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SPONTANEOUS PRESSURE DIURESIS IN CONSCIOUS RATS

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ABSTRACT

Pressure diuresis is thought to be a long-term mechanism that is essential for regulation of blood volume and arterial pressure (AP). We recently found that experimentally-induced changes in AP result in changes in urine flow (UF) within 6 seconds in anesthetized rats. To test our hypothesis that the long-term nature of pressure diuresis is the result of the cumulative sum of many short-term changes in UF occurring in response to spontaneous changes in AP, AP (via an aortic catheter) and UF (via a gravimetric method) were measured over 2 hours in 8 conscious, free-moving, chronically instrumented rats. A total of 24 2-hour recordings was obtained at a frequency of 0.1 Hz. For all trials, mean AP averaged 130.0 ± 4.1 mm Hg and mean UF averaged 25.2 ± 10.1 µl/min. A significant, positive linear relationship between UF and AP was observed in 16 (67%) of the trials, and a significant negative relationship was observed in 2 of the trials. Our results 1) demonstrate that a positive relationship between UF and AP can be observed in conscious, free-moving rats; and 2) suggest that short-term changes in UF occur in response to spontaneous changes in AP.

† † †

The property of the kidney known as pressure diuresis was first observed over 140 years ago and is characterized by a direct, positive relationship between changes in renal arterial pressure and the subsequent changes in urine flow and sodium excretion (Selkurt 1951). In 1966 Guyton and Coleman (Guyton 1990) created a computer model of the circulation which predicted that permanent, steady-state changes in arterial pressure can occur only as the result of a change in urinary salt and water excretion. Because the sustained changes in blood volume that ultimately result in changes in steady-state arterial pressure probably required hours to days to develop, Guyton and co-workers have postulated that pressure diuresis is a long-term mechanism that is essential in establishing the steady-state value of arterial pressure (Guyton et al. 1972, Guyton et al. 1980).

The hypothesis that the ultimate regulation of arterial pressure via the pressure diuresis mechanism constitutes a long-term mechanism does not mean that the direct influence of arterial pressure upon urine formation is necessarily a slow process. That is, it is not known if the influence of pressure upon urine flow requires steady-state changes in pressure that last for minutes, or if the short-lived, spontaneous changes in arterial pressure that are known to occur as often as six per minute can influence urine formation (Alper et al. 1987, DeBoer et al. 1987, Steele, Brand et al. 1993). In a recent study we investigated the dynamic urine flow responses to acute changes in arterial pressure produced by mechanical and pharmacological interventions (Steele, Brand et al. 1993). We found that significant changes in urine flow occurred within six seconds following changes in arterial pressure. Moreover, the urine flow responses to these induced changes in arterial pressure were proportionately larger than the changes in arterial pressure, particularly when pressure was increased. These results led us to hypothesize that pressure diuresis may operate short-term in response to changes in arterial pressure, and that the cumulative effect of numerous short-term changes in urine flow determines the long-term regulation of arterial pressure.

Therefore, the purpose of this study was to determine if the moment-to-moment changes in arterial pressure that occur spontaneously due to normal activities are correlated positively with changes in urine flow.

MATERIALS AND METHODS

Animal preparation

All surgical and experimental procedures in this study are in accordance with U.S. animal protection laws and were approved by the Institutional Animal Care and Use Committee of the Medial College of Ohio prior to initiation of the investigation. Eight male Sprague-Dawley rats (Harlan Sprague-Dawley, Inc., Indianapolis, Indiana) weighing 439 ± 6 g (range 420–470 g) were studied. The animals received standard rat chow (0.8% NaCl) and water ad libitum and were maintained on a 12:12 hour light-dark cycle. The rats were anesthetized with a mixture of ketamine (Aveco Co., Inc., Fort Dodge, Iowa; 100 mg/kg i.p.) and xylazine (Mobay Corp., Shawnee, Kansas; 20 mg/kg i.p.), and were placed on a heating pad to maintain normal body temperature. A mid-abdominal incision was made and the ureters exposed. Catheters (0.01" ID × 0.03" OD Tygon® tubing; Norton Plastics and Synthetics, Akron, Ohio) were inserted into the ureters with the tips placed just distal to the renal pelves. The catheters were secured to the ureters with 3-0 silk ties and to the underlying psoas muscle with 5-0 silk sutures. A 7 cm trocar, fashioned from 16 gauge stainless steel tubing, was used to tunnel the ureteral catheters through the dorsal wall of the abdomen. The catheters were then tunneled subcutaneously to exit separately at the base of the tail. The abdominal incision was closed with 5-0 and 3-0 silk interrupted sutures. Each exteriorized end of the ureteral catheter was inserted into a 2.0 cm section of 18 gauge stainless steel tubing. In order to stabilize the catheters, the sections of steel tubing were inserted approximately 1.0 cm underneath the skin, and the catheters were secured to the steel tubing with Super Glue® (alpha cyanoacrylate; International Adhesives Corp., Pembroke, Florida). The exteriorized portions of the steel tubing were secured to the skin of the tail with cranioplastic cement (Plastics One, Roanoke, Virginia) such that approximately 1.0 cm of the steel tubing protruded from the base of the tail. The ends of the exteriorized catheters were cut flush with the tip of the steel tubing.

The left femoral artery was exposed and a catheter, constructed from a 6 cm piece of Teflon® tubing (0.015" ID; Small Parts, Inc., Miami, Florida) inserted into a 25 cm piece of Tygon® tubing (0.02" ID), was placed in the femoral artery. The catheter was secured to the artery with 3-0 silk ties, tunneled dorsally beneath the animal's skin, and exited at the base of its neck. The arterial catheter was secured to the animal's skin with Super Glue®. Following surgery, the animal was returned to its home cage, given standard rat chow and water ad libitum, and weighed daily. All animals were given 3 days to recover from surgery.

Experimental set-up

The animal was housed individually in a polycarbonate cage identical in size and shape to its home cage. A siphoning system and an analytical balance were employed to continuously collect and weigh the urine produced throughout the experiment (Steele, Skarlatos et al. 1993). Briefly, Tygon® extension tubing was connected to the ureteral catheters to establish a continuous column of fluid from the urine in each ureteral catheter to a collection reservoir on the pan of the balance. The extension tubing exited the cage via a 38 × 14 cm, ┼-shaped, 5 mm wide slot in the floor of the cage. The center of the "┼" was at the center of the floor and each arm reached close to the side of the cage. By this arrangement, movement of the animals within the cage was minimally restricted during data collection. Water was available throughout the duration of the recording period.

Experimental protocol

All recording sessions were conducted in a quiet, well-lighted, 22°C room during the animals' light cycle (between 9 a.m. and 3 p.m.). This time period was selected so that animals would be relatively quiet during the recording sessions. The rats were prepared for continuous recording of arterial pressure and urine flow, and a recording of approximately 2 hours duration was made from each animal on a daily basis as long as the animal remained healthy and the catheters remained patent. Maintenance of body weight, normal grooming behavior, and arterial pressure were all factors that were taken into account when evaluating the animal's health. Changes in any one of these factors indicated possible deterioration in the animal's health, and any animal whose health was questionable was removed from the study. The goal was to obtain uninterrupted recording sessions from healthy, relatively undisturbed animals. The recording session was interrupted only if the extension tubing became excessively tangled or crimped or if the animal bit through the tubing. The situation was corrected immediately and the recording session then resumed. If the recording session had to be repeatedly interrupted (3 times within a 30 minute period), however, the session was terminated for that day due to excessive disturbance of the animal. Usable sections of data from sessions that were terminated early were included in analysis as long as data collection was able to proceed for at least 20 minutes without uninterruption. Following the recording session the animal was returned to its home cage.

Measurements

The arterial catheter was connected to a Gould-Statham P23Db pressure transducer (Gould, Medical Products Division, Oxnard, California). The signal from the transducer was amplified with a SensorMedics

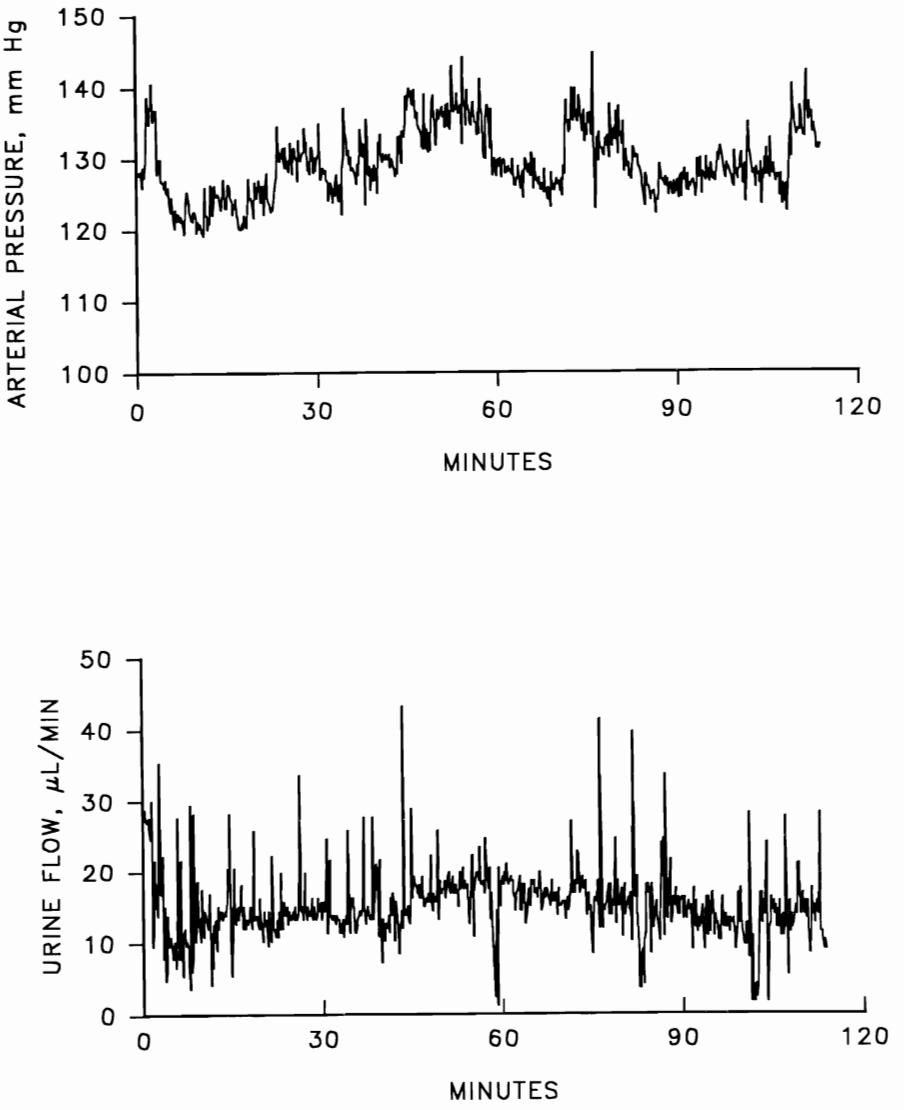

Figure 1. Line graph depicting arterial pressure and urine flow changes over time during a typical recording session (rat A, session 2).

Dynograph® Recorder R611(Anaheim, California). Mean arterial pressure (AP) was obtained by electronically damping the analog pressure signal (time constant = 0.78 sec). The voltage output was led to a Tektronix® 5031 dual beam oscilloscope (Tektronix®, Inc., Beaverton, Oregon) for display and to a DT 2801 analog-to-digital converter (Data Translation, Marlboro, Massachusetts) housed within an AST® Premium 386/33 computer (model 5V, AST® Research, Inc., Taiwan, Republic of China). The damped AP signal was digitally sampled at 20 Hz and then averaged every 10 seconds to obtain a 0.1 Hz signal. Communication between the analytical balance and the computer was established via an RS232 data interface. Data were collected to an ACSII file (Po-Ne-Mah® Digital Acquisition Analysis and Archive Systems, Po-Ne-Mah®, Inc., Storrs, Connecticut) at 0.1 Hz. Urine flow (UF) was calculated from the change in weight of the urine reservoir every 10 seconds and was expressed in μl/min. These paired AP and UF measurements, which covered the same 10-second intervals, were used in statistical analyses.

Postmortem

Following the last experimental session, animals were killed with an overdose of sodium pentobarbital and their kidneys were examined histologically for signs of infection, damage, or hydronephrosis. If any signs of kidney deterioration were observed, the last recording session for that animal was not included in data analysis.

Data analysis

The data were examined and aberrant values were discarded. Aberrant values were defined as those that

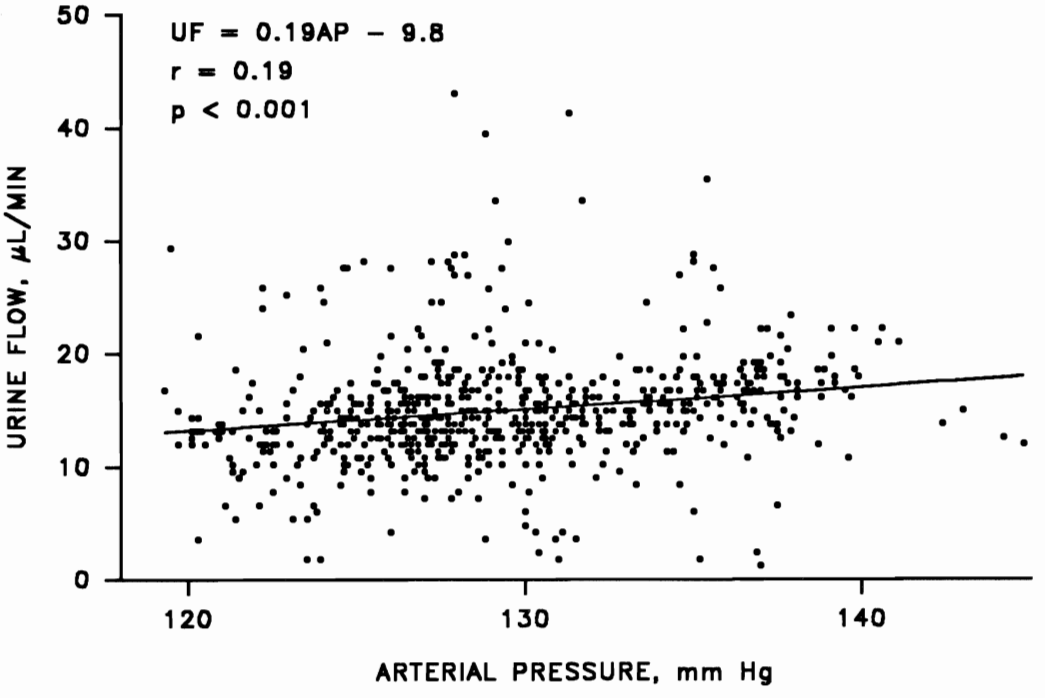

Figure 2. X-Y plot illustrating the distribution of data from a typical recording session (rat A, session 2) and the slope of the regression line for the relationship between arterial pressure and urine flow. Slope = 0.19; regression coefficient = 0.19; $p < 0.001$.

occurred paroxysmally and differed by more than 50% from preceding or following values. Observation suggested that these aberrant values arose from rapid positional changes by the animal that distorted the arterial and ureteral catheters. These discarded data represented less than 2% of the total observations. A linear regression was performed on the remaining data collected from each 2 hour recording session. The slope of the regression line, the correlation coefficient (r), and the probability (p) were determined. The null hypothesis (no linear correlation between UF and AP) would be supported if slope = 0 and $r = 0$. Significance was ascribed if $p < 0.05$.

The closed-loop gain (G_c), which represents the amplification of the influence of input on output, was calculated for each 2 hour recording as the ratio of the fractional change in UF (output) to the fractional change in AP (input). The average AP and UF for each session was used as the reference point for calculation of closed-loop gain; that is, G_c = (slope/mean UF) ÷ (1 mm Hg/mean AP). Because it is the ratio of two deltas, G_c is unitless (Jones 1973).

RESULTS

Between 1 and 4 recording sessions were obtained in each of 8 rats (A-H), for a total of 24 recordings. Of these 24 successful recording sessions, 17 lasted more than 100 minutes, and 7 were shorter (range 25 to 98 minutes), mostly because rats repeatedly chewed through the ureteral catheters. For the 24 sessions, mean AP averaged 130.0 ± 4.1 mm Hg and mean UF averaged 25.2 ± 10.1 µl/min. A significant positive linear relationship was found between UF and AP that had an average slope of 0.37 ± 0.45 µl/min/mm Hg (r=0.171). A two sample t-test revealed that the overall slope was significantly different than a slope of zero with $p < 0.0005$ (two-tailed evaluation).

The results from a typical recording session (Fig. 1, animal A, session 2) show that changes in urine flow appeared to directly follow changes in arterial pressure. An x-y plot of these same paired data revealed a positive relationship between arterial pressure and urine flow (Fig. 2). The correlation coefficient of the regression line in this example is 0.19, and the slope, 0.19, is significantly different from zero ($p < 0.001$).

Table 1. Slope of the regression line, correlation coefficient (r), level of significance (p), number of data pairs used in analyses (n), and mean (± standard deviation) arterial pressure (AP) and urine flow (UF) for each recording in which the slope of the regression line relating arterial pressure and urine flow was positive and significantly different from zero.

Rat and Session	Slope	r	p	n	AP (mm Hg)	UF (µl/min)
C2	1.32	0.38	< 0.001	658	114.9 ± 3.7	19.6 ± 13.0
A1	1.20	0.29	< 0.001	678	127.1 ± 4.5	22.1 ± 18.4
C3	1.10	0.44	< 0.001	150	124.4 ± 3.5	28.1 ± 8.9
D1	0.98	0.22	< 0.001	334	114.4 ± 2.8	26.3 ± 12.9
B4	0.92	0.38	< 0.001	634	142.6 ± 4.1	40.5 ± 10.0
H1	0.77	0.16	< 0.001	683	118.6 ± 2.5	23.1 ± 12.4
G1	0.75	0.30	< 0.001	353	135.2 ± 4.8	26.0 ± 11.9
B2	0.38	0.31	< 0.001	772	131.8 ± 4.3	26.5 ± 5.2
E4	0.38	0.17	< 0.001	680	123.2 ± 2.6	26.4 ± 5.6
E3	0.26	0.20	< 0.001	673	134.7 ± 4.0	18.5 ± 5.3
B1	0.25	0.11	< 0.005	706	122.1 ± 4.2	30.0 ± 9.4
B3	0.20	0.11	< 0.005	703	132.2 ± 4.2	21.0 ± 7.7
F3	0.20	0.14	< 0.01	270	135.4 ± 4.7	11.8 ± 6.7
A2	0.19	0.19	< 0.001	683	129.4 ± 4.8	15.0 ± 4.7
F2	0.16	0.08	< 0.05	592	126.9 ± 2.3	16.0 ± 10.2
E2	0.10	0.12	< 0.005	673	136.5 ± 4.3	16.6 ± 3.5
Mean	0.57	0.22		578	128.1	23.0
SD	0.41	0.11		182	4.0	9.1

In 16 of the 24 recordings, the slopes of the regressions between UF and AP were positive and significantly different from zero (Table 1). The positive slopes averaged 0.57 µl/min/mm Hg, with an average correlation coefficient of 0.22. The average length of recording sessions for these 16 trials was 96 ± 30 minutes. In 6 of the 24 recordings, the slopes of the regressions were not different from zero (Table 2). For these animals the slopes averaged 0.02 µl/min/mm Hg with an average correlation coefficient of 0.05. The duration of the recording for these sessions averaged 103 ± 33 minutes. In the remaining 2 recordings, the slopes of the regressions between UF and AP were negative and significantly different from zero (Table 3). The negative slopes averaged -0.15 µl/min/mm Hg with an average correlation of 0.09. The duration of these recordings averaged 113 ± 6 minutes.

The observations from all 24 recording sessions are graphically represented in Fig. 3, with the regression lines drawn over the actual range of arterial pressure for each recording. There was no significant relationship between the average AP and the slope within any of the three groups as segregated by slope. Nonetheless, the sessions in which significant positive slopes (Table 1, Fig. 3A) were obtained had an average AP (128.1 ± 4.0 mm Hg) and an average UF (23.0 ± 9.1 µl/min) that were significantly lower than the average AP (135.9 ± 4.6 mm Hg) and UF (32.4 ± 14.4 µl/min) found in the 6 sessions for which the slopes were not significantly different from zero (Table 2, Fig. 3B).

The relative magnitude of the changes in UF associated with changes in AP are revealed in the calculation of the closed-loop gain. A G_c of 1 means that AP and UF changed in exact proportion, while gains greater than 1 represent proportionally greater increases in UF. The gains ranged from 7.7 to -1.1 with G_c greater than 1 in 14 of the 24 sessions (Fig. 4). The average gain for the entire group was 1.98 ± 2.3, which means that a given increase in AP was accompanied, on the average, by an approximately two-fold greater increase in UF.

DISCUSSION

Spontaneous pressure diuresis

This study demonstrates the operation of pressure diuresis in response to spontaneous changes in arterial

Table 2. Slope of the regression line, correlation coefficient (r), level of significance (p), number of data pairs used in analyses (n), and mean (± standard deviation) arterial pressure (AP) and urine flow (UF) for each recording in which the slope of the regression line relating arterial pressure and urine flow was negative and significantly different from zero.

Rat and Session	Slope	r	p	n	AP (mm Hg)	UF (μl/min)
C1	-0.14	0.11	< 0.01	654	118.1 ± 3.6	23.5 ± 4.8
F1	-0.15	0.08	< 0.05	704	137.2 ± 2.9	18.4 ± 5.5
Mean	-0.15	0.09		679	128.0	21.0

pressure in conscious rats under physiological conditions. A positive correlation was observed between AP and UF in these intact rats in 67% (16 of 24) of the trials, with an average correlation coefficient (r) of 0.22. These data extend previous observations of spontaneous pressure diuresis in conscious dogs (Brand et al. 1991) using a new method of urine flow measurement that allowed us to observe moment-to-moment effects of AP on UF. In the previous study in the dog, G_c was about 1.4, and the r value for the correlation between UF and AP was 0.12–0.14. The higher correlations and gains in the present study in the rat (Table 1) likely reflect the greater precision of the method of measurement of urine flow. These two studies establish that pressure diuresis may be observed in conscious animals of two different species during normal operation of all of the mechanisms regulating renal function.

This approach to the study of pressure diuresis (Brand et al. 1991, Skarlatos et al. 1994) is unique because these experiments have been performed in conscious, intact animals during spontaneous changes in AP and UF. Although others have examined pressure diuresis in conscious animals, in all pervious studies arterial pressure was experimentally manipulated. These previous studies have provided important information concerning the operation of pressure diuresis (Ehmke et al. 1990, Hall et al. 1988), but were not directed at determining if operation of the pressure diuresis mechanism is detectable in the absence of experimental perturbations; that is, in the physiological state. Thus, our experimental approach examining the relationship between spontaneous changes in AP and UF in conscious animals demonstrates that pressure diuresis is expressed under physiological conditions. This approach may provide new insight into the time course over which the pressure diuresis mechanism may act, as well as insight into the interaction between pressure diuresis and baroreflex regulation of the renal circulation.

Long-term character of pressure diuresis

The apparent ability of UF to respond to moment-to-moment spontaneous changes in AP also supports the hypothesis that the long-term influence of pressure diuresis on AP is a result of the cumulative effect of many small changes in AP, UF, and, presumably, blood volume. This hypothesis has been proposed based on previous observation (Steele, Brand et al. 1993) that, in anesthetized rats, experimentally induced changes in AP are followed by changes in UF in 6 seconds. This rapid response in UF is consistent with the conclusion of

Table 3. Slope of the regression line, correlation coefficient (r), level of significance (p), number of data pairs used in analyses (n), and mean (± standard deviation) arterial pressure (AP) and urine flow (UF) for each recording in which the slope of the regression line relating arterial pressure and urine flow was not significantly different from zero.

Rat and Session	Slope	r	p	n	AP (mm Hg)	UF (μl/min)
D3	0.21	0.05	< 0.4	374	143.2 ± 4.7	40.7 ± 18.6
A3	0.15	0.06	< 0.2	608	137.3 ± 5.2	24.4 ± 12.4
D2	0.10	0.02	< 0.5	430	138.4 ± 3.7	39.1 ± 18.5
E1	0.07	0.07	< 0.1	680	133.0 ± 3.7	24.0 ± 3.9
A4	-0.20	0.07	< 0.1	642	134.6 ± 5.9	38.9 ± 17.7
G2	-0.20	0.05	< 0.2	995	128.6 ± 4.7	27.5 ± 15.1
Mean	0.02	0.05		622	135.9	32.4
SD	0.16	0.02		33	4.6	14.4

the present study, that AP and UF may be positively correlated during moment-to-moment changes in AP. Thus, we suggest that pressure diuresis is a dynamic mechanism that operates continuously to correct changes in arterial pressure. Small changes in AP and UF may cumulatively adjust extracellular fluid volume and AP to the average equilibrium point for pressure diuresis.

Gain of the pressure diuresis mechanism

The G_c for the effect of AP on UF averaged about 2 (Fig. 4). In previous work involving anesthetized rats, G_c ranged from 1 to 13 during acute changes in AP induced both pharmacologically and reflexly (Steele, Brand et al. 1993). The high gain of pressure diuresis is in accord with previous studies indicating that the effect of AP on UF is exponential in nature (Guyton 1990). As AP increases, a given change in AP has a progressively greater effect on UF. In other words, pressure diuresis may defend against increases in AP more effectively than against decreases.

In addition to a possible exponential nature of the pressure diuresis mechanism, recent work from our laboratory suggests that the predominant hemodynamic pattern of the kidney may further amplify the effect of AP on UF. Using a new model to examine renal pressure-flow relationships during spontaneous changes in AP and renal blood flow, we observed that in conscious dogs (Skarlatos, DiPaola et al. 1993) and rats (Skarlatos, Metting et al. 1993) the predominant pressure-flow pattern in the renal circulation is baroreflex-like. That is, about 38% of the time, the renal vasculature dilates when AP spontaneously increases, and constricts when AP spontaneously decreases. This baroreflex-like pattern in the circulation may act as an amplifier for the pressure diuresis mechanism. For example, our studies of the renal circulation (Skarlatos, DiPaola et al. 1993) indicated that a spontaneous increase in arterial pressure will most likely be accompanied by a decrease in renal vascular resistance. If renal vascular resistance decreases as systemic pressure increases, the increase in systemic pressure will likely be transmitted to the renal interstitium to a greater degree than if the kidney did not vasodilate, and therefore UF will increase to a greater degree than if the kidney did not vasodilate.

Pressure diuresis and Atrial Natriuretic Peptide (ANP)

In the present study, AP and UF were positively correlated in 67% of the experimental trials. In these conscious, freely-moving rats, increases in arterial pressure were most likely due to autonomic activation acting under control of "central command" (Koepke et al. 1983) as the animal moved about, groomed, drank, etc. The effects of increased autonomic activation on the kidney are anti-diuretic and oppose the pressure diuresis mechanism (Koepke et al. 1983). Changes in autonomic activity are thus unlikely to be responsible for the positive correlation observed between AP and UF. The only hormone likely to induce a diuresis under these conditions is ANP. Release of ANP, however, is induced by atrial stretch (deZeeuw et al. 1992) and is independent of the baroreflex influence on sympathetic nervous activity (Kohara et al. 1989). Inasmuch as there was no reason to expect increases in atrial or central venous pressure in the present study, it seems unlikely that the positive correlation between AP and UF could be accounted for by changes in secretion of ANP.

Perspective

These observations of spontaneous pressure diuresis in conscious rats, combined with studies of the rapidity of the pressure diuresis mechanism in anesthetized animals and investigation of the pressure-blood flow patterns in the renal circulation, provide a unique description of renal function as it occurs under physiological conditions. We propose that pressure diuresis is an ongoing, rapidly-acting mechanism with a high gain that is amplified by the baroreflex-like pattern of the renal circulation. This speculation is also supported by recent observations from our laboratory of a close, positive correlation between spontaneous changes in AP and renal interstitial hydrostatic pressure (Skarlatos et al. 1994). Thus, the cumulative effect of many small changes in UF in response to spontaneous changes in AP can account for the long-term nature of pressure diuresis.

We also speculate that the nature of pressure diuresis contributes to the control of variability in AP. That is, for any given time period, an increase in the variablilty of AP around its average value will result in an increased net excretion of urine for that period. Such an increase in UF produced by an increased AP variability (at the same average value for AP) would decrease the blood volume and presumably decrease the capacity of the cardiovascular system to produce increases in AP. Thus, an alteration in spontaneous pressure-diuresis may play a role in the increase in both the steady-state AP and its variability in hypertension.

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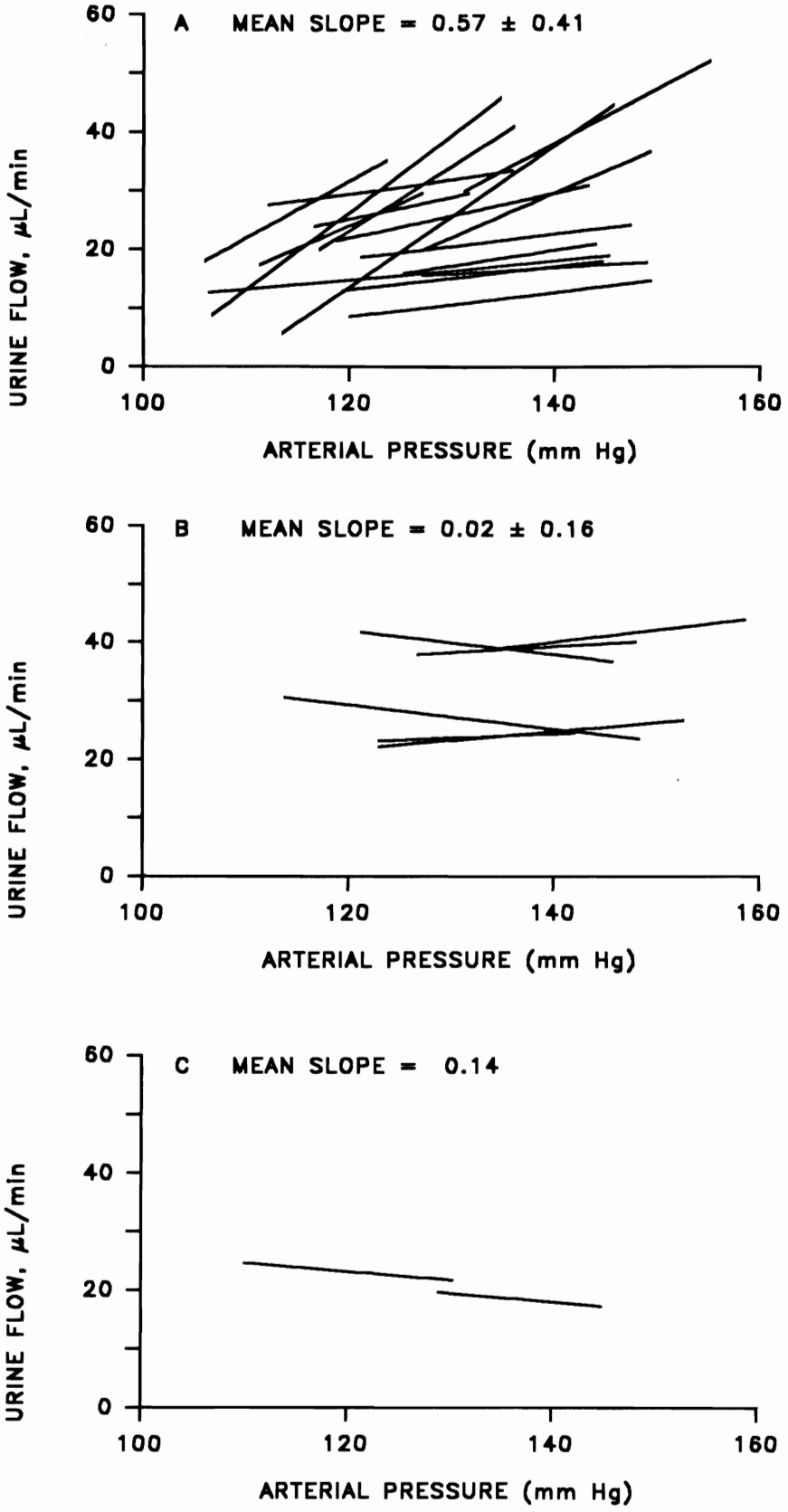

Figure 3. Slopes of the 24 regression lines for arterial pressure and urine flow when the slope is (A) significantly different from zero and positive (n = 16), (B) not significantly different from zero (n = 6), and (C) significantly different from zero and negative (n = 2). The slope of the regression line is drawn over the actual arterial pressure range for each individual recording. Mean slope (± standard error) is included on the figure for each condition.

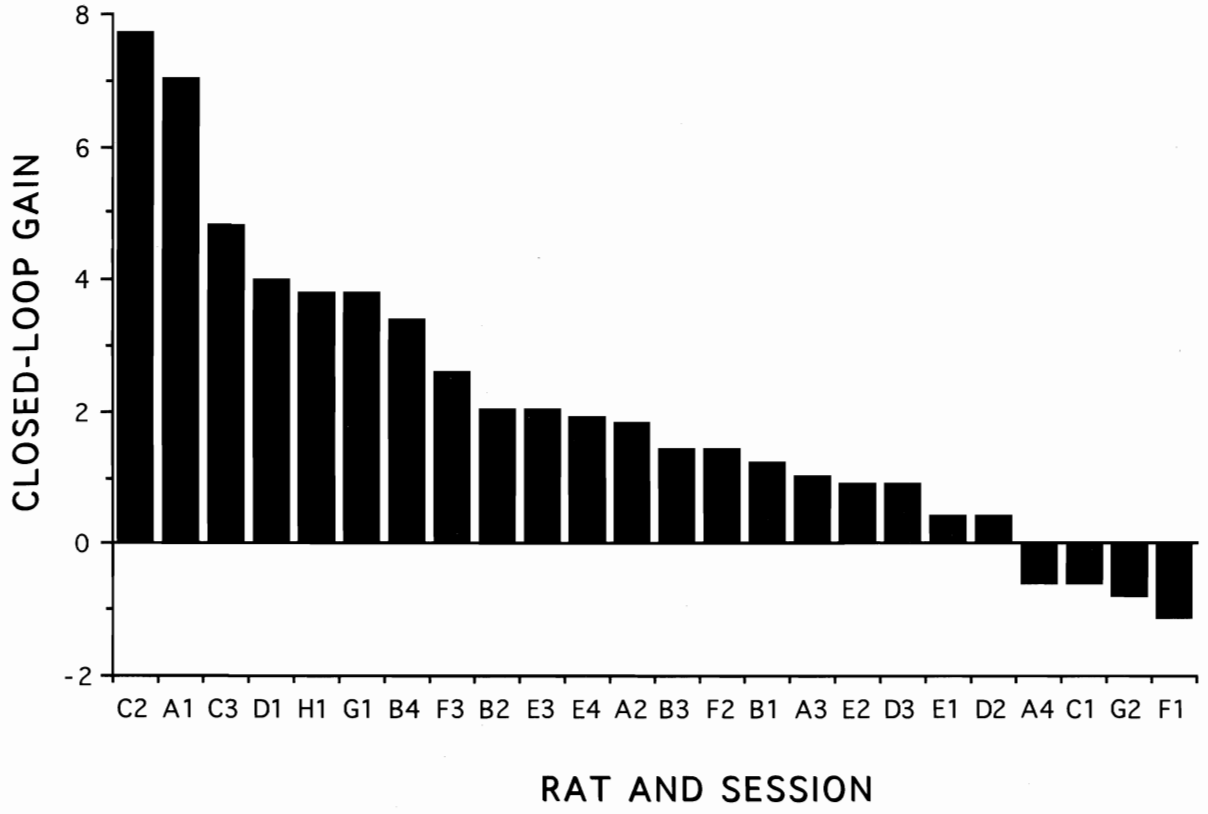

Figure 4. Closed-loop gains (G_C) for the 24 recording sessions. Mean (± SD) G_C = 1.98 ± 2.3, range G_C = 7.71 to -1.12.

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