased after TUBAL-H, and the increase persisted for 4 months. However, the most marked increase in flexibility was observed 2 months after TUBAL-H, followed by a gradual decrease. This suggests a limit in the persistency of the effects of TUBAL-H. In clinical practice, Yerushalmi et al.⁵⁾ reported the long-term outcome of microwave hyperthermia and persistence of improvement in symptoms for 8 years.

We used phentolamine as an α -adrenoceptor antagonist. It is not a selective α -adrenoceptor antagonist, but since its maximum point of action could be readily observed by monitoring the arterial pressure drop, we could easily find the starting point of the measurement. Before TUBAL-H, Comp ($\text{cm}^3/\text{cmH}_2\text{O}$) significantly increased to 0.046 ($p < 0.05$), and MCSA (cm^2) to 1.40 after phentolamine administration ($p < 0.01$). Sixteen weeks after TUBAL-H only Comp significantly increased to 0.033 after phentolamine administration ($p < 0.05$). This decrease in the response to the α -adrenoceptor antagonist 16 weeks after TUBAL-H suggests the involvement of damage to α -adrenoceptors in the increase in the flexibility of the prostatic urethra.

Suzuki et al. reported the histological changes after TUBAL-H, but further studies on the histological damage of α -adrenoceptor after TUBAL-H are needed. Other factors such as the dilatation effects of the laser balloon also must be evaluated in detail.

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(Received on March 7, 1996)

(Accepted on June 20, 1996)

和文抄録

犬モデルにおけるバルーンレーザーハイパーサーミア (TUBAL-H) 後の
近位尿道機能の経時的変化

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雑種犬6頭を用いてバルーンレーザーハイパーサーミア (TUBAL-H) を行った。TUBAL-H 後の近位尿道機能の変化を評価するために、尿道内圧と尿道断面積 (CSA, cm^2) を同時測定し、これらからコンプライアンス (Comp, $\text{cm}^3/\text{cmH}_2\text{O}$) を算出し経時的に検討した。さらに、これらの値の α ブロッカー投与による変化を、治療前、治療16週後に検討した。

TUBAL-H 前には Comp, 最大尿道断面積 (MCSA) の平均は、それぞれ0.013, 0.66であった。8週後には、は、それぞれ0.038, 1.39と有意に増加した ($p < 0.01$)。16週後には、それぞれ0.026, 1.21とやや減少したが、TUBAL-H 前に比べて有意で高

値であった ($p < 0.05$)。

α ブロッカーに対する反応性では、TUBAL-H 前ではフェントラミン投与で、Comp, MCSA の平均はそれぞれ0.46 ($p < 0.05$), 1.40 ($p < 0.01$) と増加した。16週後には、フェントラミン投与で Comp のみが、0.033 と有意に増加した ($P < 0.05$)。

TUBAL-H により近位尿道の弾性は増大し、4カ月間持続することが確認された。 α ブロッカーに対する反応性の検討から、これらの効果の一部は α 受容体の障害に起因すると考えられた。

(泌尿紀要 42: 655-661, 1996)