Journal of Clinical Investigation
Vol. 42, No. 1, 1963

FIXED AND REPRODUCIBLE ORTHOSTATIC PROTEINURIA. III. EFFECT OF INDUCED RENAL HEMODYNAMIC ALTERATIONS UPON URINARY PROTEIN EXCRETION *

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(Submitted for publication July 3, 1962; accepted September 25, 1962)

Contrary to traditional opinion, recent observations have suggested that nonhemodynamic factors are the fundamental cause of "fixed and reproducible" orthostatic proteinuria (1–3). Important findings have been the eventual appearance of overt evidence of renal disease in many patients with this disorder (3) and the description of a characteristic pattern of glomerular alteration in renal tissue from many such patients when both conventional (1) and electron microscopy (4) were used. Nevertheless, the renal circulatory response to orthostasis may still play an important secondary or modifying role in the pathogenesis of this form of orthostatic proteinuria. A basis for this proposal is provided by previous observations in patients with more advanced alterations of glomerular anatomy due to obvious renal disease. Several observers have indicated that glomerular protein transfer may be conditioned by intrarenal hemodynamic adjustments to the erect posture (5, 6).

The present study was undertaken to re-examine the relative importance and contribution of upright renal circulatory adjustments to the occurrence of fixed and reproducible orthostatic proteinuria. Controlled changes of inulin and para-aminohippurate clearance were produced in both the supine and upright posture by a variety of experimental maneuvers. A family of differing renal hemodynamic patterns was thus obtained, each of which could be related to its associated changes of urinary protein excretion in order to assess the relative importance of individual hemodynamic parameters to the occurrence of proteinuria. Although not conclusive, the results are compatible with the thesis that a normal reduction of renal blood flow during orthostasis is the most important renal circulatory determinant of upright proteinuria in these patients.

All observations were limited to patients whose orthostatic proteinuria was "fixed and reproducible." No statement may be made regarding their applicability to patients with the much more common "transient" type of orthostatic proteinuria (7).

METHODS

Fifty-five studies were carried out on 48 fasting patients with "fixed and reproducible" orthostatic proteinuria. As outlined in a previous communication (1), case material for examination was selected from a large number of Air Force recruits who had been hospitalized on a special ward for the particular evaluation of unclassified proteinuria. All patients were asymptomatic and apparently healthy young men whose ages ranged between 17 and 24 years (average: 19). With the exception of proteinuria, no disturbances of renal function were demonstrable by either radiographic or routine clinical laboratory examination.

The presence of fixed and reproducible orthostatic proteinuria was established by the results of three or more carefully supervised serial urine collection tests as described before (1). The test used has been found to be an adequate and reliable clinical means of classifying the various types of proteinuria by relating alterations of urinary protein excretion to changes of body posture (7, 8). Orthostatic proteinuria was termed "fixed and reproducible" if found consistently by repetitive examination on different days. This type of orthostatic proteinuria is to be contrasted with the more common "transient" variety; the latter is variable and inconstant in its appearance and cannot be detected reproducibly from day to day. It cannot be emphasized too strongly that only patients with fixed and reproducible orthostatic protein-

* Supported in part by Research Contract 41(657)-368 with the School of Aerospace Medicine, Brooks Air Force Base, Texas, and U. S. Public Health Service Grant No. 54-7370.

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uria were included in this study. This fact is of great importance, since it is quite possible that the two major forms of orthostatic proteinuria ("transient" and "fixed reproducible") may provide entirely different etiologic and prognostic implications.

Glomerular filtration rate was measured as the inulin clearance, and effective renal plasma flow as the para-aminohippurate (PAH) clearance with standard renal clearance techniques (9). All patients were examined in the early morning after they had been resting quietly in bed for at least 2 hours. Although some studies were initiated at a time when urine flow was low, most experiments were begun during a moderate water diuresis (5 to 8 ml per minute) produced by the oral ingestion of 500 ml of tap water about 45 minutes prior to the test. In most studies, bladder urine was collected through an indwelling bladder catheter with the aid of an air washout. After three control clearance periods of 15 to 20 minutes duration were obtained with the patient recumbent, one of the four experimental plans listed below was applied in 54 experiments. In one study, clearance values were secured in the recumbent posture only.

Response to the upright posture. After completion of the last recumbent control clearance period, 23 patients were asked to stand beside the bed in a relaxed and nonlordotic upright posture. While erect, three to four periods of 10 to 15 minutes duration each were secured. Twelve of the 23 patients then returned to the supine position in bed, and recovery clearance periods were obtained. In these and all other studies, the results of the first clearance period following a change of body posture were not included in the final calculations.

A frequent and significant problem throughout these experiments was the occurrence of dizziness, or fainting, or both, while in the erect posture. This was particularly true during the studies described below in which a vasoactive drug was administered. Many additional experiments were performed, but the appearance of either presyncopal symptoms or actual fainting precluded accurate interpretation of the results. For this reason, no experiments have been included which were complicated by the appearance of recognizable vasomotor instability. In later studies, the incidence of syncope during orthostasis was lessened by instructing the patients to rest their forearms upon a bedtable whose height had been adjusted conveniently and by then providing them with interesting reading material of their own preference.

Inflation of thigh tourniquets in the recumbent posture. By the inflation of bilateral thigh tourniquets in 11 patients, an attempt was made to produce a renal hemodynamic pattern during recumbency which resembled that which occurred while standing. The lower extremities were first covered by a light blanket and the supine control periods were obtained. Immediately thereafter, high thigh tourniquets were inflated rapidly to a cuff-pressure of 70 to 90 mm Hg, and four sequential periods of 10 to 15 minutes duration were secured. Recovery clearance periods were measured in 10 patients after tourniquet release. No undue discomfort was experienced by the patients during tourniquet inflation.

Maintenance of positive pressure to the lower extremities during the upright posture. These 12 experiments were designed to either modify or obliterate the usual renal circulatory response to standing. In 7 of the 12 patients, sequential clearance periods were obtained first during recumbency, then during unmodified orthostasis, and then during recovery after the patients had returned to the supine position in bed. Immediately after the last recumbent recovery period, a lower extremity, positive-pressure suit was inflated rapidly; the patients were then requested to stand upright while three to four clearance periods were obtained during the maintenance of positive pressure. The degree of pressurization was not standardized from patient to patient, although the suit pressure was held steady throughout each individual experiment. In the remaining five patients, upright positive pressure was applied immediately after the first supine control periods, and erect control clearance periods without pressure application were not obtained.

Response to standing after prior administration of hydralazine.[1] In eight experiments hydralazine was administered during recumbency in order to assess the subsequent effects of orthostasis upon urine protein excretion during the presence of renal hyperemia. Control clearance periods were obtained sequentially during the recumbent, erect, and recumbent positions as described before. After the last recumbent recovery period, intravenous hydralizine hydrochloride (0.25 mg per kg) was administered, and two additional supine periods of 15 minutes duration were obtained. The patients were then asked to stand upright beside the bed while two to four clearance periods were secured during the time of near maximal drug effect. Owing to the long duration of these experiments, supine recovery periods were not measured after completion of the upright posthydralazine periods. Although syncope did not occur during any of the eight experiments reported here, one study was included in the final calculations which was terminated because of a complaint of "giddiness" toward the end of the third upright posthydralazine clearance period. Only the two upright periods which were unattended by vasomotor instability were utilized.

Inulin was measured in urine and unyeasted plasma by the resorcinol method of Roe as modified by Schreiner (10). Para-aminohippurate was determined by the procedure of Selkurt (11). The peripheral venous hematocrit was measured in duplicate by the Wintrobe technique. Effective renal blood flow (ERBF) was calculated from the PAH clearance and the venous hematocrit. The renal extraction percentage of PAH was not determined.

The albumin concentration of unconcentrated urine was quantified immunochemically by use of a double-diffusion column method similar to that of Oakley and Fulthorpe (12) and Preer (13). This method required that the fraction-specific rabbit antihuman albumin serum be separated in the diffusion column from the urine perfusate by

[1] Apresoline, Ciba Pharmaceutical Products, Inc., Summit, N. J.

TABLE I

*Average figures for renal hemodynamics and urinary protein excretion during the supine posture in patients with fixed and reproducible orthostatic proteinuria**

Glomerular filtration rate (C_{in}) †	121.0±SD	17.4 *ml/min*
Effective renal plasma flow (C_{pah}) †	614 ±SD	123 *ml/min*
Effective renal blood flow (ERBF) †	1117 ±SD	234 *ml/min*
Filtration fraction (FF) †	20.2±SD	3.0%
Urinary albumin excretion ($U_{alb}V$) ‡	24.3±SD	10.0 *μg/min*
Urinary total protein excretion ($U_{t.p.}V$) §	53.1±SD	20.6 *μg/min*

* All values are corrected to 1.73 m² BSA.
† Fifty-five experiments; each figure represents the average of 174 clearance periods.
‡ Twenty-one experiments.
§ Forty-one experiments.

10 mm of clear agar (13, 14). In this manner, urine albumin diffused downward, the antibody moved upward, and the position of the precipitin zone could be related to the albumin concentration of urine by reference to a standard curve. This was best accomplished by regressing the "P" value (ratio of the diffusion distance of urine albumin to that of antialbumin) (13) onto the $\sqrt[4]{\text{albumin concentration}}$ of urine albumin standards prepared as follows: albumin was precipitated from a large pool of normal human urine by the use of 10 per cent trichloroacetic acid. The supernatant fraction from this precipitation was found to be albumin-free when assayed in simple diffusion columns (15). Sufficient lyophilized ethanol-precipitated fraction V (albumin) was then triturated into the albumin-free substrate to give a concentration of 100 mg per 100 ml. For accurate quantitation, it was essential that the standard concentrations be as similar as possible to those of the unknowns (16). All urine samples were analyzed in duplicate double-diffusion columns; appropriate standard solutions were allowed to react with antialbumin sera during each separate run. Cathetometric measurement of the position of the albumin-antialbumin precipitin system was made after 72 hours at 30 ±.01° C (14). From such measurements, diffusivity ratios (13) could be calculated and substituted into the slope equation for the appropriate standard curve, and the albumin concentration of the unknown then calculated. Statistical analysis of standard albumin curves (17) indicated that, on the average, urine albumin concentration differences of 1.52 mg per 100 ml could be detected reliably at the 5 per cent probability level within the range of 0.782 to 25.0 mg per 100 ml. For purposes of this study, any urine samples that contained less than 0.5 mg of albumin per 100 ml were considered arbitrarily to be "negative" for albumin. This method provides accurate quantitation only of that amount of urine albumin which is similar immunologically to that of normal pooled human serum.

Total urine protein was measured by a modification of the Folin-Ciocalteu procedure as described by Lowry (18). Because several constituents of normal urine may react with the Folin reagent, all urine samples were prepared as follows: a 10- to 20-ml portion of each sample was lyophilized, reconstituted in 0.5 to 2.0 ml of water, precipitated with 10 per cent trichloroacetic acid, and centrifuged. After centrifugation, the centrifuge tube was inverted and the supernatant fraction allowed to drain; the precipitate was then dissolved in dilute alkali, and appropriate dilutions were made. The recovery of protein added to normal human urine averaged 94 per cent by this procedure. The approximate concentration of urine globulin was obtained from the difference between the measured albumin and total protein concentrations.

RESULTS

Average values for renal hemodynamics and urinary protein excretion during all supine control clearance periods are shown in Table I. Measurements of inulin and PAH clearance, effective renal blood flow, and filtration fraction were made during 55 experiments, and the average results were well within the range accepted as normal (19). The urinary excretion of total protein was determined during recumbency in 41 studies and averaged 53 μg per minute (Table I). Accurate quantitation of supine albumin excretion was secured in only 21 experiments because the relatively high urine flow during many supine control periods caused dilution of urine albumin to a level below that measurable by our technique. In the 21 experiments in which accurate measurements were obtained, albumin excretion averaged 24 μg per minute (Table I) and accounted for an average 45 per cent of the total urinary excretion of protein. These values are within the range of those reported by others (20, 21) for normal urinary protein excretion, although strict comparison cannot be made because of methodologic differences and the fact that published normal figures have been obtained from pooled 24-hour urine collections. It is not known what percentage of the normal 24-hour excretion of protein is excreted during the erect as contrasted to the supine posture.

Response to the upright posture. Renal hemodynamic and urinary protein excretion values are presented in Table II for those patients in whom both supine and upright clearance measurements were obtained. Patients have been listed according to descending figures for supine inulin clearance. In almost all patients, similar and significant changes of renal hemodynamics and urinary protein excretion were observed upon assumption and maintenance of the upright posture. Inulin clearance fell in all but one patient (E. P.) and, on the average, decreased to a value 28 per cent lower

than the average supine figure (Table II; p = <.01). PAH clearance diminished in all patients to an average figure which was 38 per cent less than that obtained during the control period (p = <.01). As a result of the disproportionate reduction of inulin and PAH clearance, filtration fraction increased significantly (average: 17 per cent; p = <.01) in all but three patients (J. K., J. S., and A. M.). During recumbent recovery periods in 12 patients, inulin clearance averaged 125 ± 18 ml per minute, ERBF was 1,142 ± 204 ml per minute, and filtration fraction equaled 20.7 ± 4.3 per cent. Although changes of the renal extraction of PAH during orthostasis cannot be excluded, the associated reduction of filtration rate, the prompt return of clearance values to control supine levels, and the similarity of these alterations to those described in normal subjects (2, 19, 22) upon standing suggest that the reduction of PAH clearance was largely a consequence of a reduced renal plasma flow.

Although the order of magnitude varied widely, values for both total protein and total albumin excretion rose in all subjects (Table II). On the average, urinary albumin excretion increased after standing to a value 555 per cent greater (p = <.02) than the figure (22 ± 6 μg per minute) obtained for those 10 patients in whom albumin concentrations could be determined accurately during recumbency. When compared to the average urinary albumin excretion figure of all recumbent patients (Table I), a percentage rise of similar magnitude was found (500 per cent; p = <.01).

The urinary excretion of total protein rose, on the average, to 362 per cent of the supine figure (Table II; p = <.01). Because the excretion rate of albumin rose to a greater degree than did that of total protein, albumin contributed somewhat more to total protein excretion during standing (59 per cent) than during the supine posture (42 per cent). No statistical correlation was found between the magnitude of change exhibited by the three hemodynamic parameters and that of either urinary albumin or total protein excretion.

Inflation of thigh tourniquets in the recumbent posture. In 11 patients (Figure 1), thigh tourniquet inflation produced an average 15.1 per cent reduction of inulin clearance, from 116.9 ± 16.3 to 99.2 ± 14.7 ml per minute (p = <.01). PAH clearance diminished proportionately (16.9 per

TABLE II

*Renal hemodynamics and urinary protein excretion during the upright posture in patients with fixed and reproducible orthostatic proteinuria**

Subject	Age	Supine						Upright					
		C_{in}	C_{pah}	ERBF	FF	$U_{alb}V$ †	$U_{tp}V$	C_{in}	C_{pah}	ERBF	FF	$U_{alb}V$	$U_{tp}V$
		ml/min	*ml/min*	*ml/min*	%	*μg/min*	*μg/min*	*ml/min*	*ml/min*	*ml/min*	%	*μg/min*	*μg/min*
M.L.	17	146.6	769	1305	19.1	<40	40	96.0	401	730	23.9	103	174
D.G.	18	142.4	848	1502	16.8	<53	73	86.5	408	741	21.2	74	127
A.E.	17	142.1	631	1097	22.5	<46	56	86.1	347	603	24.8	79	139
P.Z.	17	139.5	850	1603	16.4	34	85	101.2	389	749	26.0	433	575
S.F.	17	129.0	700	1187	18.4	19	55	108.6	551	984	19.7	37	103
N.M.	17	128.6	508	863	25.3	9	27	106.3	398	676	26.7	81	156
D.H.	20	126.7	661	1212	19.2	12	29	78.4	338	669	23.2	126	254
D.W.	17	126.6	500	847	25.6	<29	27	92.7	271	459	34.2	108	184
J.K.	18	125.6	692	1473	18.2	<28	47	42.0	331	704	14.0	81	
L.A.	18	124.6	778	1441	16.0	11	63	92.0	541	1002	17.0	349	463
R.H.	17	122.6	464	866	26.4	<43	48	116.4	424	785	27.5	96	186
J.S.	19	121.8	532	1004	22.9	<37	77	68.2	320	639	21.3	121	167
T.M.	19	119.1	570	1075	20.9	28	35	107.6	471	686	22.8	54	94
F.D.	18	112.2	626	1129	17.9	21	56	81.1	304	548	26.7	154	231
B.Y.	22	111.3	518	864	21.4	29	79	65.8	226	400	29.1	72	124
C.D.	17	110.2	559	981	19.7	<35	77	89.1	368	658	24.2	162	369
C.B.	18	109.8	563	954	19.5	33	62	81.4	361	644	22.6	96	207
A.M.	17	108.9	447	812	24.4	<40	60	82.0	340	618	24.1	104	253
M.S.	25	107.3	678	1190	15.8	<36	52	74.2	396	720	18.7	133	280
S.M.	17	103.5	499	951	20.7	19	43	70.2	261	498	26.9	103	194
J.M.	18	100.4	454	811	22.2	<40	63	92.3	372	664	24.8	115	211
M.R.	19	97.5	500	894	19.5	<22	20	64.6	279	499	23.1	492	595
E.P.	17	87.5	375	728	23.3	< 6		87.5	331	643	26.4	127	310
Average	18	119.3	597	1078	20.5	22	53	85.7	366	666	23.9	144	245
±SD		15.4	132	250	3.1	6	19	17.1	80	142	4.2	117	141

* Supine values are the average of at least three clearance periods. Upright values represent the average of two to three clearance determinations. All figures have been corrected to 1.73 m^2 BSA. Abbreviations: C_{in} = inulin clearance; C_{pah} = para-aminohippurate (PAH) clearance; ERBF = effective renal blood flow; FF = filtration fraction; $U_{alb}V$ = urinary albumin excretion; $U_{tp}V$ = urinary total protein excretion.

† Samples which were too dilute for accurate albumin analysis are preceded by a "less than" (<) sign. Such figures represent the least amount of albumin which could have been detected accurately by our technique. Only those samples whose concentrations were actually measured are included in the average value.

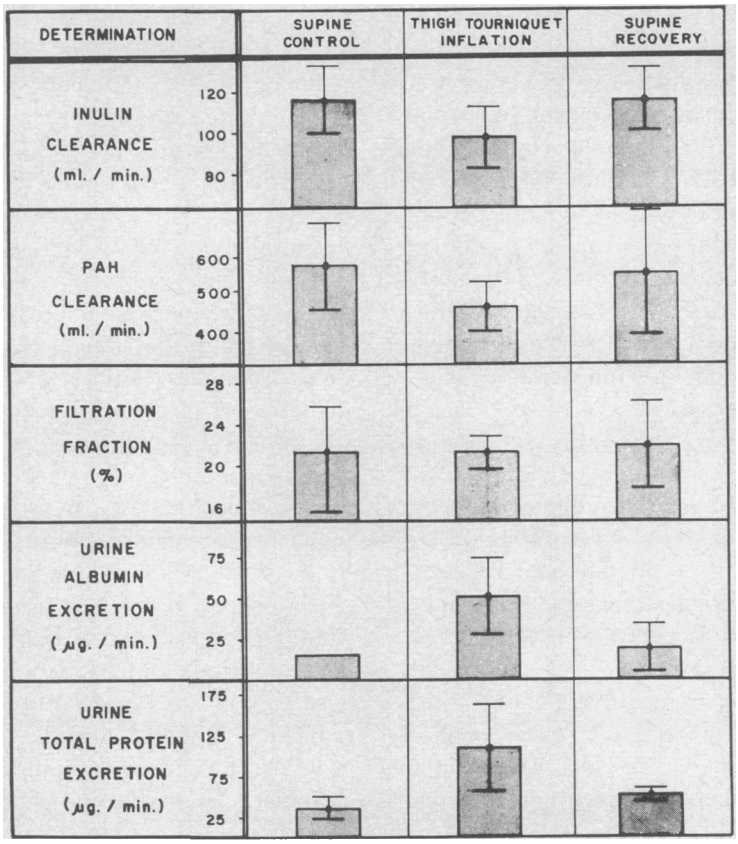

FIG. 1. EFFECT OF SUPINE, THIGH TOURNIQUET INFLATION UPON RENAL HEMODYNAMICS AND URINARY PROTEIN EXCRETION IN 11 PATIENTS WITH FIXED AND REPRODUCIBLE ORTHOSTATIC PROTEINURIA. Vertical bars represent average values for the entire group. Standard deviation is indicated by the brackets. Urine albumin was measured in only 3 patients during the supine control period.

cent) from an average supine figure of 562 ± 108 ml per minute to an average value of 467 ± 60 ml per minute during tourniquet inflation ($p = <.01$). Filtration fraction increased in two patients, decreased in four, and was essentialy unchanged during the remaining five studies. Because of the equal and parallel average reduction of inulin and PAH clearance, however, the average value for filtration fraction did not change significantly (Figure 1; $p = >.10$). The hemodynamic response to tourniquet application resembled that seen upon standing in that similar directional changes of inulin and PAH clearance occurred. The response differed in that the reduction of these clearances was of somewhat lesser magnitude and it was unassociated with an average rise of filtration fraction. After tourniquet release, all hemodynamic values returned promptly to the approximate levels observed previously during the control supine clearance periods (Figure 1).

These experiments are of interest because significant proteinuria occurred in all patients despite the absence of an average rise of filtration fraction. Values for urinary albumin excretion increased from an average of 15 μg per minute during the control period (three patients only) to 50 ± 23 μg per minute during tourniquet inflation (233 per cent increase). Although the paucity of urine albumin measurements during the supine control periods prevented an evaluation of statistical significance within this group, comparison of the figure for albumin excretion during tourniquet inflation with that of the supine control periods of all subjects (24.3 ± 10.0 μg per minute; Table I) revealed a significant difference ($p = <.01$). Similarly, total protein excretion in-

creased 220 per cent from an average value of 33.2 ± 12.7 μg per minute during the control period to an average figure of 106.2 ± 53.4 μg per minute during thigh tourniquet inflation ($p = < .01$). The relative contribution of albumin to total protein excretion was unchanged both before and during tourniquet inflation (45 and 47 per cent respectively). After tourniquet release, protein excretion in all patients returned to the supine control values (Figure 1). Again, no statistical correlation was established between changes of inulin or PAH clearance and the degree of proteinuria produced by tourniquet inflation.

Maintenance of positive pressure to the lower extremities during the upright posture. The effects of positive pressure applied to the lower extremities during the assumption and maintenance of the upright posture are shown in Table III. Upright clearance periods were obtained with and without pressure-suit inflation in 7 of the 12 patients. The control hemodynamic responses of these 7 patients to standing were similar both qualitatively and quantitatively to those of other patients. During orthostasis with pressure suit inflation, however, a different type of response was observed in many of the 12 patients. Filtration rate was well maintained in all but 3 patients (P. Z., D. D., and G. M.) and averaged

TABLE III

*Effect of lower extremity positive pressure upon renal hemodynamics and urinary protein excretion during orthostasis**

Patient	Posture	C_{in}	C_{pah}	ERBF	FF	$U_{alb}V$	$U_{tp}V$
		ml/min	*ml/min*	*ml/min*		*μg/min*	*μg/min*
S.F.	Supine	129	700	1187	.184	18.8	55.3
	Upright	109	551	984	.197	37.1	103.2
	Supine	149	748	1268	.199	24.4	60.0
	Upright-P †	132	611	1075	.216	50.0	67.0
C.D.	Supine	110	559	981	.197	<35.0	77.1
	Upright	89	368	658	.242	162.3	368.6
	Supine	102	494	882	.206	45.6	103.0
	Upright-P	108	471	674	.230	75.8	154.0
M.S.	Supine	107	678	1190	.158	<36.3	52.1
	Upright	74	396	720	.187	132.8	280.5
	Supine	123	674	1184	.183	59.4	92.7
	Upright-P	122	615	1098	.198	55.4	116.1
D.G.	Supine	142	848	1502	.168	<53.2	73.4
	Upright	86	408	741	.212	73.7	127.2
	Supine	133	709	1267	.187	39.4	76.3
	Upright-P	144	704	1304	.204	82.0	141.7
M.L.	Supine	147	769	1305	.191	<39.7	39.6
	Upright	96	401	730	.239	103.2	174.5
	Supine	133	574	989	.232	31.4	46.9
	Upright-P	135	555	991	.243	73.1	149.2
P.Z.	Supine	140	850	1603	.164	34.1	85.2
	Upright	101	389	749	.260	433.0	575.4
	Supine	133	666	1293	.199	49.0	98.9
	Upright-P	119	449	885	.264	119.0	186.2
T.M.	Supine	119	570	1075	.209	28.3	35.2
	Upright	108	471	686	.228	54.3	93.6
	Supine	123	451	835	.274	34.2	54.0
	Upright-P	130	500	980	.260	32.6	51.6
J.W.	Supine	122	555	1111	.220	27.2	41.3
	Upright-P	125	535	1028	.233	85.2	217.5
R.G.	Supine	130	639	1183	.203	14.6	31.6
	Upright-P	136	598	1108	.228	79.7	138.2
D.D.	Supine	128	616	1082	.208	<30.2	56.7
	Upright-P	109	480	814	.228	102.6	151.4
D.E.	Supine	134	653	1156	.205	43.1	52.5
	Upright-P	129	552	994	.233	53.2	93.0
G.M.	Supine	109	447	812	.244	<40.0	60.5
	Upright-P	86	340	618	.252	70.0	112.7
Average ±SD	Supine	126 ± 13	657 ± 122	1183 ± 215	.196 ± .022	27.3 ± 10.3	55.0 ± 16.9
	Upright	95 ± 12	426 ± 64	753 ± 99	.224 ± .026	142.3 ± 135.4	246.1 ± 176.8
	Supine	128 ± 13	644 ± 130	1145 ± 218	.204 ± .036	38.1 ± 12.8	72.7 ± 23.1
	Upright-P	123 ± 16	534 ± 95	964 ± 190	.232 ± .030	73.2 + 23.6	131.6 + 47.1

* Each figure represents the average of two to three clearance periods. All values are corrected to 1.73 m^2 BSA. Abbreviations as in Table II.
† "Upright-P" refers to those periods obtained while the patient maintained the upright posture during the application of positive pressure to the lower extremities.

TABLE IV

*Effect of prior treatment with hydralazine upon renal circulatory adjustments and urinary protein excretion during orthostasis in eight patients with fixed and reproducible orthostatic proteinuria**

Determination	Supine		Upright		Supine post-hydralazine		Upright post-hydralazine†	
	Av.	SD	Av.	SD	Av.	SD	Av.	SD
Glomerular filtration rate, *ml/min*	116	± 11	87	± 14	117	± 15	92	± 16
Effective renal plasma flow, *ml/min*	518	± 57	303	± 69	709	± 168	528	± 80
Effective renal blood flow, *ml/min*	906	± 112	534	± 115	1265	± 319	892	± 115
Filtration fraction, %	22.7	± 2.9	29.2	± 3.9	17.0	± 3.1	17.5	± 3.0
Urine albumin excretion,‡ *μg/min*	27.1	± 10.2	107.1	± 28.7	28.7	± 12.6	44.9	± 14.6
Urine total protein excretion, *μg/min*	54.9	± 23.2	182.2	± 38.4	56.6	± 20.4	81.1	± 27.9

* All figures are corrected to 1.73 m^2 BSA. Two to three clearance periods were obtained during each change of posture.

† Hydralazine, 0.25 mg per kg i.v., was administered to patients while supine, approximately 30 minutes before standing.

‡ Urine albumin could be measured during the control supine periods of four patients only.

only 3 per cent less than the average figure of the supine control periods (Table III). This value differed significantly from that obtained when the patients were standing upright without pressure support ($p = <.01$). Despite pressure-suit inflation, however, PAH clearance fell in all but 4 patients (J. W., T. M., D. G., and R. G.) to an average value 19 per cent lower than that observed while supine. Although this reduction of PAH clearance was not significantly different from the average supine control value of all 51 patients examined ($p = >.10$), paired data analysis of this group alone revealed it to be significantly different from the first supine control value ($p = <.01$) and the figure obtained during orthostasis without pressure-suit support ($p = <.02$). Because, on the average, inulin clearance was maintained despite a modest reduction of PAH clearance, filtration fraction rose 18 per cent when the patients were standing erect during pressure-suit inflation (Table III). This hemodynamic response was always associated with the appearance of significant proteinuria. Albumin excretion rose, on the average, to a value of 168 per cent ($p = <.01$) higher than the first supine control value, and average total protein excretion increased to 139 per cent of the first supine figure (Table III). The degree of proteinuria, however, was not so marked as that observed when the patients were standing upright without pressure-suit inflation (Tables II and III).

Response to standing after prior administration of hydralazine. The effect of prior treatment with hydralazine upon the usual renal circulatory adjustment and change of protein excretion in response to standing is shown in Table IV. In these patients, the renal hemodynamic response to the unmodified upright posture before hydralazine administration was similar to that described before. After hydralazine administration, a significant ($p = <.01$) average rise of PAH clearance occurred in all subjects while in the recumbent posture which was associated with maintenance of inulin clearance and a fall of filtration fraction. The ability of this drug to increase the clearance of PAH has been described previously (23). When the upright posture was assumed and maintained during the time of maximal drug action, average inulin and PAH clearance values fell proportionately so that no significant change of filtration fraction occurred (Table IV). This pattern of response was similar to that seen during the application of thigh tourniquets in the supine position. It differed perhaps accidentally, in that the absolute average figure for PAH clearance was no different ($p = >.10$) from that of the supine period prior to hydralazine administration (Table IV). The average values for both inulin clear-

ance and filtration fraction, however, were significantly lower than those of the supine periods (21 and 23 per cent decreased, respectively; $p = <.01$ and $<.01$). Thus, pretreatment with hydralazine appeared to prevent PAH clearance from falling during orthostasis to the absolute lower levels observed during periods of unmodified standing prior to drug administration.

The average excretion of albumin and total protein during upright standing after hydralazine administration was much less than that during the prehydralazine upright posture and only slightly higher than that of the supine control period (Table IV). Although albumin and total protein excretion rose 66 and 48 per cent, respectively, from the control supine figure, these values should be contrasted to increases of 295 per cent for albumin excretion and 232 per cent for total protein excretion during unmodified standing.

DISCUSSION

The renal hemodynamic response to standing in these patients was characterized by a moderate reduction of inulin and PAH clearance and an elevation of filtration fraction. In almost all respects, the character of this response resembled closely that described by others in healthy, nonproteinuric subjects (2, 19, 22). If, as seems likely, the lowered clearance of PAH was the consequence of a diminished renal plasma flow, then the rise of filtration fraction may be attributed to efferent arteriolar constriction as part of the usual vasoconstrictive response to orthostasis. King and Baldwin (2) have reported similar findings in other patients with orthostatic proteinuria and, on the basis of comparable control measurements on normal subjects, first proposed that the postural adjustments of inulin and PAH clearance in such patients were indistinguishable from the normal. The present results are in agreement with this proposal, although the lack of similar observations on normal subjects prevents its full confirmation.

The demonstration of a normal postural response of inulin and PAH clearance does not necessarily exclude the coexistence of an abnormal adjustment of other hemodynamic variables. Despite an apparently normal filtration fraction, disturbances of intraglomerular pressure may still exist, since there is some question as to the validity of this measurement as an index of glomerular hydrostatic pressure under all conditions (19). Complete acceptance of the normalcy of total renal circulatory function in this disorder must await the measurement of such variables as renal venous pressure, cardiac output, and mean arterial blood pressure. Although not excluded, the presence of other hemodynamic alterations would seem unlikely, however, since vascular alterations of sufficient intensity to affect protein transfer at the glomerulus would logically be expected to produce associated disturbances of either filtration rate, renal plasma flow, or filtration fraction. Consequently, the present findings, although not conclusive, must be regarded as additional support to the recent proposal that factors of a nonhemodynamic nature are of primary etiologic importance to fixed and reproducible orthostatic proteinuria (1, 2).

A typical histologic pattern of glomerular alteration in renal tissue from patients with this type of orthostatic proteinuria has been described (1, 4). The possible causes and clinical significance of this histologic finding have been the subject of previous communications (1, 4). Although the possibility remains that it is the secondary effect of an underlying hemodynamic alteration, present considerations best support the concept that the structural defect itself is the primary cause of fixed and reproducible orthostatic proteinuria. This opinion rests on the histologic nature of the glomerular defect, the presumptive normalcy of filtration rate, renal plasma flow, and filtration fraction during orthostasis, and the observation that many patients with this disorder eventually develop overt evidence of renal disease (3).

Assuming that a fixed and underlying defect of the glomerular capillary wall is the primary cause of this disorder, even a normal circulatory adjustment to orthostasis may be of the appropriate nature and magnitude to effect an increased transfer of protein through a glomerular structure which is already defective. A similar concept appears applicable to patients with early but definite renal disease (6). Although still of importance, hemodynamic factors may then be relegated to a "permissive" rather than a primary role in the genesis of fixed and reproducible orthostatic pro-

teinuria. If valid, such a proposal offers the distinct advantage of combining the demonstration of an anatomic defect and a presumably normal vascular response to orthostasis into a single pathogenetic concept.

Regardless of whether vascular adjustments in this condition are normal or abnormal, several observers have emphasized their contribution to urinary protein excretion in both patients with orthostatic proteinuria and with overt forms of renal disease (5, 6, 24, 25). General agreement has not been reached as to which renal hemodynamic parameter is of most importance in this regard. Factors such as the rate and velocity of glomerular blood flow, filtration rate, and intraglomerular or renal venous hydrostatic pressure have all been considered of varying relative importance. King has proposed that the normal filtration fraction elevation of orthostasis is most causally related to the appearance of orthostatic proteinuria (7). Others have suggested that filtration rate and renal blood flow are of equal or greater importance in other forms of proteinuria (24, 26). Although only limited conclusions are permitted by the present observations, diminished renal blood flow appears to be of most hemodynamic importance to the occurrence of fixed and reproducible orthostatic proteinuria.

Neither filtration rate nor filtration fraction seems of first order importance to the initiation of proteinuria in view of filtration fraction stability during thigh tourniquet inflation and the maintenance of filtration rate during pressure-suit inflation. Despite the constancy of these two variables, significant proteinuria occurred during both experimental procedures. By exclusion then, a reduced renal blood flow seems to be the most important circulatory determinant of proteinuria because an average moderate reduction of PAH clearance occurred during both pressure-suit and tourniquet inflation. Since proteinuria was somewhat less during these two maneuvers than during unmodified orthostasis, however, both filtration fraction and filtration rate may still contribute to either its initiation or maintenance. On the other hand, these factors may be of little or no importance, and the lower rate of protein excretion during tourniquet and pressure-suit inflation may be related solely to the less reduced renal blood flow.

Further evidence that the reduction of renal blood flow is of first importance is provided by the results of the hydralazine experiments. In these patients, maintenance of the average PAH clearance value during orthostasis at a level approximating that of the supine posture was associated with the occurrence of only minimal proteinuria. It is reasonable to suspect that the relative reduction of blood flow which did occur upon standing was not only of insufficient magnitude to effect a large increase of glomerular protein transfer, but that a certain critical flow level must first be reached in each patient before the proteinuria appears. The oral ingestion of another, less potent vasodilator drug (caffeine citrate) has also been reported to depress the intensity of exercise proteinuria (27).

Considered together, these experiments imply that the upright reduction of renal blood flow is the most important hemodynamic determinant of glomerular protein transfer for the following reasons: *1*) significant proteinuria occurred regularly in the absence of changes of either filtration rate or filtration fraction; *2*) proteinuria was rarely observed without an associated reduction of PAH clearance; and *3*) maintenance of PAH clearance during orthostasis at an absolute average level equal to that of recumbency was attended by a significant depression of upright proteinuria. Nevertheless, lesser contributions of filtration rate, or intraglomerular pressure to postural proteinuria, or both, have not been rigidly excluded, and the absence of statistical correlation between changes of protein excretion and those of any hemodynamic variable prevents the formation of definite conclusions on the exact role of circulatory factors in this disorder.

No explanation is available for the mechanism by which a reduction of blood flow might increase the glomerular transfer of protein. Its exact definition must await better knowledge of the fundamental process responsible for the passage of protein molecules across capillary walls, a problem which has been the subject of several recent communications (24, 26, 28). In studies of patients with obvious renal disease, Lathem demonstrated a correlation between the relative fall of PAH clearance and the rise of protein clearance during the administration of catecholamines

(24). He suggested tentatively that a diminished glomerular blood flow might permit an increased transfer of protein across the capillary wall by lengthening the exposure time of protein molecules to the endothelial surfaces of the glomerular capillaries. As in the present study, he concluded that changes of filtration rate and filtration fraction were not the major hemodynamic determinants of an increased glomerular passage of protein (24).

Throughout these experiments it has been assumed that altered glomerular function is the primary cause of orthostatic proteinuria. The occurrence of diminished tubular reabsorption of protein during orthostasis, however, has not been excluded. In fact, varying degrees of tubular reabsorptive activity among patients could explain the lack of quantitative correlation between postural hemodynamic responses and protein excretion in these experiments. Other observers have also noted a similar lack of correlation between various circulatory responses and the minute excretion rate of protein in urine (6). Albumin or total protein clearance values, if available, might have permitted the appearance of such a correlation.

The production of recumbent proteinuria (thigh tourniquet inflation) in patients with this disorder is an important finding that deserves brief comment. Since tourniquet inflation fails to produce recumbent proteinuria in normal individuals (7), and since there is no reason to believe that the circulatory response to this maneuver is different in patients with orthostatic proteinuria, the production of supine proteinuria as described here may be interpreted as further indirect evidence of the underlying importance of nonhemodynamic factors. In addition, this observation implies that neither the erect posture nor other anatomic factors such as upright hepatic compression of the inferior vena cava (29) are essential to the appearance of this type of proteinuria. Nevertheless, a similar but nonmechanical elevation of renal venous pressure induced by tourniquet inflation itself cannot be ruled out explicitly without a direct estimation of renal venous pressure. Lastly, the appearance of recumbent proteinuria in these patients does not exclude a contributory role of upright anatomic factors to the production of "transient" orthostatic proteinuria, a variety of orthostatic proteinuria that is much more prevalent than the "fixed and reproducible" type considered in this report (7).

SUMMARY

1. The effects of induced renal hemodynamic alterations upon urinary albumin and total protein excretion were studied in patients with fixed and reproducible orthostatic proteinuria. Differing types of renal circulatory patterns were produced by unmodified orthostasis, recumbent thigh tourniquet inflation, application of positive pressure to the lower extremities during standing, and by orthostasis after the prior administration of hydralazine.

2. Recumbent values for inulin and para-aminohippurate (PAH) clearance and filtration fraction were normal. Upon standing, a disproportionate reduction of inulin and PAH clearance occurred, filtration fraction rose, and urinary protein excretion increased significantly. The circulatory response to standing was of the same nature and magnitude as that described by others in healthy, nonproteinuric subjects.

3. Supine, thigh tourniquet inflation was associated with reduced inulin and PAH clearance but no change of filtration fraction, and upright pressure support to the lower extremities was attended by maintenance of filtration rate and a modest average reduction of PAH clearance and rise of filtration fraction. Despite filtration fraction stability during thigh tourniquet inflation and the maintenance of filtration rate during the application of lower extremity positive pressure, each of these experimental maneuvers was accompanied by proteinuria.

4. Prior treatment with hydralazine during recumbency prevented the usual average reduction of PAH clearance upon standing, and the small rise of protein excretion that occurred was much less than that observed before drug treatment.

5. As in other patients with more severe glomerular defects, this combination of findings is compatible with the proposal that a normal reduction of renal blood flow during standing is the main hemodynamic determinant of upright protein excretion in patients with fixed and reproducible orthostatic proteinuria.

ACKNOWLEDGMENTS

The authors wish to thank Mr. Robert N. Graham, A 1/c Chandler R. Monk, and Mrs. Nancy Langley for their technical assistance; Mr. Alton Rahe for his statistical aid with the albumin analyses; and Lt. Col. Wilbur L. Kenoyer for his advice and support throughout the study.

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