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HOW IS THE BLADDER BEHAVIOUR INFLUENCED BY THE OSMOLARITY OF URINE?

Hypothesis / aims of study
In terms of the bladder behaviour in response to diuresis, it is generally understood that both the bladder volume (BV) and the frequency of micturition are increased when urine output is increased. Little has known, however, about the mechanisms of these voiding phenomena. Although several animal studies have recently demonstrated that bladder capacity is affected by urine osmolarity, its detailed mechanism has not been clarified yet. The purpose of present study is then to investigate how the responses of BV and urinary frequency to diuresis are regulated by the urine osmolarity. We investigated firstly the bladder behaviour in response to diuresis and urinary specific gravity (SG) using data set derived from the frequency volume chart (FVC) and the measurement of SG in healthy normal volunteers. Secondly, performing telemetric voiding cystometries to male beagle dogs, we also evaluated the bladder capacity in response to the osmolarity of urine by infusing water and diluted their own urine. Subsequently, we used the electrolytes, and hyperosmotic solutions to verify the effects of urine components and osmotic pressure on bladder capacity.

Study design, materials and methods
Study 1: Five normal male volunteers without lower urinary tract symptoms, post void residual urine, and significant urinary tract infection were included to this study. All subjects were asked to complete a 3-day FVC in the daytime. Hourly urine output rate (UOR) was then calculated by dividing the volume voided by the interval between 2 successive micturitions. In addition, a SG of urine was measured at every occasion of voiding. Thus, the following four parameters were used for this study: 1) voided volume (VV, ml) as BV at voiding, 2) micturition frequency (F, number of voids / hour: h^{-1}), 3) UOR (ml/h), and 4) urine SG as a substitutional parameter of urine osmolarity (because there is a good correlation between osmolarity and SG in a clear urine).
Study 2: Three male beagle dogs were used. Under intravenous pentobarbital anaesthesia, a double-lumened polyethylene catheter was placed in the bladder dome as the rout of infusion and the pressure measurement line for conducting the telemetric voiding cystometry. Following two weeks after surgery, the measurement was performed with infusing water, their own urine, urine diluted by water (50%), KCl, NaCl, mannitol, or glucose into the urinary bladder continuously (180mL/hr) under unanaesthetized and unrestrained conditions. Parameters (number and interval of void, VV, intra-vesical pressure) were also monitored continuously during 4 hours infusion. Each value was expressed as mean ± SEM.

Results
Study 1: In response to UOR, both VV and F significantly increased in each normal subject. Overall result clearly demonstrated a significant correlation between UOR and VV (p<0.01), as well as F (p<0.01) (Figure 1a, b). As shown in Figure 1c, SG was significantly correlated to UOR (p<0.01). Indeed, both VV and F also had a significant negative correlation to SG (r=-0.5472, p<0.01 and r=-0.5779, p<0.01, respectively). Study 2: In comparison to the results of infusing water, the data of urodynamic parameters obtained from the telemetric voiding cystometry using own urine were dramatically different in dogs; the increased number of voids (275.7 ± 90.1 %), the shortened interval of voids (61.0 ± 22.9 %), the decreased VV (66.7 ± 27.1 %), and the increased maximal intra-vesical pressure (139.0 ± 20.8 %). Infusion of various concentrations of NaCl and KCl also resulted in an increase in the number of voids, decrease in the interval of voids and VV in a concentration dependent manner (Table 1). In contrast, no increase in number of voids was observed with hyperosmotic mannitol nor glucose solutions; whereas hyperosmotic NaCl clearly enhanced the voiding frequency (Table 2).

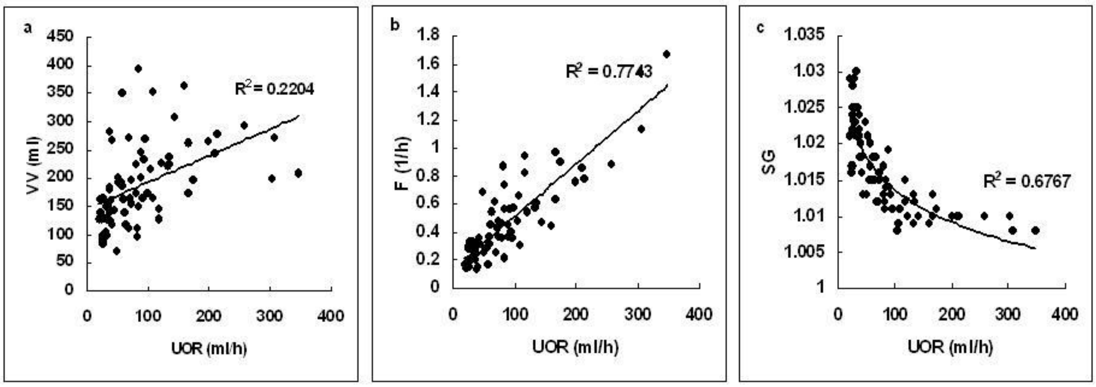

Figure 1: Correlations between UOR and VV (a), F (b), SG (c).

Table 1. Numerical values of urodynamic parameters with various concentrations of NaCl and KCl.

Solution	Concentration (%)	Number of Voids (%)	Interval of Voids (%)	VV (%)
NaCl	0.9	100	100	100
	2.7	103.3 ± 4.7	109.2 ± 4.0	113.1 ± 4.3
	4.5	166.7 ± 29.9	69.6 ± 7.7	79.0 ± 10.9
KCl	1.2	121.5 ± 2.1	81.0 ± 1.8	79.0 ± 0.0
	3.6	106.0 ± 19.8	94.5 ± 16.4	92.5 ± 7.8
	9.6	351.0 ± 267.3	40.2 ± 28.4	39.0 ± 28.3

Except for Concentration, each value is presented a percentage of NaCl (0.9 %) as 100 %.

Table 2. Numerical values of urodynamic parameters with various osmotic pressures of NaCl, Mannitol and Glucose.

Solution	Concentration (%)	Osmotic Pressure (mOsm/L)	Number of Voids (%)	Interval of Voids (%)	VV (%)
NaCl	**0.9**	**285**	**100**	**100**	**100**
	2.7	**855**	**103.3 ± 4.7**	**109.2 ± 4.0**	**113.1 ± 4.3**
	4.5	**1425**	**166.7 ± 29.9**	**69.6 ± 7.7**	**79.0 ± 10.9**
Mannitol	**5.2**	**287**	**164.8 ± 13.0**	**65.7 ± 4.0**	**62.8 ± 4.1**
	13.2	**873**	**68.9 ± 2.7**	**141.1 ± 5.8**	**152.2 ± 5.4**
	19.9	**1470**	**65.1 ± 2.7**	**140.9 ± 4.8**	**163.0 ± 5.7**
Glucose	**5.2**	**287**	**173.7 ± 18.6**	**79.4 ± 8.3**	**198.9 ± 27.2**
	13.2	**873**	**77.8 ± 9.4**	**149.2 ± 16.6**	**86.1 ± 5.4**
	19.9	**1470**	**81.7 ± 5.9**	**130.5 ± 2.7**	**126.7 ± 13.8**

Except for Concentration and Osmotic pressure, each value is presented a percentage of NaCl (0.9 %) as 100 %.

Interpretation of results

The present study clearly demonstrated that in healthy male volunteers the low urinary osmolarity following the increased diuresis enhanced F and BV; whereas the high osmolarity following the decreased diuresis resulted in the decrease of F and BV. These observations suggest that the urine osmolarity is likely to play an important role for the regulation of normal bladder behaviour in response to dieresis. There was no observation of increase in urinary frequency when the high osmotic pressure of infusion medium without electrolytes was used during the voiding cystometry in dogs; whereas the high osmotic pressure (concentration) of KCl and NaCl in infusion medium caused increaseing the voiding frequency and decreaseing in VV. With these regards, it is suggested that osmotic pressure may not act on the changes of urinary frequency as well as BV by itself but be capable of regulating such responses when combined with certain concentrations of electrolytes which can stimulate the afferent bladder sensory pathways via ion channels existing on the urothelium e.g. epithelial sodium channels.

Concluding message

In conclusion, our findings may imply the contribution of urinary osmolarity and component especially electrolytes (Na^+ as well as K^+) to the regulation mechanism of urinary frequency and BV.

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Is this a clinical trial?	**No**
What were the subjects in the study?	**ANIMAL**
Were guidelines for care and use of laboratory animals followed or ethical committee approval obtained?	**Yes**
Name of ethics committee	**IRB and the Animal Ethics Committee of Fukushima Medical University**