The Effect of Vasopressin on Solute and Water Excretion during and after Surgical Operations

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The relationship between the concentration of plasma arginine vasopressin (AVP), urine volume, and osmolality during and after an abdominal operation was studied in nine patients. In all patients the AVP level rose well above that necessary for maximal antidiuresis (5 fmol ml^{-1}) and then returned to within the normal range (0.5–5.0 fmol ml^{-1}) usually over the next 24 hours. During this period of raised AVP concentration the urine volume, which varied considerably, was closely related to osmolar excretion. With the fall of AVP to normal levels, all but one of the patients eventually exhibited positive free water clearance. However, in most patients the urine remained hypertonic for some hours and its volume continued to be determined mainly by osmolar load which was itself apparently related to glomerular filtration rate. At no time was there a significant relationship between changes in plasma AVP concentration and urinary volume.

A DIMINISHED URINE FLOW in the early hours after operation was first reported by Pringle and his colleagues in 1905 and was ascribed to the effects of anesthesia on renal function.[1] By the 1950s, studies of renal function during and after surgical operation had led to the conclusion that it was trauma rather than anesthesia that altered renal performance[2,3] and that the underlying reason for this alteration was probably "hormonal imbalance".[4,5] Le Quesne and Lewis[6] demonstrated how salt and water excretion could be affected separately, and suggested that the antidiuretic hormone arginine vasopressin (AVP) was responsible for the diminished urine flow and raised urinary concentration seen in the early postoperative period, though it was soon recognized that throughout this period urinary volume depended to some extent on solute excretion.[7]

Using a bioassay, Eisen and Lewis[8] demonstrated AVP in large amounts in the urine of postoperative patients, and some years later it was shown by Moran and others[9,10] that the magnitude and duration of the secretory response were proportional to the severity of the surgical procedure. However, levels of the hormone at the time of operation were generally far higher than was required to achieve a maximal antidiuresis and it was noted that, although in general there was some relationship between the increase in plasma AVP levels and the duration of the changes in free water clearance, it was not possible to demonstrate a regression between AVP levels and urinary free water clearance.

Much of this early work based on the use of bioassays has been repeated and confirmed[11,12] using the more precise radioimmunoassay of AVP. However, the exact relationship, if any, between changes in AVP concentration and changes in urine volume in the early postoperative period remains uncertain. The purpose of this study on surgical patients was to assess the role of AVP in determining renal function during and after surgery by examining in detail the relationship between urinary volume and concentration and plasma levels of the hormone.

Patients and Methods

Studies were carried out on nine patients undergoing abdominal operation requiring general anesthesia and the routine use of a urinary catheter. No standard protocol for anesthesia or fluid intake was used, and the choice of premedication, anesthetic agents, and administered drugs and fluids was left to the anesthetist and the clinician in charge of each case.

In each patient, following premedication, a central venous catheter was inserted under local anesthesia *via* a cubital vein. Prior to induction of anesthesia, a 5-ml sample of blood was taken for base-line measurements

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TABLE 1. *Patient Data*

Patient No.	Sex	Age	Wt. (Kg)	Pre-med	Operation	Duration (Minutes)
1	F	55	61	A*	Excision of insulinoma	90
2	F	57	47	A	Polya gastrectomy	185
3	F	37	37	A	Oophorectomy	60
4	M	48	70	A	Ileo-transverse anastomosis	105
5	F	53	53	A	Pharyngo-laryngectomy	265
6	F	77	64	B†	Left hemicolectomy	75
7	F	77	55	B	Sigmoid colectomy	160
8	F	58	46	A	Laparotomy (gastric biopsy)	105
9	M	47	71	A	Laparotomy (Kirschner oesophageal bypass)	175

* A = Omnopon + scopolamine.

† B = Pethidine and atropine.

of plasma AVP and osmolality (*vide infra*). Once the patient was anesthetized, a urinary catheter was inserted and the operation was started as near as possible to 9:00. Urine was then collected every 2 hours for calculation of urinary flow rate, osmolar clearance, and free water clearance over each 2-hour period, the dead space of the collecting system being ignored. Half-way through each period of urine collection, a 5-ml sample of blood was taken and centrifuged immediately. An aliquot of plasma was frozen for determination later of AVP, as described by Aziz et al.,[13] and on the remainder of the sample, plasma osmolality and, in certain cases, plasma creatinine were measured. During the operation period, more frequent blood samples were taken for AVP determination, while in the early patients studied, as technique was being developed, some overnight blood samples were omitted. The osmolality of each sample of plasma and urine was determined with a Knauer Halbmikro® osmometer by measurement of freezing point depression, and the creatinine content of selected plasma and urine samples corresponding with different urinary outputs was measured by the Jaffee reaction using a Beckman Astra® autoanalyzer.

The studies were continued until urinary output increased with the development of positive free water clearance. Changes in urinary osmolality and volume were analyzed graphically by plotting the logarithm of the urinary osmolality against the logarithm of the urinary volume, as described in a previous publication.[14]

Results

The sex, age, and weight of the patients studied, together with their premedication, their operation, and its duration are shown in Table 1.†

In all of the patients, plasma AVP rose during the study period to a maximum level far in excess of that at which the hormone is considered to have its maximum antidiuretic effect under normal resting conditions (5.0 fmol ml^{-1}).[15] In most patients this rise occurred within 1 hour of the beginning of operation, but in two (Patients 3 and 5) it was delayed until after the end of operation. The range of maximum plasma AVP concentration was 25.2 to 100.8 fmol ml^{-1} with a median value of 59.5 fmol ml^{-1}. Plasma AVP returned to below 5.0 fmol ml^{-1} within 24-hours of the end of operation in eight patients and by 32 hours in the ninth (Patient 9) (Table 3). Following this fall, in some of the cases the level of the hormone remained low, while in others relatively small intermittent rises continued to occur (Fig. 1.).

In six of the nine patients studied, when the level of AVP was above 5 fmol ml^{-1}, the urine was invariably hyperosmolar, the maximum concentration ranging from 589 to 941 mosm L^{-1} with a median value of 792 mosm L^{-1}. However, in three patients (2, 4, and 8), positive free water clearance occurred despite a raised plasma AVP level, the longest documented period over which this was found being 5 hours. Thus, of the 32 occasions on which positive free water clearance occurred throughout the study, 10 were when plasma AVP was above 5 fmol ml^{-1}.

Plasma osmolality (initial range 271–287 mosm kg^{-1}, median 284 mosm kg^{-1}) reached a maximum within 12 hours of the end of operation, rising between 0 and 8 mosm kg^{-1} (median 3 mosm kg^{-1}). A subsequent fall occurred in every case (range 6–30 mosm kg^{-1}, median 19 mosm kg^{-1}) with final osmolalities in the range 256–284 kg^{-1} (median 276 mosm kg^{-1}).‡

The relationship between plasma AVP concentration and urinary output is shown in Figure 2, a conventional

† All of the plasma AVP concentrations, urinary excretion rates, urinary osmolalities, and glomerular filtration rates that were measured are shown in Table 2.

‡ Table 4 gives details of these measurements in individual patients.

plot of urinary volume, osmolar clearance, and free water clearance combined with a graph of the plasma concentrations of AVP in patient 1. In this patient's case, it is clear that the fall in AVP level to below 5 fmol ml^{-1} was associated with the development of positive free water clearance. Inspection of the graphs suggests also that a relationship exists between urinary volume and solute excretion. This relationship is more readily apparent if the same data are plotted sequentially on logarithmic scales[14] (Fig. 3). By this method it is evident that when AVP levels were above 5 fmol ml^{-1}, urinary volume varied from period to period in well-defined oscillations that coincided with changes in solute excretion. The development of free water clearance that occurred once plasma AVP fell into its normal range (0.5–5.0 fmol ml^{-1}) is also well shown by the graphical analysis of this case. In other patients though, the development of free water clearance following the fall of plasma AVP was generally seen only after a delay of several hours (Table 3), during which period urine production continued to be primarily determined by solute excretion. In patient 9, solute-governed excretion of urine was seen exclusively, with no free water clearance observed even at the end of the 72-hour study despite a fall of AVP to normal levels 40 hours previously (Fig. 4).

There was no significant relationship between urinary volume and the plasma concentration of AVP (over the range of 0.7 to 100.8 fmol ml^{-1}) either in individual patients or in the group as a whole, regardless of whether the plasma level of the hormone was above 5 fmol ml^{-1} or within the normal range, and regardless of whether or not there was positive free water clearance.

As a measure of glomerular filtration rate (GFR) creatinine clearance was calculated for 70 periods at various times throughout the studies on seven of the cases. Both solute excretion (UosmV) and osmolar clearance (Cosm) were found to be significantly related to GFR (Fig. 5).

Discussion

A rise in plasma AVP concentration is well-recognized as one of the factors involved in the metabolic response to trauma and has been assumed to be of crucial importance in determining urine production after surgery. In this present investigation no formal study was made of the factors responsible for AVP secretion in the perioperative period. For this reason no attempt was made to standardize anesthetic agents, drugs, or fluids, and while it is known that somatic pain, visceral pain, changes in plasma osmolality, blood volume, arterial and venous blood pressure, and body temperature, as well as various drugs and anesthetic agents can all affect AVP secretion,[15] no additional information has been produced concerning the ways in which these factors may operate. Furthermore, it is evident that there exists considerable individual variation in the pituitary response to perioperative stimuli, for although plasma levels of AVP rose significantly in every case, two patients (3 and 5) failed to exhibit this response until after operation, and in one of these cases (5) this was despite the use of hypotensive anesthesia. In most cases an initial perioperative AVP peak was followed by a second, often larger secretory peak that occurred as the patient recovered from anesthesia (Fig. 1). In the two patients 3 and 5, it was this postoperative peak (which has previously been described by Haas and Glick[12] and was attributed by them to pain) that was seen by itself.

In addition to the individual variation seen in the secretory response to stimulation, the pattern of the return of AVP levels back to the normal range also seemed to vary from patient to patient. In the longer studies, extended periods of low AVP levels could be interrupted by further small increases in secretion, perhaps caused by postoperative pain. The pattern of a postoperative plateau followed by a slow decline over several days, described by Moran, was not observed and it may be that this pattern was simply due to a coincidence of small peaks of AVP secretion with plasma samples taken only infrequently. Indeed, in this series a normal level of AVP was achieved much earlier than reported by Moran (and other workers), with the fall completed by 24 hours after the end of operation in eight out of the nine cases studied.

While plasma AVP was at levels above the normal range, urinary volume was, as might be expected, unrelated to plasma levels of the hormone; furthermore, there was no relationship between these two factors even when the plasma AVP concentration was below 5 fmol ml^{-1}. The importance of urinary solute load in determining urinary volume in the early postoperative period has been demonstrated before,[7] but this study graphically illustrates the intimate association of these two variables throughout the course of the changes in output that occurred (Figs. 3 and 4). These constant oscillations are often seen in published data, but the reason for them and their physiological significance is unknown. Although changes in aldosterone secretion may undoubtedly modify sodium excretion after surgery, studies of perioperative plasma levels of the hormone[16] suggest that these changes are not rapid enough to account for the variations in solute excretion identified in this study.

The degree to which urine output may be dissociated from AVP secretion is emphasized by the observation that low perioperative urine volumes were produced in

TABLE 2. *Plasma AVP Concentrations, Urinary Volumes and Osmolalities, and Glomerular Filtration Rates*

	Patient										
	1			2				3			
Period*	AVP	V	Uosm	AVP	V	Uosm	GFR	AVP	V	Uosm	GFR
1	59.5	0.62	413	17.3	1.25	384	21	19.4	0.63	540	77
2	29.5	0.98	488	34.3	1.54	522	46	7.9	1.08	690	—
3	25.9	0.83	502	34.8	1.0	548	57	25.2	0.79	790	—
4	30.7	0.95	525	22.8	0.46	592	—	16.3	0.08	780	80
5	25.7	1.08	589	41.5	0.24	622	—	2.9	0.08	820	106
6	—	0.88	609	25.0	0.38	615	55	10.5	0.86	840	121
7	—	0.5	661	26.4	0.89	607	—	7.9	0.86	800	110
8	—	0.71	691	19.0	0.92	243	—	—	0.61	800	144
9	—	0.63	608	—	0.71	218	—	—	2.63	237	167
10	—	0.87	490	—	0.85	364	—	—	5.8	83	131
11	10.3	1.13	430	17.5	0.67	234	—	5.0	1.37	161	236
12	2.0	5.0	155	6.5	3.0	189	86				
13	2.6	3.17	227	5.8	2.58	151	—				
14	—	4.25	229	5.0	1.21	297	49				
15	—	5.08	132	10.3	2.25	186	74				
16	5.0	1.21	308								

	Patient										
	4				5				6			
Period*	AVP	V	Uosm	GFR	AVP	V	Uosm	GFR	AVP	V	Uosm	GFR
1	14.9	0.4	261	25	2.2	0.18	109	12	98.2	0.23	736	—
2	14.6	0.75	306	—	0.5	0.08	120	5	82.3	1.04	618	—
3	41.3	0.79	738	—	2.2	0.5	223	68	62.9	1.54	651	—
4	22.3	0.42	742	62	0.7	2.08	516	121	45.8	1.21	650	73
5	7.2	0.38	768	—	0.8	0.79	612	69	58.3	1.0	653	—
6	2.9	1.46	463	99	43.7	0.5	660	63	18.7	0.91	702	67
7	1.2	2.17	574	29	38.4	0.37	722	—	9.4	1.36	690	—
8	9.6	3.0	162	91	51.4	0.58	760	—	—	0.54	780	—
9	16.1	1.21	309	—	43.2	0.58	775	—	6.5	0.5	810	49
10	24.0	1.17	312	—	24.5	0.63	795	87	5.8	0.52	810	—
11	9.4	0.58	758	—	2.9	0.63	807	—	8.9	2.67	430	132
12	10.8	0.46	558	—	4.6	0.15	830	24	2.4	0.55	476	—
13	15.4	0.46	615	89	20.2	0.63	836	—	2.6	0.38	688	46
14	7.4	0.42	630	—	17.8	0.42	840	—	1.0	0.67	736	—
15	21.6	0.16	618	—	4.0	0.63	830	—	3.4	1.17	706	—
16	9.4	0.06	640	24	5.3	0.5	780	74	1.4	1.04	658	101
17	6.1	1.33	336	—	4.0	0.58	764	78	3.4	1.5	450	84
18	—	1.0	273	90	3.8	1.42	383	97	4.8	1.17	509	—
19					6.0	0.46	503	59	5.5	0.35	540	27
20					4.1	0.29	775	—	2.6	0.65	672	—
21					28.8	0.63	855	—	18.7	0.6	705	—
22					—	0.5	680	—	4.3	0.42	640	57
23					1.2	0.5	795	104	6.0	0.4	745	78
24					2.9	1.54	512	199	2.2	1.83	495	185
25					4.8	2.17	685	186	2.2	2.16	264	103
26					4.8	0.92	338	—	2.6	0.75	260	36
27					3.6	2.08	93	46	5.2	1.71	412	—
28					2.9	1.5	448	—	4.6	1.21	458	—
29									2.9	1.5	571	—
30									—	1.88	616	—
31									1.7	1.88	249	—
32									1.9	2.2	304	—

	Patient										
	7				8†				9		
Period*	AVP	V	Uosm	GFR	AVP	V	Uosm	GFR	AVP	V	Uosm
1	36.5	0.31	500	—	11.3	0.25	540	22	78	0.16	640
2	90.1	0.58	602	—	41.3	0.25	550	—	29.5	1.13	720

TABLE 2. (*Continued*)

	Patient										
	7				8†				9		
Period*	AVP	V	Uosm	GFR	AVP	V	Uosm	GFR	AVP	V	Uosm
3	62.1	0.02	620	2	38.1	0.07	572	—	45.6	0.85	702
4	49.2	1.63	571	148	20.6	0.25	591	50	47.0	0.82	730
5	49.7	0.88	615	—	7.9	0.4	681	33	19.2	0.86	753
6	28.1	0.79	630	—	6.7	0.27	782	—	18.0	1.17	720
7	52.8	1.0	665	—	58.1	0.33	810	—	17.5	1.12	713
8	22.8	0.22	548	—	78.7	0.43	848	—	14.2	0.66	725
9	11.3	1.04	509	—	100.8	0.33	895	—	17.3	0.43	745
10	4.3	0.42	491	—	61.2	0.35	900	—	33.1	0.63	749
11	4.3	0.33	560	—	34.6	0.23	919	—	59.0	0.46	735
12	3.6	1.96	297	110	25.4	0.42	932	—	43.4	0.5	725
13	2.4	0.83	343	45	13.0	0.40	941	86	17.3	0.53	730
14	1.9	1.96	240	—	20.2	0.53	940	133	27.6	0.77	748
15	1.7	2.31	133	—	13.9	0.53	920	—	10.1	1.11	740
16	3.6	4.17	110	230	13.7	0.63	865	—	2.4	0.85	736
17	4.3	1.42	259	22	27.4	0.48	860	—	3.1	0.75	771
18					47.5	3.0	334	184	4.1	0.7	787
19					11.8	8.83	61	82	4.8	0.47	788
20					40.1	8.67	55	81	13.9	0.47	792
21					7.7	6.33	73	—	14.3	0.38	783
22					37.7	2.42	184	78	31.9	0.97	770
23					8.4	1.63	242	—	4.6	0.54	761
24					12.7	1.7	363	107	3.8	0.46	761
25					3.4	0.67	258	32	7.7	0.5	766
26					5.0	0.8	513	—	18.5	0.83	766
27									5.5	0.53	755
28									3.6	0.46	788
29									2.2	0.28	780
30									2.4	0.2	768
31									2.4	0.47	760
32									2.6	0.53	771

AVP = fmol ml^{-1}; V = ml min^{-1}; Uosm = mosm kg^{-1}; and GFR = ml min^{-1}.

* Periods are 2 hourly.
† In the case of patient 8, periods are hourly.

the two patients (3 and 5) in whom the rise in hormone level did not occur until after the end of their operation. In patient 5, two creatinine clearances measured during surgery were particularly low at 12 and 5 ml $minute^{-1}$, and although the accuracy of these figures as an absolute indication of GFR may be questioned at this low level, the possibility is raised that GFR might play a direct part in determining urinary volume in a manner independent of the effect of AVP. Indeed, an examination of the data from all the studies supports the view that, after rising to normal levels, GFR continues to influence urinary output, and that this influence is exerted by an

TABLE 3. *AVP Secretion—Its Relation to Operation and Onset of Free Water Excretion*

Patient	Preop AVP fmol ml^{-1}	Time to AVP >5 fmol ml^{-1} Hours	Maximum AVP fmol ml^{-1}	Time to AVP <5 fmol ml^{-1} Hours	Subsequent Time to +ve C_{H_2O} Hours
1	6.5	0	59.5	25	0
2	3.6	1	41.5	25	2
3	2.4	3	25.2	9	8
4	6.5	0	41.3	11	4
5	4.3	11	51.4	21	32
6	6.2	0	98.2	23	26
7	3.6	<1	90.1	19	8
8	1.7	1	100.8	25	−6
9	2.4	<1	78.0	32	—

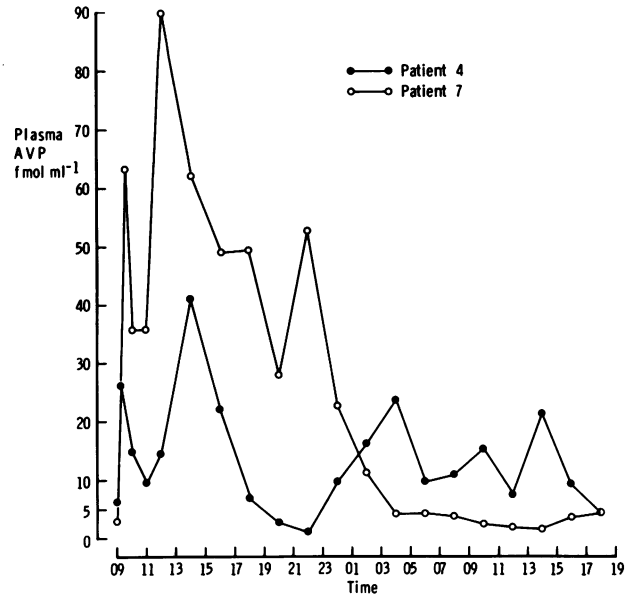

FIG. 1. Two patterns of AVP secretion.

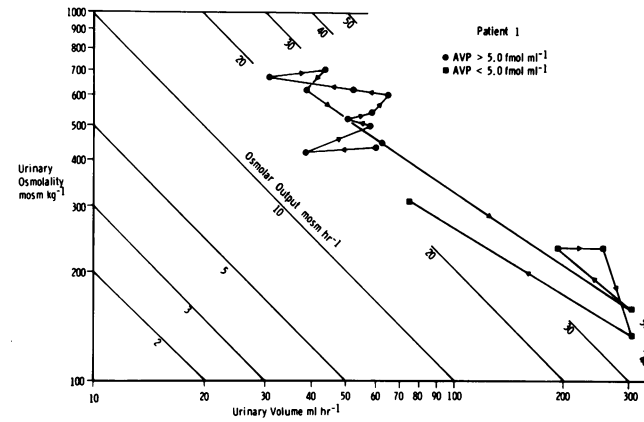

FIG. 3. Logarithmic plot of urinary osmolality *vs.* urinary volume with osmolar output—Patient 1. The 2 hourly urinary volumes and osmolalities are plotted sequentially on log scales so that isopleths representing constant osmolar excretion (UosmV) appear as parallel diagonals across the graph. Changes in urine volume due primarily to changes in solute excretion appear as changes across these isopleths parallel to the horizontal axis. Variations in urine volume attributable to changes in water excretion alone follow the isopleths, and positive free water clearance exists where urinary osmolality is lower than plasma osmolality (about 290 mosm kg^{-1}).

effect on solute excretion, an effect previously noted by Ukai and his colleagues in their studies on dogs.[17]

It might be argued that osmolar excretion itself (UosmV) is bound to show some relationship to creatinine clearance $\left(\frac{\text{UcrV}}{\text{Pcr}}\right)$ since plasma creatinine concentration (Pcr) is relatively constant over the period of the study and urinary volume (V) contributes equally to the value of both terms. Moreover urinary creatinine concentration (Ucr) and urinary osmolality (Uosm) are related as a result of the extraction of water from the collecting duct. However, osmolar clearance $\left(\frac{\text{UosmV}}{\text{Posm}}\right)$ was also found to be related to GFR (Fig. 5). This relationship pertains even though the clearance of the main osmotically active components of the urine is determined by a complex series of processes, and creatinine clearance depends largely on GFR. GFR must therefore either affect solute excretion directly, or both processes must be determined by some common factor.

The importance of GFR in determining a different

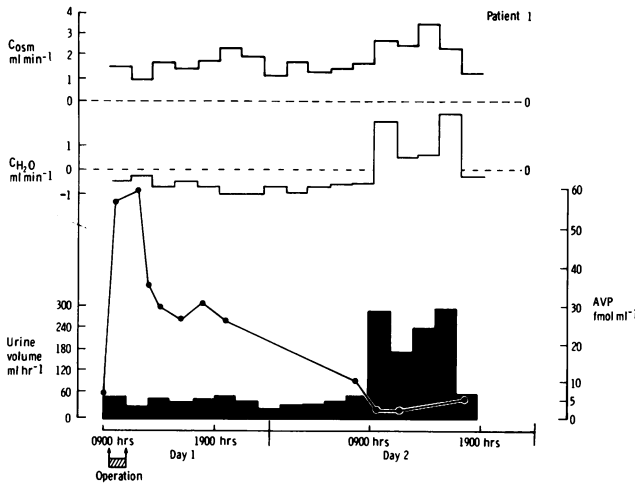

FIG. 2. Plasma AVP, urinary volume, osmolar clearance, and free water clearance—Patient 1.

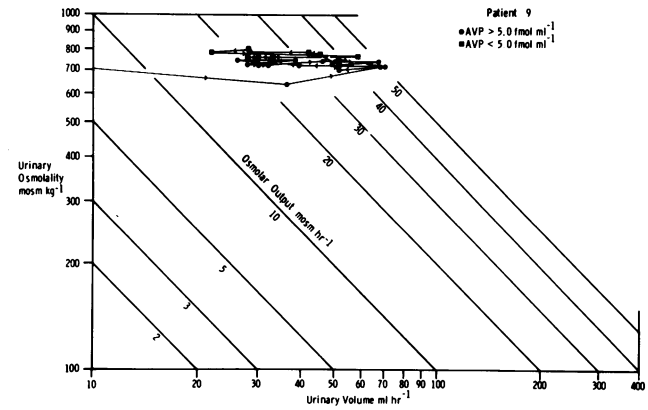

FIG. 4. Logarithmic plot of urinary osmolality *vs.* urinary volume with osmolar output—Patient 9.

aspect of renal function in the perioperative period has previously been demonstrated by Gullick and Raisz,[18] who pointed out that the maximum urinary osmolality that could be produced at this time was reduced compared with preoperative, or late postoperative, values obtained on administration of exogenous AVP. This effect was attributed to a decreased flow of solute into the renal medulla which reduced its tonicity. Under these circumstances, even with maximum permeability of the renal collecting ducts to water, urinary osmolality could rise no further than that of the less than maximally hypertonic medulla. The present study confirms this previously reported finding.

When AVP fell to below a maximally antidiuretic level (5 fmol ml^{-1}), one patient (1) promptly developed a diuresis. This was almost entirely due to an increase in free water excretion with very little change in the excretion of solute. In the eight other patients studied, the fall in plasma AVP did not coincide with an increase in free water excretion, and variations in solute excretion and urinary volume followed their original pattern at least for a number of hours. In this regard it is important to note that in this study no deductions could be made concerning the secretion of AVP from observations on the urine. In particular, negative free water clearance was an unreliable indicator of the presence of high levels of AVP in the plasma.

The conditions necessary for a fall in plasma AVP concentration to produce a water diuresis have not yet been clarified, but it is evident that such a fall is not necessarily sufficient in itself to reduce the amount of water that crosses the collecting duct wall into the renal medulla. At any given plasma level of AVP this quantity will obviously depend on the osmolality of the medullary interstitium. In the immediate postoperative period this is probably highly variable as a result of changes not only in GFR, but also in intrarenal hemodynamics, which are in turn influenced by a multitude of factors including AVP itself, circulating catecholamines, kinins, renin, prostaglandins, autonomic activity, hematocrit, plasma protein concentration, and plasma sodium. None of these variables is stable at this time, and the renal medulla in different patients may well behave differently and require different conditions of perfusion and AVP activity to permit a water diuresis. There is also the possibility that AVP activity is itself modulated by a number of renal factors, including prostaglandins. In addition, the circulating half-time of AVP in plasma is considerably shorter than the hormones' duration of action in the kidney.[19] For all of these reasons it is not surprising that no direct relationship can be demonstrated between plasma AVP levels and urinary volume and concentration in the postoperative period, even when the AVP level is within the normal daily range. Indeed it is quite clear that changes in AVP secretion are not responsible for fluctuations in urine volume during the period of diminished urine flow after operation. Nevertheless, the fact that the hormone is secreted in large quantities by patients undergoing operation is relevant to their management, for as long as AVP levels are raised, patients are in general unable to excrete free water, with the result that an excess water intake may readily lead to overhydration.

TABLE 4. *Plasma Osmolality* (Hours after Surgery)*

Patient	Initial	Maximum	Minimum	Final
1	284	286 (7)	278 (25)	279 (31)
2	276	282 (−1)	257 (11)	260 (25)
3	286	286 (1)	266 (13)	276 (21)
4	271	272 (11)	260 (31)	260 (34)
5	283	285 (−1)	253 (39)	256 (51)
6	287	295 (5)	267 (72)	270 (79)
7	286	291 (2)	279 (26)	279 (30)
8	284	290 (2)	278 (16)	284 (24)
9	287	290 (9)	268 (47)	270 (69)

* mosm Kg^{-1}.

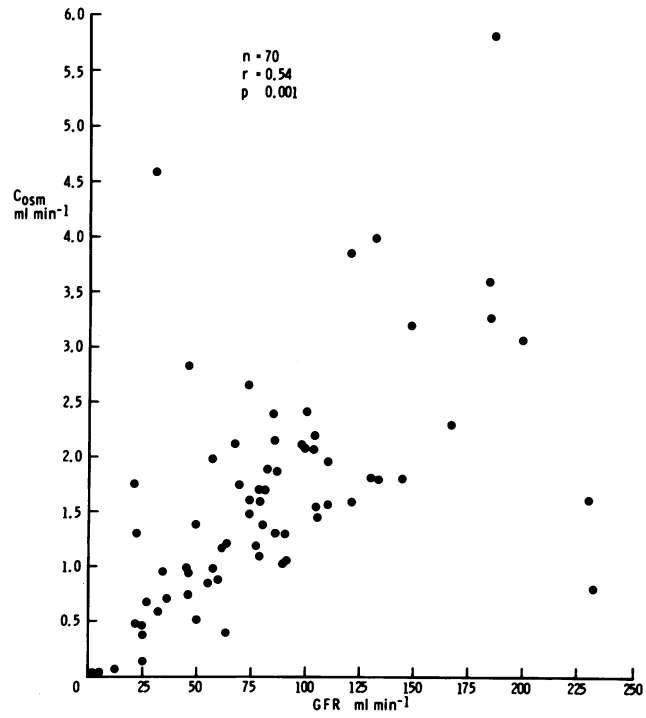

FIG. 5. Osmolar clearance *vs.* glomerular filtration rate.

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