Renal Response to Pyrogen in Normotensive and Hypertensive Man

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SUMMARY

Pyrogen, when administered intravenously to normotensive and hypertensive men, produced initially vasoconstriction and subsequently marked renal vasodilatation, both resulting from direct effects on the renal vasculature. The absolute renal plasma flow, both during control observations and at the height of renal hyperemia, was greater in normotensives, but the percentage change was greater in hypertensive subjects. Extraction of *p*-aminohippurate diminished during renal hyperemia. Medullary renal plasma flow was higher in normotensive subjects both during control observations and at the height of renal hyperemia. Simultaneously with the development of renal hyperemia, sodium excretion increased without alterations in filtered load of sodium and was prompt in its development in normotensives and delayed in hypertensives. This is attributed to a transient, small, yet probably significant decrease in filtered load of sodium during vasoconstriction immediately following the administration of pyrogen.

Simultaneously with the development of renal hyperemia, there was in both groups an increase in solute excretion and tubular reabsorption of solute-free water.

Additional Indexing Words:
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p-Aminohippurate extraction
Medullary blood flow

THE RENAL CONCENTRATING capacity in patients with essential hypertension, even in the early stages of their disease, has been shown to be lower than that of normal subjects at similar solute loads.[1] This impairment is interpreted by some investigators as being due to increased sodium reabsorption at sites proximal in the nephron, leading to diminished sodium delivery to the ascending limb of the loop of Hendle. It is in that area that sodium reabsorption must occur in quantities sufficient to maintain a hypertonic medulla that during hydropenia facilitates backdiffusion of water from the collecting ducts.

Another variable thought of as affecting medullary tonicity is renal blood flow, medullary in particular. Since it was suggested that renal vascular disease or altered renal vascular reactivity may influence renal blood flow and thus be involved in the etiology of essential hypertension, we have embarked upon examining the question whether varying renal blood flow could produce differences between functional responses of normal subjects and those with essential hypertension.

Methods

We have examined the effect of renal hyperemia produced by intravenous administration of pyrogen* on renal hemodynamics, systemic

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*Supplied as Piromen (a mixture of nucleic acids and a polysaccharide complex that contains lipid and nitrogen) by Baxter Laboratories, Inc., Morton Grove, Illinois.

blood pressure, and excretion of sodium and total solute. Ten normotensive subjects without evidence of cardiovascular renal disease and 10 patients with essential hypertension, judged as being in early stages of the disease, and without clinical evidence of renal disease, were studied. All control subjects and those with essential hypertension were males.

Fluid was withheld for 8 hours preceding the test which was performed in the morning with the patient in the fasting state. Urine was collected through an indwelling catheter, and the bladder was emptied by means of air. After the administration of suitable priming doses of inulin and *p*-aminohippurate (PAH), sustaining infusion of these substances dissolved in normal saline was administered through a constant infusion pump at a rate of 1.8 ml/min. Three base-line control periods totaling 30 to 45 minutes were measured for the determination of glomerular filtration rate (GFR), renal plasma flow (RPF), sodium excretion ($U_{Na}V$), and solute clearance (C_{osm}). Thereafter 1.2 g of acetylsalicylic acid was given orally (for suppression of fewer responses) and followed by intravenous administration of pyrogen in doses of 0.15 μg/kg of body weight.

Separate collections of urine were continued for 180 to 210 minutes after administration of pyrogen and at appropriate intervals blood samples were drawn from an indwelling needle in the antecubital vein. Renal extraction of PAH (E_{PAH}) was examined simultaneously with the clearance determination before pyrogen and at the height of the pyrogen response in four normal subjects and in four hypertensive patients. Catheters were passed through the femoral vein into the right renal vein by the percutaneous route. Blood levels of PAH as observed in the antecubital vein were substituted for arterial blood. Blood levels of PAH were maintained between 1.2 and 1.8 mg/100 ml. Systemic blood pressures were measured every 15 minutes throughout the study by the auscultatory method. Pulse rate was recorded at the same time while body temperature was measured orally every 30 minutes. Chemical methods for the determination of inulin and *p*-aminohippurate have been reported elsewhere.[2] Sodium concentrations were measured by flame photometry with lithium as an internal standard. Osmolality of plasma and urine was measured by osmometry.

In order to evaluate whether "significant" changes in renal plasma flow attributable to pyrogen administration had occurred, the percentage random variation from the mean of three consecutive urine collection periods was examined for 28 normal subjects and 34 patients with essential hypertension while receiving sustaining infusions of *p*-aminohippurate in normal saline at rates of 1.8 ml/min.

The two groups were combined for this statistical evaluation. The variation amounted to 2.96% $\pm$ 1.53 (1 SD) of mean control RPF. Based on this comparison hyperemia was judged to be present when RPF increased more than 2 SD above the mean control values.

Calculations

The renal extraction of PAH was calculated from the formula $E\ (A-V)/A$ where A is the peripheral venous concentration of PAH assumed to be identical to the renal arterial concentration and V is the renal venous concentration of PAH. Total renal plasma flow (TRPF) was calculated as C_{PAH}/E_{PAH}. Noncortical plasma flow was assumed to be representative of medullary renal plasma flow (MRPF) and calculated as TRPF-C_{PAH}. Calculations of the excretion fraction of sodium (EF_{Na}), solute clearance (C_{osm}), and tubular concentrating operation (T^cH_2O) have been reported elsewhere.[1] Renal resistance was calculated according to the method of Gomez.[3]

Results

General Effects

Based on the effect of pyrogen on renal plasma flow two phases were distinguishable in the post-pyrogen periods: One (phase 1) started immediately after pyrogen administration. This phase was characterized by intense renal vasoconstriction and lasted 30 to 60 minutes. Phase 2 started 60 to 90 minutes after pyrogen administration and reached full development 100 to 210 minutes after pyrogen administration. This phase was characterized by progressive renal vasodilatation.

During phase 1, some subjects experienced headache and developed mild muscular aches. These complaints subsided shortly, but some felt chilly and required blankets to be comfortable. During phase 2, diaphoresis developed regularly and was followed by a return of a generalized feeling of well-being. Slight increase in temperature was observed in several instances, but fever above 100 F has never developed, possibly due to pretreatment with acetylsalicylic acid.

Specific Effects

Mean Blood Pressure (Tables 1, 2, and 3). This was unaffected by pyrogen in normoten-

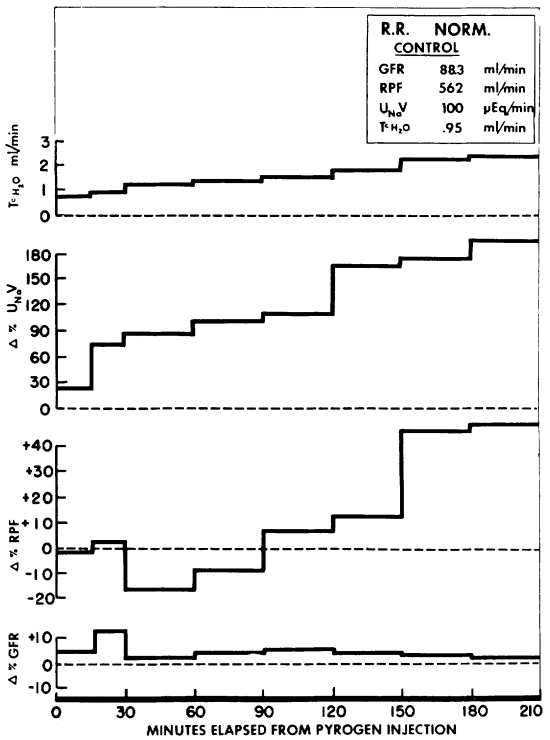

Figure 1

Effect of pyrogen on GFR, RPF, $U_{Na}V$, and $T^c_{H_2O}$ in a normotensive subject.

sives during either phase (from 90.8 to 90.5 mm Hg), while in hypertensives it declined slightly at the height of phase 2 (from 121 to 112 mm Hg).

Pulse Rate (*Tables 1 and 2*). This increased in all normotensives and in eight of the hypertensives.

Glomerular Filtration Rate (Table 3 and Figs. 1 and 2). During phase 1, GFR declined in some normotensives while it increased in others. The mean trend for the group was that of a slight decrease. During phase 2, GFR returned to, or slightly increased above, control values in all subjects. Mean GFR for the entire group increased slightly from 109 during control observations to 113 ml/min at the height of hyperemia (+4 or 3.68%).

In hypertensives, during phase 1, GFR decreased in six, and was unaffected in four. At the height of phase 2, this function returned to the base line or was above that value in nine hypertensive subjects. Mean GFR decreased slightly from the control value of 99.2 to 97.2 ml/min at the height of hyperemia (−2 or 2.02%).

Renal Plasma Flow (*Tables 1, 2, and 3 and Figs. 1, 2, and 3*). During phase 1, RPF diminished in two normotensives and this was followed by a reversal over the subsequent 30 minutes; a generalized increase in RPF occurred from then on in all normotensives. During phase 2, the augmentation continued in all normotensives and did not abate during the remainder of the observation.* In seven hypertensives, during phase 1, RPF diminished. Hyperemia developed subsequently in all hypertensives, and the trend was maintained throughout phase 2. The mean maximum increase in RPF was from 509 during control observations to 697 ml/min at the height of hyperemia (+188 or 36.0%) in normotensives and from 344 to 521 ml/min (+177 or 51.7%) in hypertensive subjects.

Renal Extraction of p-Aminohippurate (E_{PAH}) (Tables 1 and 2 and Fig. 4). During the control observations E_{PAH} ranged between 82.6 and 89.4% in normotensives and 76.2 and 92.7% in hypertensives. During hyperemia, E_{PAH} decreased uniformly. The change was comparable in the two groups.

Renal Resistance (*RR*) (*Tables 1, 2, and 3*). During phase 1, RR decreased or was unaffected in both normotensives and hypertensives, while during phase 2, RR decreased in all. The mean decrease from control values to those observed at the height of phase 2 was from 7,259 to 5,345 dynes-sec cm^{-5} (−1,914 or 26.5%) in normotensives and from 15,412 to 9,416 dynes-sec cm^{-5} (−5,951 or 38.8%) in hypertensives.

Sodium Excretion ($U_{Na}V$) (*Tables 1 and 2 and Figs. 5 and 6*). The effect on $U_{Na}V$ was examined in 10 normotensives and nine

*One of the hypertensive patients (P.A.) was on "low" sodium intake when the study was performed, but values obtained for renal hemodynamics did not appear markedly different from those of patients on regular diets with normal sodium content.

Table 1

Effect of Pyrogen on Renal Hemodynamics: Excretion of Sodium and Total Solute in Normal Subjects

Subject, age (yr), & hct	Dosage of pyrogen (μg i.v.)	Time from pyrogen admin. (min)	Urine volume (ml/min)	C_{IN} (ml/min)	C_{PAH} (ml/min)	FF (%)	RR (dynes-sec cm^{-5})
		Control*	1.36	96.2	304	31.6	10,813
J.B.–35	12	15	1.47	112	368	30.4	8,932
		30	1.09	92.4	292	31.6	11,099
		60	0.79	90.1	302	29.8	12,724
		90	0.59	102	325	31.4	10,114
		120	0.71	104	357	29.1	9,726
Hct 42.1%		150	0.68	109	357	30.5	8,948
		180	0.68	104	403	25.8	7,582
		230	0.70	99.7	446	22.3	7,163
		Control*	1.96	120	660	18.2	5,942
H.B.–34	9	15	2.61	110	626	17.6	5,783
		30	1.26	102	548	18.6	7,373
		60	1.31	116	629	18.4	6,224
		90	1.35	118	668	17.7	5,483
		120	1.16	115	695	16.5	5,391
Hct 47.1%		150	1.12	122	727	16.8	5,096
		190	1.23	126	792	15.9	4,411
		210	1.23	125	796	15.7	4,416
		Control*	5.89	111	551	20.1	5,034
W.M.–39	9	15	7.36	116	616	18.8	4,637
		30	9.35	124	620	20.0	4,874
		60	4.78	119	632	18.8	4,912
		90	3.59	126	642	19.6	4,965
Hct 48.0%		130	2.21	126	650	19.4	
		180	2.98	110	690	15.9	4,380
		210	3.00	112	694	16.1	4,378
		Control*	1.63	92.2	421	21.9	10,783
P.R.–43	12	15	1.39	77.0	356	21.6	12,472
		30	1.39	79.6	357	22.3	12,158
		60	1.51	85.4	418	20.4	10,622
		90	3.63	101	445	22.7	9,529
Hct 37.4%		120	2.39	102	514	19.8	7,764
		160	1.61	101	546	18.5	7,035
		210	1.61	101	556	18.2	7,627
		Control*	0.82	88.3	562	15.7	5,996
R.R.–40	10	15	0.96	92.0	557	16.5	6,487
		30	1.39	100	579	17.3	6,310
		60	1.33	90.0	477	18.9	7,405
		90	1.74	94.0	520	18.1	6,948
Hct 49.2%		130	1.64	94.6	590	16.0	5,780
		180	1.16	92.2	784	11.8	4,557
		210	1.15	90.1	790	11.4	4,549
		Control*	1.24	108	496	21.8	6,641
B.J.–41	10	15	2.41	114	511	22.3	6,773
		30	1.85	106	496	21.4	6,978
		60	2.44	117	516	22.7	6,465
Hct 47.6%		90	1.65	127	579	21.9	5,905
		120	1.23	123	661	18.6	5,362

$U_{Na}V$ (μEq/min)	EF_{NA} (%)	C_{osm} (ml/min)	$T^c_{H_2O}$ (ml/min)	E_{PAH} (%)	Mean blood pressure (mm Hg)	Pulse rate/min	RPF (ml/min) Total	RPF (ml/min) Medullary
150	1.11	2.40	1.04	82.9	81	68	368	64
162	1.03	2.94	1.47		81	64		
146	1.12	2.30	1.21		80	78		
123	0.97	1.84	1.05		93	76		
143	1.00	1.44	0.84		81	80		
182	1.25	1.72	1.01		85	86		
189	1.24	1.66	0.99		79	90		
193	1.32	1.68	1.01		76	92		
184	1.31	1.65	0.98	73.1	79	90	610	164
228	1.36	2.96	1.00	89.1	103	86	740	80
212	1.38	2.79	0.18		96	92		
174	1.22	2.30	1.04		106	88		
220	1.35	2.85	1.54		103	82		
303	1.84	3.11	1.76		97	88		
192	1.20	2.51	1.35		99	96		
176	1.03	2.32	1.33		98	102		
276	1.57	3.16	1.70		93	104		
280	1.60	3.18	1.72	72.9	94	100	1,090	298
239	1.54	3.41	− 2.48		77	74		
324	1.99	5.09	− 2.27		79	78		
284	1.63	5.42	− 3.93		83	72		
293	1.75	4.78	0.00		85	82		
359	2.03	4.47	0.88		87	84		
254	1.44	4.07	1.86					
318	2.06	4.95	1.97		83	96		
320	2.09	5.00	2.00		84	94		
223	1.73	2.30	0.67		101	88		
188	1.74	1.95	0.56		99	90		
195	1.74	1.98	0.59		97	90		
223	1.86	2.28	0.77		99	86		
229	1.62	2.36	− 1.27		95	94		
244	1.71	2.24	− 0.05		90	96		
258	1.82	2.54	1.93		87	96		
361	2.54	3.01	2.00		95	102		
100	0.80	1.77	0.95	82.6	93	70	681	119
126	0.97	1.95	0.99		99	64		
175	1.25	2.65	1.26		100	68		
189	1.50	2.63	1.30	87.6	97	72	543	66
210	1.59	3.29	1.55		99	82		
219	1.65	3.39	1.75		94	86		
267	2.07	3.47	2.31		98	86		
272	2.16	3.49	2.34	77.9	98	82	1,010	226
178	1.18	1.99	0.75		89	62		
229	1.43	2.62	0.21		93	68		
191	1.29	2.15	0.30		93	84		
215	1.31	2.33	0.11		90	92		
333	1.87	3.01	1.36		92	102		
294	1.71	2.86	1.63		95	116		

Table 1 (continued)

Subject, age (yr), & hct	Dosage of pyrogen (μg i.v.)	Time from pyrogen admin. (min)	Urine volume (ml/min)	C_{IN} (ml/min)	C_{PAH} (ml/min)	FF (%)	RR (dynes-sec cm^{-5})
		Control*	0.96	129	483	26.7	8,515
H.S.–51	12	15	1.22	119	479	24.8	8,300
		30	2.10	117	469	24.9	8,087
		60	2.36	121	492	24.6	8,081
		100	2.17	125	513	24.4	7,126
Hct 42.7%		140	1.98	129	562	22.9	6,424
		180	1.95	125	578	21.6	6,404
		210	1.30	127	698	18.2	5,696
		Control*	0.71	102	502	20.3	6,712
O.V.–42	8	15	0.81	98.2	498	19.7	6,522
		30	0.92	90.0	500	18.0	5,602
		60	0.86	95.6	529	18.1	5,065
Hct 49.1%		90	1.16	97.2	587	16.6	5,049
		130	1.21	103	649	15.9	4,629
		164	1.28	110	709	15.5	4,409
		Control*	1.00	112	516	21.7	5,933
J.S.–52	10	15	0.76	92.1	501	18.4	6,486
		45	0.86	96.4	486	19.8	6,687
		80	1.00	107	510	21.0	6,741
Hct 41.0%		120	1.31	119	582	20.4	5,664
		165	1.27	116	659	17.6	5,288
		210	1.38	120	728	16.5	4,852
		Control*	0.68	136	598	22.7	6,227
M.L.–40	10	30	0.65	112	641	17.5	5,809
		60	0.66	116	656	17.7	5,874
		90	0.82	121	672	18.0	5,734
		120	0.96	128	717	17.8	5,253
Hct 45.7%		158	1.12	134	762	17.6	4,716
		190	1.21	136	823	16.5	4,261
		210	1.18	132	870	15.2	4,081

*Control values represent a mean of three consecutive collection periods.

hypertensives. In the normotensive subjects during phase 1, $U_{Na}V$ increased in seven and was unaffected in three. During phase 2 natriuresis was present in all. In hypertensives during phase 1, $U_{Na}V$ diminished in five, remained unchanged in one, and increased in three. During phase 2, six patients had increased sodium excretion. The mean maximum increase in sodium excretion from control to that at the height of hyperemia was 31.8% for normotensives and 66.2% for hypertensives.

Solute Clearance (C_{osm}) (*Tables 1 and 2 and Fig. 7*). In normotensives during phase 1, C_{osm} increased promptly in seven, diminished in two and was unchanged in one, while during phase 2, C_{osm} was above control values in seven. By comparison, during phase 1 it diminished in six of the hypertensives, was unchanged in two and increased in two. During phase 2, increased solute excretion from control was present in seven normotensive and nine hypertensive subjects. The mean maximum increase from control was 37.0% for the normotensive and 52.0% for the hypertensive group.

Tubular Reabsorption of Solute-Free Water ($T^c_{H_2O}$) (*Tables 1 and 2, Fig. 7*). During phase 1 in normotensive subjects $T^c_{H_2O}$ varied. It increased in three, decreased or remained unchanged in six. In one patient undergoing water diuresis during control observations, $T^c_{H_2O}$ increased even further. During phase 1 in hypertensives, $T^c_{H_2O}$ decreased or remained unchanged in seven,

$U_{Na}V$ (μEq/min)	EF_{NA} (%)	C_{osm} (ml/min)	$T^c_{H_2O}$ (ml/min)	E_{PAH} (%)	Mean blood pressure (mm Hg)	Pulse rate/min	RPF (ml/min) Total	RPF (ml/min) Medullary
178	0.98	2.09	1.13		100	84		
172	1.03	2.01	0.79		97	90		
186	1.13	1.93	— 0.17		93	86		
179	1.06	2.10	— 0.26		97	92		
186	1.06	2.19	0.02		90	100		
190	1.05	2.45	0.47		89	102		
194	1.11	2.99	1.04		91	110		
192	1.08	3.95	2.65		97	116		
80	0.56	1.60	0.89		93	80		
89	0.64	1.74	0.93		90	88		
101	0.80	1.86	0.94		79	92		
123	0.91	2.16	1.30		76	94		
137	1.00	2.45	1.29		83	90		
159	1.10	2.71	1.50		84	100		
177	1.15	3.11	1.83		87	108		
212	1.35	2.17	1.17	89.4	75	62	578	62
190	1.47	2.26	1.50		79	64		
158	1.17	2.01	1.15		79	68		
178	1.19	2.17	1.17		83	70		
216	1.29	2.29	1.98		80	76		
284	1.74	2.96	1.69		84	84		
318	1.89	3.93	2.55	84.2	85	92	864	136
174	0.91	1.68	1.00		96	82		
182	1.16	1.51	0.86		96	84		
188	1.16	1.62	0.96		99	78		
196	1.16	1.92	1.10		99	80		
222	1.24	2.34	1.38		97	82		
241	1.28	2.80	1.68		93	90		
263	1.39	3.21	2.00		92	92		
284	1.54	3.65	2.47		92	98		

increased in three. During phase 2, $T^c_{H_2O}$ rose above control values in eight normotensives, was lower than during control in one, and became positive in the patient who was producing hypotonic urine during control observations. In hypertensives, $T^c_{H_2O}$ increased above control values in eight and diminished in two. The mean maximum increase in $T^c_{H_2O}$ from control values of those observed at the height of hyperemia averaged 109.0% in normotensive and 35% in hypertensive subjects.

Comment

Our data demonstrate that pyrogen, when administered intravenously, produces immediate, marked renal vasoconstriction, more prominent and more regularly occurring in hypertensive patients. In our study this effect was reflected in increased RR and decreased RPF; both pre-glomerular and post-glomerular vascular beds were affected, and in the majority of all subjects there was a slight decrease in GFR.

The vasodilative effect of pyrogen was more pronounced in the hypertensive subjects. Pyrogens failed to affect mean systemic pressure during phase 2 in the normotensive group while in the hypertensive group mean blood pressure declined. This must then be interpreted as being due to simultaneous peripheral vasodilatation. Renal resistance diminished to a greater extent in hypertensives, due primarily to the greater renal vasodilative effect of pyrogens.

The systemic effects of pyrogen have been investigated by others. Cardiac output was

Table 2

Effect of Pyrogen on Renal Hemodynamics: Excretion of Sodium and Total Solute in Patients with Essential Hypertension

Subject, age (yr), & hct	Dosage of pyrogen (μg i.v.)	Time from pyrogen admin. (min)	Urine volume (ml/min)	C_{IN} (ml/min)	C_{PAH} (ml/min)	FF (%)	RR (dynes-sec cm^{-5})
		Control*	0.53	108	364	29.7	14,320
D.S.–41 yr	15	20	0.43	106	331	32.0	15,243
		50	0.31	121	339	35.7	15,622
		80	0.30	120	380	31.6	15,717
		120	0.34	124	416	29.8	11,026
Hct 48.0%		150	0.27	116	457	25.4	10,128
		180	0.20	109	491	22.2	9,342
		210	0.21	110	500	22.0	9,331
		Control*	0.25	76.3	232	32.9	22,616
P.A.–45†	15	30	0.13	63.9	144	44.4	36,437
		60	0.10	55.2	104	53.1	52,286
		90	0.15	67.3	162	41.5	32,388
		135	0.15	72.0	323	22.3	16,392
Hct 40.1%		160	0.15	79.1	382	20.7	13,360
		185	0.46	87.7	417	21.0	11,438
		210	0.40	80.9	418	19.3	11,440
		Control*	0.84	80.3	263	30.5	15,951
B.N.–57	12	30	0.62	70.0	219	32.0	19,754
		70	0.19	73.1	250	29.2	18,354
		110	0.37	71.6	262	27.3	17,346
		140	0.57	67.8	320	21.2	12,836
Hct 45.2%		160	1.36	73.1	435	16.8	9,644
		180	1.33	80.0	453	17.7	9,550
		210	1.35	81.0	460	17.6	9,540
		Control*	3.08	120	420	28.6	10,349
G.A.–39	15	15	4.64	122	504	24.2	9,042
		30	4.58	124	488	25.4	9,079
		60	4.79	122	509	24.0	8,124
		30	3.61	128	515	24.8	7,948
		110	6.26	131	518	25.3	7,494
Hct 47.1%		150	6.81	130	572	22.7	6,861
		180	6.25	128	681	18.8	5,762
		210	6.28	126	684	18.4	5,759
		Control*	0.82	84.6	276	30.6	21,438
A.S.–42	15	30	0.80	64.1	215	29.8	27,065
		60	0.83	58.9	217	27.1	27,492
		80	0.86	74.3	242	30.7	24,045
		110	0.75	64.1	242	26.5	24,045
		130	0.82	66.1	300	22.0	19,234
Hct 38.6%		160	0.90	75.3	350	21.5	16,486
		180	1.16	72.5	408	19.8	13,423
		210	1.18	80.0	410	19.5	13,419
		Control*	0.70	62.0	260	23.0	20,257
S.J.–42	10	30	0.37	63.2	263	24.0	23,082
		60	0.32	63.1	270	23.4	20,359
		90	0.26	63.0	272	23.2	20,912
		115	0.64	64.6	325	19.9	16,619
Hct 40.0%		130	1.33	73.7	360	20.5	14,472

$U_{Na}V$ (μEq/min)	EF_{NA} (%)	C_{osm} (ml/min)	$T^c_{H_2O}$ (ml/min)	E_{PAH} (%)	Mean blood pressure (mm Hg)	Pulse (bt/min)	RPF (ml/min) Total	RPF (ml/min) Medullary
149	0.98	1.77	1.24		135	90		
125	0.83	1.97	1.54		131	86		
98	0.57	1.60	1.29		137	90		
96	0.57	1.59	1.29		135	102		
99	0.56	1.75	1.41		120	106		
56	0.34	1.23	0.96		121	102		
20	0.13	0.97	0.77		120	98		
22	0.13	0.95	0.74		121	96		
17	1.63	0.81	0.56	81.3	120	82	286	54
27	0.31	0.62	0.49		120	82		
9	0.12	0.50	0.40		124	76		
16	0.17	0.41	0.26		120	82		
21	0.22	0.34	0.19		121	90		
37	0.35	0.51	0.36		117	96		
76	0.62	1.18	0.72		110	92		
78	0.68	1.18	0.78	79.2	111	92	527	110
183	1.62	2.11	1.27		106	68		
139	1.42	1.62	1.00		109	72		
28	0.28	0.56	0.38		115	76		
33	0.33	0.98	0.62		114	82		
47	0.49	0.95	0.39		104	88		
177	1.74	2.25	0.89		106	82		
194	1.73	2.37	1.04		109	86		
200	1.75	2.38	1.03		110	88		
507	3.02	6.45	3.37	92.7	113	82	453	33
1,002	5.86	8.75	4.11		118	90		
742	4.26	8.60	4.02		115	88		
805	4.71	8.90	4.11		108	78		
758	4.23	7.75	4.14		107	82		
1,102	6.02	11.1	4.84		102	90		
1,049	5.76	11.9	5.09		103	92		
1,175	6.56	11.3	5.05		103	94		
1,180	6.59	11.5	5.22	86.8	102	94	787	106
189	1.59	2.10	1.30		131	68		
203	2.26	2.00	1.20		129	70		
189	2.29	2.00	1.20		132	70		
193	1.86	2.10	1.24		129	76		
172	1.92	2.00	1.25		129	74		
210	2.27	2.21	1.37		128	78		
226	2.13	2.40	1.50		128	84		
292	2.86	3.00	1.84		122	82		
298	2.90	3.10	1.92		121	86		
166	1.87	1.84	1.14	76.2	124	96	281	12
61	0.68	1.07	0.70		137	92		
37	0.41	0.62	0.30		125	90		
29	0.32	0.76	0.49		129	88		
148	1.63	1.72	1.08		123	92		
314	3.02	2.93	1.59		119	96		

Table 2 (continued)

Subject, age (yr), & hct	Dosage of pyrogen (μg i.v.)	Time from pyrogen admin. (min)	Urine volume (ml/min)	C_{IN} (ml/min)	C_{PAH} (ml/min)	FF (%)	RR (dynes·sec cm^{-5})
S.jT. (cont.)		145	1.79	76.1	389	19.6	13,148
		180	3.01	83.0	389	21.3	13,148
		210	3.10	82.8	390	21.2	13,147
		Control*	0.81	125	481	26.0	10,225
Mc.K.R.–51	12	30	0.66	106	445	23.8	11,573
		60	0.64	102	467	21.8	11,326
		90	0.65	97	477	20.3	10,700
		120	0.62	97	510	19.0	9,825
Hct 41.7%		150	0.88	109	604	18.0	8,527
		180	1.32	108	681	15.6	7,252
		210	1.35	110	694	15.9	7,250
		Control*	1.20	122	465	26.2	12,126
E.L.C.–31	10	20	1.12	123	415	29.6	13,159
		50	0.82	123	457	26.9	10,201
		80	0.99	124	462	26.8	10,859
Hct 44.3%		110	1.28	125	592	21.1	8,475
		Control*	1.43	105	304	34.5	15,272
S.P.–56	12	30	2.19	97.8	278	35.2	16,858
		60	1.95	102	288	35.4	15,360
		90	1.70	107	313	34.2	13,014
Hct 45.0%		120	1.80	106	346	30.6	12,026
		150	1.49	109	390	27.9	10,444
		180	2.09	126	430	29.3	9,473
		Control*	0.34	109	372	29.3	11,572
M.E.–39	10	15	0.33	105	376	27.9	11,885
		30	0.27	91	419	21.7	10,470
		50	0.30	95	435	21.8	9,802
		80	0.23	98	473	20.7	8,928
		110	0.22	96	475	20.2	8,631
Hct 48.6%		140	0.28	107	606	17.6	6,359
		170	0.28	105	600	17.5	6,013
		210	0.33	108	614	17.6	5,809

*Control values represent a mean of three consecutive collection periods.
†On low sodium diet.

found to increase in normal subjects in the flush phase after pyrogen administration.[4] While normotensive subjects seem capable of maintaining cardiac output during pyrogen-induced peripheral vasodilatation, hypertensive patients are unable to maintain peripheral resistance, this being associated with a fall in cardiac output[5] and decrease in systemic arterial blood pressure.

Extraction of PAH diminished during phase 2 in all four normotensive and four hypertensive subjects tested. Factors determining E_{PAH} are poorly understood. Anatomic considerations in evaluation of medullary circulation[6] are congruent with the concept advanced by some,[7–9] that blood leaving juxtamedullary glomeruli and continuing into vasa recta does not perfuse sufficient cortical convolutions to allow for complete extraction of PAH. Thurau and Deetjen[10] suggested that medullary blood flow is not autoregulated and is thus more readily affected by changes in perfusion pressure than cortical blood flow. Earley and Friedler[11] observed that in the dog during aortic constriction resulting in reduced perfusion pressure and decreased

$U_{Na}V$ (μEq/min)	EF_{NA} (%)	C_{osm} (ml/min)	$T^c_{H_2O}$ (ml/min)	E_{PAH} (%)	Mean blood pressure (mm Hg)	Pulse (bt/min)	RPF (ml/min) Total	RPF (ml/min) Medullary
412	3.85	3.51	1.72		117	102		
644	5.55	5.01	2.00		117	98		
648	5.56	5.09	1.99	72.7	117	96	535	146
167	0.95	2.29	1.49	90.1	116	74	534	53
143	0.96	2.05	1.38		121	68		
151	1.06	2.06	1.42		124	70		
162	1.19	2.17	1.52		120	76		
154	1.13	2.14	1.52		118	82		
224	1.47	2.91	2.03		121	88		
359	2.38	3.91	2.59		118	90		
361	2.39	4.00	2.65	81.7	118	92	847	156
135	0.78	2.49	1.13		137	68		
97	0.56	2.20	1.08		133	72		
47	0.27	1.60	0.77		115	76		
58	0.33	1.20	0.20		123	72		
104	0.59	2.37	1.09		123	80		
343	2.33	3.79	2.36		116	80		
556	4.06	5.16	2.97		117	76		
484	3.39	4.71	2.76		111	84		
422	2.82	4.38	2.68		103	82		
457	3.07	4.61	2.81		105	80		
387	2.59	3.89	2.40		103	78		
560	3.17	5.39	3.30		103	82		
		0.87	0.53		115	86		
		0.91	0.58		119	90		
		0.78	0.51		117	100		
		0.70	0.40		114	88		
		0.70	0.46		113	92		
		0.66	0.44		110	98		
		0.85	0.56		104	102		
		0.89	0.61		98	110		
		1.08	0.74		97	108		

medullary blood flow, E_{PAH} increased. In our studies evidence obtained in man supports the view that maintenance of cortical renal blood flow or increase in medullary blood flow results in diminished extraction of PAH, presumably reflecting channelling of blood into areas not participating in secretion of PAH.

When total renal plasma flow is calculated utilizing correction applied due to incomplete extraction of PAH, the percentage increase in total renal plasma flow appears to be comparable in the two groups (fig. 4). Increase in noncortical renal plasma flow, assumed as medullary renal plasma flow (MRPF), appears to be much greater in the normotensive group. In this population, MRPF was higher during control periods in all four normotensives than in the four hypertensive patients. During the hyperemic phase the increment was greater in three of the four normotensive patients, but the mean increments for the two groups expressed as a percentage increase were comparable.

Antinatriuresis during phase 1 occurred in our studies in both normotensives and hypertensives but was most prominent in the latter group (fig. 6). Lathem[12] found, after typhoid-paratyphoid-induced pyrogenic renal hyperemia in normotensive man, no systemic

Table 3

*Summary of Effect of Pyrogen on Mean Pressure and Renal Hemodynamics**

Subjects	No.	Mean pressure				Control (ml/min)
		Control (mm Hg)	Response†			
			Actual (mm Hg)	Δ (mm Hg)	Δ (%)	
Normotensive	10	90.8	90.5	−0.3	−0.34	509
Hypertensive	10	121	112	−9.0	−7.43	344

*All values represent means; Δ = change from control.
†"Response" indicates the mean of the maximal change from control values.

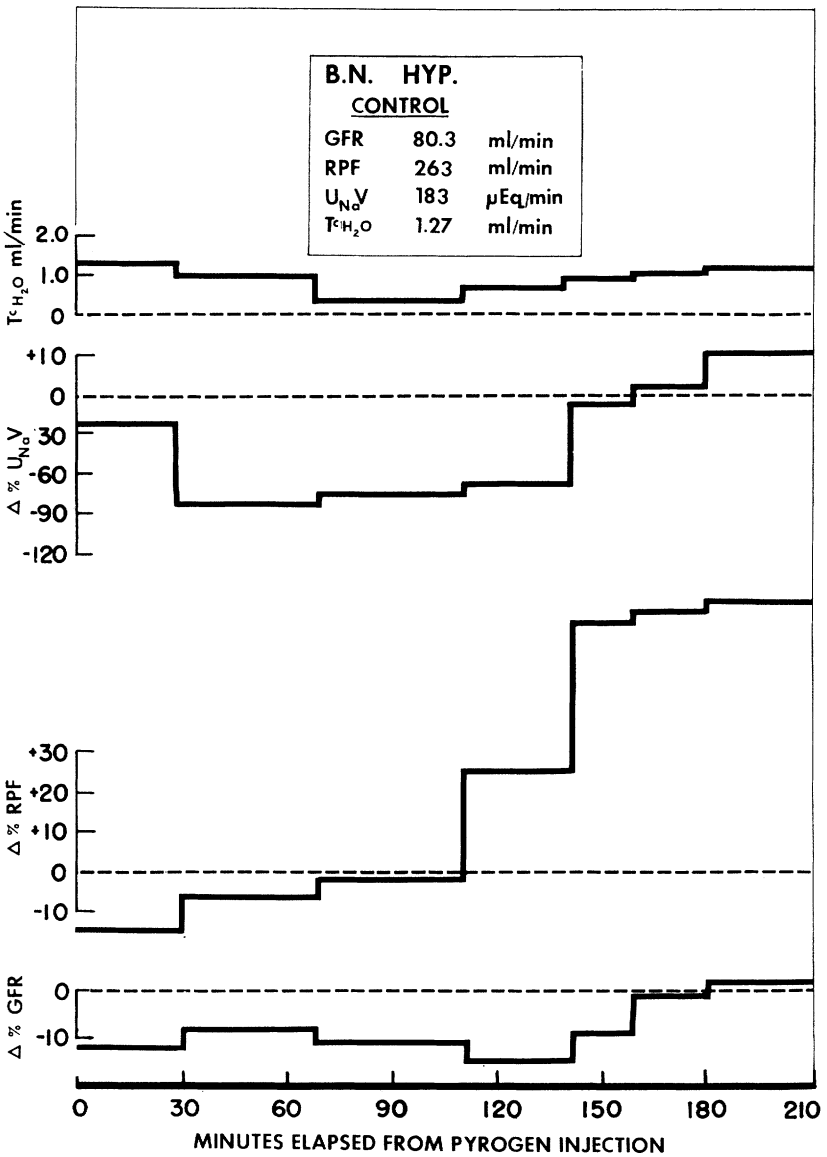

Figure 2

Effect of pyrogen on GFR, RPF, $U_{Na}V$, and $T^c_{H_2O}$ in a hypertensive subject.

Renal plasma flow			Renal resistance			
	Response†			Response†		
Actual (ml/min)	Δ (ml/min)	Δ (%)	Control (dynes-sec cm^{-5})	Actual (dynes-sec cm^{-5})	Δ (dynes-sec cm^{-5})	Δ (%)
697	+ 188	+ 36.0	7,259	5,345	— 1,914	— 26.5
521	+ 177	+ 51.7	15,412	9,461	— 5,951	— 38.8

Table 3 (continued)

		Glomerular filtration rate				Filtration fraction			
			Response†				Response†		
Subjects	No.	Control (ml/min)	Actual (ml/min)	Δ (ml/min)	Δ (%)	Control	Actual	Δ	Δ (%)
Normotensive	10	109	113	+ 4	+ 3.68	0.220	0.167	— 0.053	— 24.1
Hypertensive	10	99.2	97.2	— 2	— 2.02	0.291	0.189	— 0.102	— 35.1

change in excretion of sodium. In our studies, in normotensives natriuresis developed simultaneously with the supervening hyperemia while in hypertensives this response was delayed. While a small decrement in GFR has occurred during phase 1 in both groups, the intensity of pre-glomerular (afferent) vasoconstriction was greater in hypertensive subjects. The effect of this variable on sodium excretion can readily be examined by correlating $U_{Na}V$ with changes in GFR. In normotensives, increases in EF_{Na} developed even during the early, though minimal, vasoconstrictive phase and the increased saluresis continued unabated throughout the observation. It is likely that the early vasoconstrictive

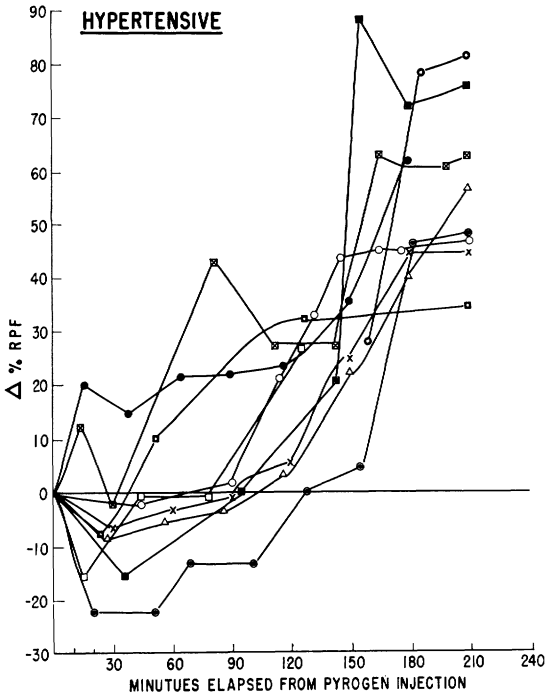

Figure 3

Effect of pyrogen on RPF in hypertensive subjects.

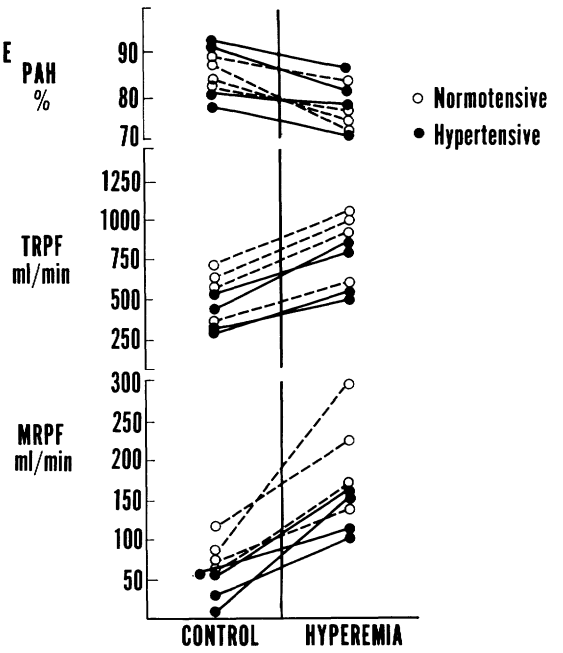

Figure 4

Pyrogen-induced changes in E_{PAH}, TRPF, and MRPF in normotensive and hypertensive subjects.

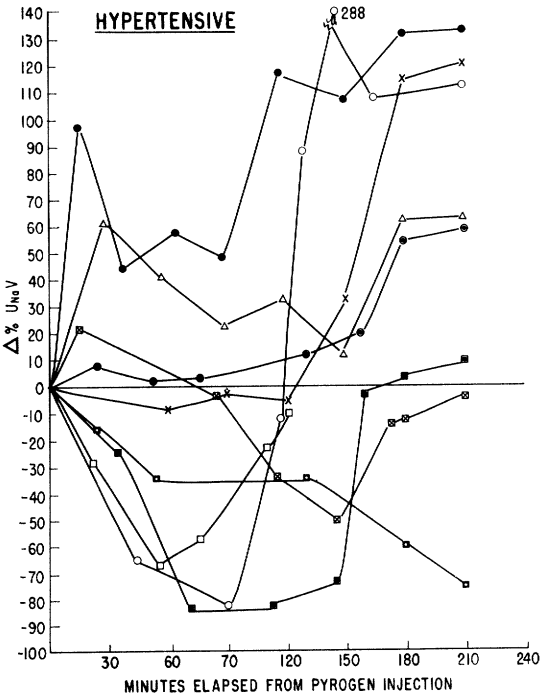

Figure 5

Effect of pyrogen on $U_{Na}V$ in hypertensive subjects.

phase seen in hypertensives, with its somewhat greater effect on glomerular filtration, is responsible for the antinatriuresis which persisted during the early part of phase 2. The natriuretic effect of phase 2 was thus delayed, and only late was there a discernible

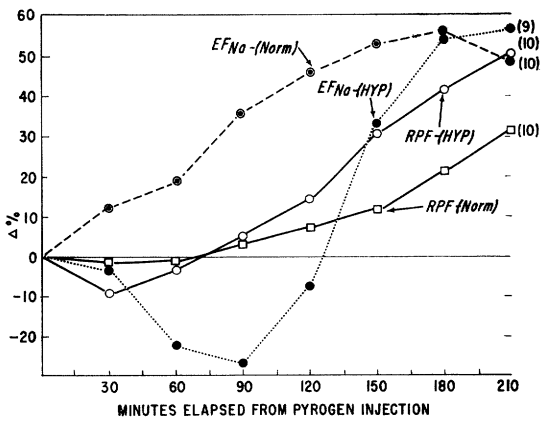

Figure 6

Effect of pyrogen on RPF and EF_{Na} in normotensive (Norm) and hypertensive (Hyp) subjects.

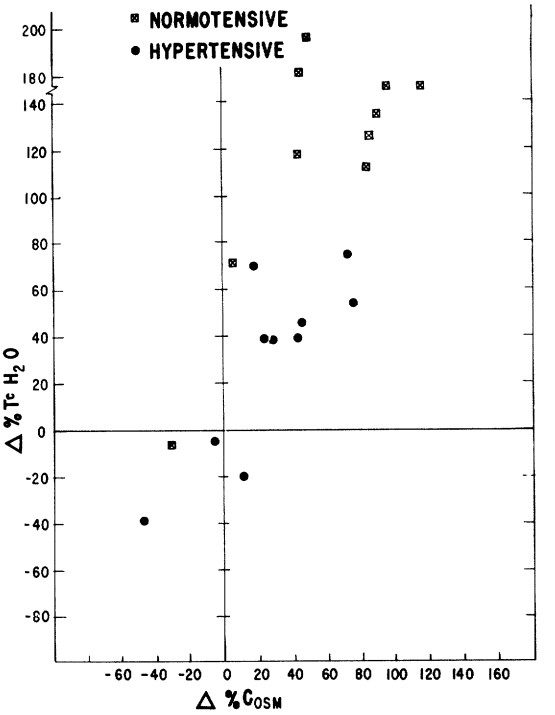

Figure 7

Effect on pyrogen on C_{OSM} and $T^c_{H_2O}$ in normotensive and hypertensive subjects. Data represent percentage changes from control values to those observed at the height of the maximum effect of pyrogen.

increase in saluresis which finally was of comparable magnitude for the two groups. The absolute rate of this increase in sodium excretion was not of the extent observed by Baldwin and associates[13] who found higher saluresis in hypertensives in response to low rate infusions of saline or hypotonic glucose.

A defect in concentrating capacity seen at low solute loads is present in hypertensive patients. This impairment is being attributed to excessive sodium reabsorption in the proximal tubule, thus impairing the capacity to maintain medullary tonicity.[1] In our study this propensity for increased sodium reabsorption during phase 1 seemed again prominent in the hypertensive group. The increase in solute excretion during the hyperemic phase was seen in both normotensives and hypertensives and has to be attributed to a decrease in sodium reabsorption. As C_{osm} increased,

$T^c_{H_2O}$ increased also, suggesting in addition an increase in antidiuretic hormone activity. The mean C_{osm} in the two groups were comparable both during control observations and at the height of hyperemia: for *normotensives* from 2.23 to 3.38 ml/min, an increase of 1.15 ml or 51.5%; for *hypertensives* from 2.45 to 3.67 ml/min, an increase of 1.22 ml or 49.8%. The mean $T^c_{H_2O}$ during the same period in the two groups were also comparable although the percentage increase was greater in normotensives: for *normotensives* from 0.96 to 2.01 ml/min, an increase of 1.05 ml or 109%; for *hypertensives* from 1.43 to 1.94 ml/min, an increase of 0.51 or 35.6%. It is thought that medullary hyperemia minimizes medullary tonicity. In our study the pyrogen-induced increase in MRPF was greater in normotensives than in hypertensives, yet the magnitude of the tubular concentrating operation was comparable in the two populations. This suggests that medullary hyperemia, at least acutely, does not affect medullary tonicity.

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Renal Response to Pyrogen in Normotensive and Hypertensive Man

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