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Research Article

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ABSTRACT To study limb vascular responses to K^+ in man, paired intrabrachial arterial infusions of isosmolar NaCl (control) and isosmolar KCl (0.077, 0.154, and 0.307 meq K^+/min) in isosmolar NaCl were made in 20 normotensive men and 20 men with essential hypertension of mild to moderate severity. Limb blood pressures were monitored, limb blood flow was measured by indicator-dilution, and limb vascular resistance was calculated as mm Hg/ml flow/min/100 cm^3 limb volume. Measured concentrations of K^+ in limb venous plasma during infusion of 0.307 meq K^+/min ranged from 4.8 to 9.0 meq/liter. Changes in limb venous hematocrit, sodium, calcium, magnesium, and osmolality were similar during control and KCl infusions. The infusions did not significantly change systemic blood K^+ concentration or blood pressures. Compared to NaCl, KCl decreased limb resistance ($P < 0.05$) in both normotensives and hypertensives, in a dose-related manner. Resting limb vascular resistances (IR) in hypertensives were greater ($P < 0.05$) than those in normotensives. Despite a positive correlation ($P < 0.05$) between IR and magnitude of response to K^+, responses in hypertensives to K^+ were not greater than those in normotensives. Further, analysis of covariance indicated that responses to 0.307 meq K^+/min in hypertensives as a group were, in fact, less ($P = 0.02$) than those in normotensives. These results indicate that the vasodilator response to K^+ may be attenuated in a significant proportion of essential hypertensive men, as it is in renal hypertensive animals. These abnormal responses to K^+ in hypertensives may indicate an underlying defect in vascular K^+ metabolism.

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INTRODUCTION

Modest increases in the potassium concentration of plasma evoke vasodilation in several vascular beds of men and animals (1–7). This effect is probably related to the critical role played by potassium ion in the excitation processes of vascular smooth muscle cells (8). The magnitude of this K^+-induced vasodilation may be attenuated in hypertensive animals (9, 10); we have reported previously our evidence suggesting that limb vasodilator responses to K^+ in renal hypertensive dogs (9) and rats (10) are less than those in normotensive control animals. These abnormal responses in renal hypertensive animals suggest to us that there may be an underlying defect in the K^+ metabolism of vascular smooth muscle cells.

We were most interested in determining whether such abnormalities were also present in hypertensive men. Therefore, in the present study we measured limb vascular responses in normotensive and essential hypertensive men to acute increments in K^+ concentrations in limb plasma. Our findings indicate that a significant proportion of essential hypertensive men may also have attenuated vasodilator responses to the potassium ion and perhaps share an underlying vascular metabolic defect with renal hypertensives.

METHODS

We studied limb vascular responses in 40 male inpatients at the Veterans Administration Hospital, Saginaw, Mich. 20 patients had normotension documented by several normal (< 140/90 mm Hg) casual blood pressures taken during hospitalization. These normotensive patients had been hospitalized for diseases not felt to affect vascular responsive-

ness. At time of study the normotensive subjects were convalescing, afebrile, and not receiving vasoactive drugs, including digitalis preparations.

20 patients had essential hypertension of mild to moderate severity documented by thorough study which included hospital diastolic blood pressures averaging above 90 mm Hg during hospital days 4–6, normal rapid sequence intravenous pyelograms, normal 24 h urine vanilmandelic acid excretion, and normal serum sodium, potassium, and calcium concentrations. Renal angiography was performed on one patient (C. L. V.) and interpreted as indicating no abnormalities. Severity indices in hypertensives were calculated according to the criteria of the Veterans Administration Cooperative Study (11). No hypertensives had retinal hemorrhages, exudates, or papilledema. All antihypertensive or vasoactive drugs and diets were discontinued at least 4 wk before the response study (except in the case of W. E. D., whose guanethidine and hydrochlorothiazide were continued until 1 wk and 48 h, respectively, before study). Two hypertensives were receiving maintenance doses of digitoxin, but these and the other subjects had no clinically discernible cardiac insufficiency. No subjects had elevated serum creatinine or blood urea nitrogen concentrations, or significant proteinuria.

All subjects participating were fully informed by the authors of the purposes, procedures, and hazards of the experiment; written consent was obtained.

These volunteers were studied in the resting, postabsorptive state, and supine position with laboratory temperature ranging from 26 to 27°C. The procedures employed for infusions and measurement of limb intravascular pressures and calculation of blood flows by indicator-dilution have been described in detail (12, 13). Briefly, we used a jet injection system to infuse solutions intrabrachial arterially at 8.2 ml/min and at 37°C. All solutions contained indicator, approximately 0.06 μCi ^{131}I/ml (^{131}I-labeled human serum albumin in isotonic sodium chloride solution, Albumotope, E. R. Squibb & Sons, Princeton, N. J., or IHSA I 131, Mallinckrodt Chemical Works, St. Louis, Mo.). In 25 subjects an additional indicator was added to all solutions: approximately 0.05 mg indocyanine green dye/ml (Cardio-Green, contributed by Hynson, Westcott & Dunning, Inc., Baltimore, Md.). The experimental solutions also contained isosmolar (285 mosmol/liter) KCl. Control and experimental solutions were brought to volume with isosmolar NaCl solution. Infused at 8.2 ml/min, the solutions containing KCl delivered 0.077, 0.154, or 0.307 meq K^+/min to brachial arterial blood. The solutions containing KCl were always administered in order of increasing dose. The effect of each infusion of KCl was compared with "resting" hemodynamics measured during a preceding paired infusion of control solution.

During infusions, dye concentrations in ipsilateral limb venous blood were monitored in 15 normotensive and 10 hypertensive subjects by withdrawing venous blood at 2.2 ml/min through a cuvette-densitometer system (model DTL, Gilson Medical Electronics, Inc., Middleton, Wis.), as previously described (13). When a reasonably steady-state venous dye concentration was detected (8–13 min after beginning the infusion), we sampled ipsilateral cephalic and basilic venous and contralateral brachial arterial blood simultaneously. In the remaining subjects we sampled blood at the 10th and 15th min of each infusion. We calculated blood flow from the isotope concentrations of these samples. In 15 normotensive and 10 hypertensive subjects we also measured hematocrit, serum sodium and potassium concentrations, and osmolality of these samples as previously described (14). Serum calcium and magnesium concentrations were measured on a Perkin-Elmer Atomic Absorption Spectrometer (model 290, Perkin-Elmer Corp., Norwalk, Conn.). In addition we studied the effect of the control and KCl infusions on limb blood hematocrit and plasma calcium and magnesium concentrations by comparing limb output concentrations directly measured in cephalic venous serum with calculated limb input concentrations. The calculating equation for input concentrations, which adjusted limb arterial concentrations for the dilutional effect of the 8.2 ml/min infusion, has been presented (13).

During infusions, we recorded pressures in the ipsilateral cephalic and basilic veins and contralateral brachial artery. The calculating equations for limb blood flow and vascular resistance have been presented (13). Flows and resistances were expressed on a per limb volume basis. All experiments reported were considered technically satisfactory by our defined criteria (13).

Additional laboratory studies were performed on 12 hypertensive subjects. These studies included 24-h creatinine clearances in duplicate, 24 h urine Na^+ and K^+ excretion, and measurement of plasma renin activity both after 8 h recumbency and after 4 h ambulation. In all but two subjects antihypertensive therapy had been discontinued 2–4 wk before this additional testing (one subject (C. L. V.) was receiving a combination of hydrochlorothiazide, hydralazine, methyldopa, and guanethidine; one subject (W. L. E.) was receiving hydrochlorothiazide). No subject was on a sodium-restricted diet. Plasma renin activity was measured by radioimmunoassay using procedures described by Haber, Koerner, Page, Kliman, and Purode (14).

For data analysis we used the paired Student t test (15) to compare responses to control isosmolar NaCl solution with those to the paired isosmolar KCl solution, to compare responses in hypertensives with those in normotensives, to compare serum electrolyte concentrations during saline and KCl infusions, and to compare the additional measurements made in the two groups of hypertensive patients. In hypertensives and in normotensives linear correlation and regression coefficients were calculated for each dose level of KCl to determine if there were significant relationships between limb initial resistance (IR: resistance during the paired control isosmolar NaCl infusion), and magnitude of response to KCl (ΔR).[1] Homogeneity of regression coefficients was tested. Analysis of covariance was then used to compare regression-adjusted responses in hypertensives with those in normotensives.

RESULTS

Clinical data on the subjects are presented in Table I. The two groups had similar racial composition (25% blacks, 75% whites), body weights, limb volumes, blood hematocrits, and serum potassium, sodium, magnesium, and calcium concentrations. The hypertensive group was slightly but significantly older than the control group. There were highly significant differences between the mean arterial pressures of the two groups directly measured at the time of the response study. We classified hypertensive disease in two-thirds of the patients as of moderate severity and in the remainder as mild.

[1] *Abbreviations used in this paper:* IR, initial resistance; ΔR, change in resistance; PRA, plasma renin activity.

TABLE I
Clinical Data

	Normotensives	Hypertensives
Age, *yr*	42.5±2.3	49.5±1.1*
Body wt, *kg*	79.0±4.1	85.7±3.4
Limb vol, cm^3	1635±71	1720±56
$\bar{P}_A$, *mm Hg*§	91.3±1.8	126.9±3.6‡
Hct, *ml/100 ml*	45.8±0.6	46.8±0.6
Serum [K^+], *meq/liter*	4.29±0.07	4.32±0.08

Means±SEM.
P value for comparison of groups: * $P < 0.05$; ‡$P < 0.01$.
§ Mean arterial pressure measured during procedure by arterial puncture.

The intrabrachial arterial infusions altered the hematocrit and electrolyte composition of ipsilateral limb venous blood without significantly changing systemic arterial blood composition. Changes induced in limb venous blood are indicated in Table II. By dilutional effects the 8.2 ml/min control saline infusions significantly reduced limb venous hematocrit by 10.7%, potassium concentration by 11.4%, calcium concentration by 12.1%, and magnesium concentration by 16.1% ($P < 0.01$ in all cases), without changing limb venous sodium concentration and osmolality. As compared with venous concentrations during the control NaCl infusion, infusion of isosmolar KCl at 0.154 and 0.307 meq K^+/min increased mean limb venous potassium concentrations by 1.86 and 3.43 meq/liter, respectively. In contrast, limb venous hematocrit and limb serum concentrations of calcium, magnesium, sodium, and osmolality during KCl infusions did not significantly differ from those during control NaCl infusions. During NaCl or KCl infusions we detected no significant differences between venous concentrations in normotensives and hypertensives.

The hemodynamic effects of these intrabrachial arterial infusions are presented in Table III. Neither control nor experimental infusions had significant effects on systemic arterial or venous pressures in either group of subjects ($P > 0.1$). Over the course of the experiments, limb resistance measured during the control infusions did not significantly change in either group ($P > 0.2$). In contrast, infusion of 0.154 or 0.307 meq K^+/min decreased limb vascular resistance and increased limb blood flow in both hypertensive and normotensive subjects ($P < 0.001$). In hypertensives, increases in limb blood flow and decreases in vascular resistance were not significantly different from those values in normotensives ($P > 0.05$). Indocyanine green dye concentrations in ipsilateral venous blood during infusions indicated that a steady-state blood flow was usually achieved during both NaCl and KCl infusions; that the response to the KCl infusion did not tend to wane with time; that there was a steady return to, but not below, base-line flow levels during the following control infusion; and that there were no apparent qualitative differences in responses in hypertensives and normotensives. Responses in subjects in whom indocyanine green dye was used were not dissimilar from those in whom it was not used.

During KCl infusion, we often noted flushing of skin of the ipsilateral forearm and hand, and most subjects noted mild and not uncomfortable sensations in that hand, but not elsewhere in the body. They described these sensations as "warmth," "burning," "tingling," "numbness" and/or "pressure." Sensations were apparently similar in normotensives and hypertensives.

"Base-line" limb vascular resistances (during control infusions of isosmolar NaCl solution) were significantly greater ($P < 0.05$) in hypertensives than in normotensives. Because there is evidence that the magnitude of vascular response (ΔR) to K^+ is a function of the

TABLE II
Limb Venous Concentrations

	Infusion rate, *meq K^+/min*			
	0.000 (control)	0.077	0.154	0.307
[K^+], meq/liter	3.6±0.1 (22)	—	5.4±0.2 (8)*	7.0±0.3 (17)*
[Na^+], meq/liter	141.6±1.4 (22)	—	138.4±1.7 (8)	139.3±1.6 (17)
[Ca^{++}], meq/liter	3.7±0.1 (22)	—	3.9±0.1 (8)	3.7±0.1 (18)
[Mg^{++}], meq/liter	1.82±0.02 (22)	—	1.85±0.12 (8)	1.85±0.06 (18)
Hct, *ml/100 ml*	42.1±0.5 (74)	42.8±0.9 (24)	42.8±0.8 (25)	43.2±1.1 (25)

Means±SEM; number of observations indicated in parentheses.
* $P < 0.01$, for comparison of limb venous concentration during infusion of isosmolar KCl solution with that during infusion of control isosmolar NaCl solution (represented as 0.000 meq K^+/min).

TABLE III

*Limb Hemodynamic Responses to Intra-arterial Infusions**

Infusion	meq K^+/min	Limb blood flow		$\bar{P}_A$	$\bar{P}v$	Vascular resistance	ΔR	
							Unadjusted	Adjusted‖
		ml/min	*ml/min/100 cm³*	*mm Hg*	*mm Hg*		*mm Hg/ml/min/100 cm³*	
Normotensives								
Isosmolar NaCl	0.000	84.8±8.5*	5.12±0.43*	91.3±1.8*	9.6±0.5*	18.27±1.69*		
Isosmolar KCl	0.077	83.8±6.7*	5.10±0.34*	90.8±2.0*	9.6±0.9*	17.52±1.58*	−0.75±1.01*	−1.43±1.11*
Isosmolar NaCl	0.000	77.2±8.0	4.69±0.47	92.8±1.7	9.8±0.4	20.61±1.83		
Isosmolar KCl	0.154	97.6±8.5	5.99±0.48	93.6±1.7	10.6±0.4	15.73±1.38	−4.88±1.07	−7.03±0.83
Isosmolar NaCl	0.000	75.3±6.7	4.60±0.39	95.2±2.0	10.2±0.5	21.13±2.06		
Isosmolar KCl	0.307	123.3±8.2*	7.88±0.59*	96.1±2.2*	10.7±0.5*	11.96±0.97*	−9.12±1.60*	−12.83±1.24*
Hypertensives								
Isosmolar NaCl	0.000	86.5±9.6	5.01±0.55	126.9±3.6§	11.3±0.7	28.97±3.50‡		
Isosmolar KCl	0.077	96.4±10.8	5.59±0.61	126.5±3.7§	11.6±0.8‡	26.08±3.31	−2.89±1.04	−2.24±1.08
Isosmolar NaCl	0.000	82.8±10.3	4.79±0.59	127.2±4.0§	11.3±0.8	30.59±3.76‡		
Isosmolar KCl	0.154	100.3±10.0	5.83±0.57	128.5±3.9§	11.1±0.6	23.40±2.22	−7.19±1.81	−5.04±0.83
Isosmolar NaCl	0.000	74.8±7.7	4.34±0.43	127.2±3.4§	11.1±0.7	32.10±3.55‡		
Isosmolar KCl	0.307	117.1±10.7	6.82±0.58	130.2±3.7§	12.0±0.5	19.93±1.86	−12.16±2.70	−8.64±1.20‡

Values are means±SEM (of 20 measurements, unless noted * [$n = 19$]). $\bar{P}_A$ = mean brachial arterial pressure; $\bar{P}v$ = mean basilic or cephalic venous pressure.

‡ Statistically significant ($P < 0.05$).

§ Statistically highly significant ($P < 0.01$). Significance values are for comparison of variables in hypertensives with appropriate variables in normotensives.

‖ Adjusted by analysis of covariance for regression on IR.

level of limb IR (9, 10), we calculated linear correlation coefficients for IR vs. ΔR at each dose level of K^+. For infusions of 0.077, 0.154, and 0.307 meq K^+/min these correlation coefficients were 0.417 ($0.10 < P > 0.05$), 0.657 ($P < 0.01$), and 0.911 ($P < 0.01$), respectively, in normotensives and 0.325 ($P > 0.1$), 0.918 ($P < 0.01$), and 0.858 ($P < 0.01$), respectively, in hypertensives. (Combining data in normotensives and hypertensives, we found the correlation coefficient for infusion of 0.077 meq K^+/min was 0.390 [$P < 0.05$].) We also compared regression coefficients in normotensives and hypertensives at each dose level. For infusions of 0.077, 0.154, and 0.307 meq K^+/min the P values for this test were > 0.2, > 0.6, and > 0.8, respectively, indicating homogeneity.

The significant correlations between IR and magnitude of response to K^+ infusions are illustrated in Figs. 1*a*, *b*, and *c* representing response points in individual subjects to the infusions of 0.077, 0.154, and 0.307 meq K^+/min, respectively. In these figures the regression line and the 95% confidence intervals for predicted values were calculated for response points in normotensive subjects (represented by solid circles). In the cases of infusions of 0.077 and 0.154 meq K^+/min, the response points in hypertensives (open circles) fall within the confidence intervals. In contrast, in the case of infusions of 0.307 meq K^+/min, response points in 6 out of the 20 hypertensive subjects fell above the 95% confidence intervals, suggesting that responses to K^+ in at least these essential hypertensive subjects were attenuated.

Because there were significant correlations between IR and ΔR and because IR was significantly greater in hypertensives than in normotensives, we also compared responses in hypertensives and normotensives by using analysis of covariance, which adjusted responses for their regression on initial resistance. The means of these adjusted ΔR ±SEM are also presented in Table III. Analysis of covariance corroborated the impression from Fig. 1*c* that responses in hypertensives to 0.307 meq K^+/min were significantly less than those in normotensives ($P = 0.02$). If responses from the six hypertensives falling above the 95% confidence intervals were omitted, however, analysis of covariance would no longer indicate significant differences between normotensives and hypertensives at this dose level ($P > 0.05$). In addition there were no significant differences in responses at the two lesser dose levels of KCl. We used covariance analysis-adjusted means plus SEM from Table III to construct log dose-response curves for normotensives and hypertensives and found them to be linear.

The hypertensive group was older than the normotensive group. Therefore we repeated analysis of covariance omitting responses in the five youngest normotensive subjects so there was no longer a significant difference in ages. Results of this analysis were similar to the results using data from the entire group; responses

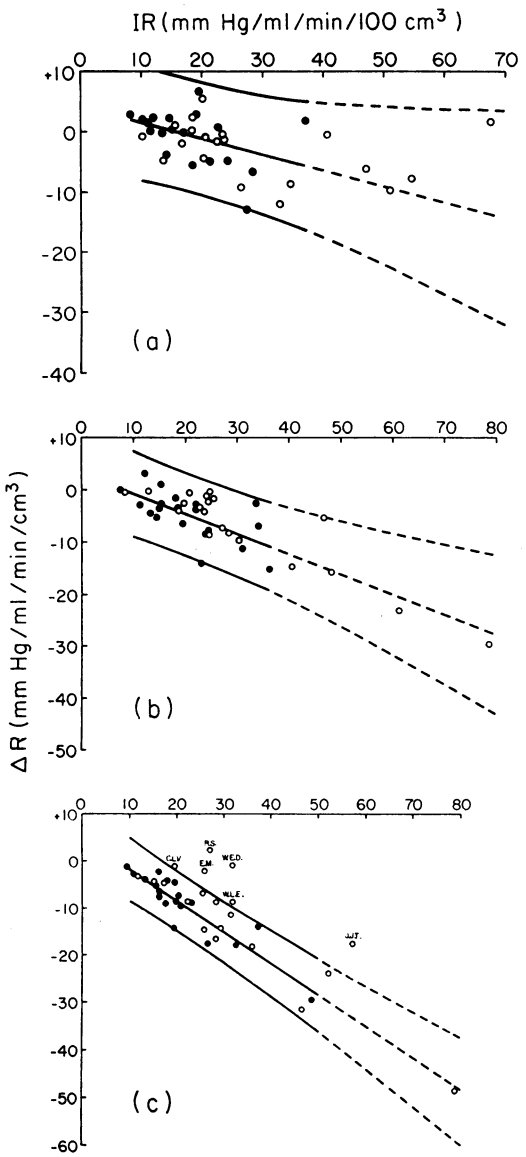

FIGURE 1 Limb vascular responses to intrabrachial arterial infusions of isosmolar KCl, 0.077 (*a*), 0.154 (*b*), and 0.307 (*c*) meq K^+/min, plotted against level of limb initial vascular resistance in individual subjects. ● and ○ indicate responses in normotensive and essential hypertensive subjects, respectively. Regression lines and 95% confidence intervals for predicted values drawn for responses in normotensives. Initials identify six hypertensive subjects.

in hypertensives to 0.307 meq K^+/min remained significantly lower ($P = 0.04$) than those in normotensives.

We performed additional studies on 12 hypertensive subjects, attempting to asses the status of renal function and plasma renin activities (PRA). Five of these were among the subjects with markedly attenuated responses to 0.307 meq K^+/min ("low" responders). Seven subjects had responses falling within the 95% confidence intervals (Fig. 1*c*) ("normal" responders). Values obtained in the two groups are presented in Table IV. Creatinine clearances, urine Na^+ and K^+ excretions, serum K^+ levels, and PRA were not significantly different in the two groups of hypertensives. Mean rise in PRA with ambulation was 284 and 222% in normal and low responders, respectively. Incidentally, the mean PRA in each group of hypertensives did not significantly differ from mean values reported for normotensives (14). Five of the six (83%) low responders and 71% of normal responders were considered to have hypertension of moderate severity.

Finally, there were no significant differences between calculated limb input and measured output (cephalic venous) hematocrits, indicating that the infusions formed a simple volume additive to brachial arterial blood, as has been reported by others in the case of saline infusions (16). In contrast, measured output concentrations of calcium and magnesium significantly exceeded ($P < 0.05$) calculated input concentrations during the control NaCl infusions. This finding confirms our previous report (13) and suggests that during the saline infusions calcium and magnesium ions move along concentration gradients from the extravascular into the intravascular space. Interestingly, we detected no similar shifts during infusion of KCl. We detected no differences between such ion shifts in hypertensives and normotensives.

DISCUSSION

The results of the present studies indicate that in man intrabrachial arterial infusions of KCl, producing modest increments in limb plasma potassium concentrations, decrease limb vascular resistance in a dose-related manner. The KCl infusions do not change limb concentrations of calcium or magnesium; hence, the decrease in limb resistance is probably not an effect of induced changes in these other vasoactive ions. Previous studies indicate that the response is to the potassium rather than to the chloride ion (3).

We attribute the observed reduction in limb resistance to vasodilation because the KCl infusions did not alter limb blood hematocrit and because there is evidence that blood viscosity is not decreased by K^+ (17).

Potassium-evoked dilation in the limb vascular bed of man has been previously reported (4, 5) and is similar to that which has been observed by many investigators in vivo and in vitro in vessels of other species (1–3, 6, 7, 18). In man the vasodilation is not attributable to release of histamine, acetylcholine, or to beta-adrenergic stimulation (4).

The infusion of K^+ at the rates we used changed neither systemic K^+ concentrations nor systemic blood pressures in our patients. Thus the vasodilation we observed is probably a local effect of potassium on the

TABLE IV

Comparison of Normal and Low Responders

Subject	Severity	Approximate duration of hypertension	Creatinine* clearance	Urine Na^+	Urine K^+	Serum K^+	PRA‡	
							Recumbent	Ambulatory
		yr	*ml/min*	*meq/24 h*	*meq/24 h*	*meq/liter*	*ng/ml/h*	
Normal responders								
J. Y.	moderate	10.0	—	—	—	4.1	0.00	0.05
M. D. S.	moderate	7.0	58.2	108	78	5.0	1.65	4.35
R. D. C.	moderate	15.0	—	—	—	4.5	0.85	3.05
A. L. M.	mild	1.0	98.9	305	89	3.9	0.65	0.50
J. A. K.	moderate	5.0	75.5	103	56	4.0	0.80	6.50
B. H.	mild	1.0	95.3	246	105	4.5	0.80	2.30
D. V. S.	mild	21.0	81.6	274	76	4.7	0.00	1.50
Mean		8.6	81.9	207	81	4.4	0.68	2.61
±SEM		±2.8	±7.3	±43	±8	±0.2	±0.22	±0.85
Low responders								
R. S.	moderate	37.0	118.8	257	34	3.7	0.00	2.35
E. M.	mild	14.0	70.2	204	64	4.9	1.75	2.70
W. L. E.	moderate	4.0	28.3	110	24	4.2	3.20	10.00
C. L. V.	moderate	9.0	76.3	197	96	4.8	1.50	5.25
J. J. T.	moderate	13.0	99.5	187	119	4.2	0.00	0.45
Mean		15.4	78.6	191	67	4.4	1.29	4.15
±SEM		±5.7	±15.3	±24	±18	±0.2	±0.60	±1.65
P§		>0.3	>0.5	>0.5	>0.5	>0.5	>0.3	>0.4

* Corrected to 1.73 m^2 body surface area.

‡ PRA measured after 8 h recumbency and then again after 4 h ambulatory.

§ *P* value for comparison of the low responders with normal responders.

limb, rather than a response to systemic effects of the ion (3, 19). It is likely that the response we observed is, at least in part, independent of local neural structures (20), because in the dog the response is not blocked by phentolamine or nerve section (3). Furthermore, the response is observed in vitro and is not blocked by tetrodotoxin (18).

There is electrophysiological evidence that the vasoactivity evoked by K^+ involves direct action on membrane phenomena in the vascular smooth muscle cells (21). In this regard it is noteworthy that the Nernst and Goldman relationships predict that elevating external K^+ concentrations would depolarize the membrane of excitable cells. Depolarization, in the case of vascular muscle, would tend to evoke contraction. Thus, as pointed out by Chen, Brace, Scott, Anderson, and Haddy (22), the K^+-induced vasodilation we have observed cannot be explained by passive ion fluxes (Nernst equation) or by an electroneutral pump (Goldman equation). Rather, modest increases in external K^+ concentrations must in some way hyperpolarize vascular cell membranes. As discussed by the Somlyos (8), the mechanism of such hyperpolarization might be induced changes in cell membrane K^+ permeability (increase) or Na^+ permeability (decrease), or, alternatively, induced hyperactivity of the cellular electrogenic pump. We favor this latter alternative, because Chen et al. (22) have observed that ouabain pretreatment attenuates, blocks, or even reverses this K^+-induced vasodilation. Thus Chen et al. proposed that modest increases in plasma K^+ concentrations evoke vasodilation by stimulating Na^+-K^+-activated ATPase enzyme systems in vascular smooth muscle, thereby driving the cellular electrogenic pump. Wolowyk, Kidwai, and Daniel (23) demonstrated that such ATPase enzyme systems are present in vascular smooth muscle.

Recalling the blocking effects of ouabain, potassium-induced vasodilation is attenuated in the limbs of renal hypertensive dogs (9) and rats (10). This K^+ abnormality in hypertensives is apparently specific, because we have found no evidence for altered responses to a number of other vasoactive cations and agents (9, 24). These observations have naturally led us to speculate that there may be an underlying defect in Na^+-K^+-ATPase enzyme systems in vascular smooth muscle in renal hypertensives (9). Such a defect could decrease the activity of the cellular electrogenic pump, tending to depolarize cell membranes, either generally, or in specific

"pacemaker" cells (25). Membrane depolarization might account for the impaired vascular relaxation and decreased stimulatory thresholds (26) in hypertension. Inhibition of the electrogenic pump might also help explain some abnormalities which have been observed in vascular wall composition in hypertensives (27).

Our present data indicate that, like renal hypertensive animals a significant proportion of essential hypertensive men also appear to have attenuated vasodilator responses to K^+. We reached this conclusion by interpreting our data in terms of the highly significant positive relationship in both normotensives and hypertensives between magnitude of response to K^+ (ΔR) and the level of IR. Considering this relationship, one would expect that hypertensives, with higher limb resistances than normotensives, would have greater vasodilator responses to K^+, as they do to other vasodilator agents (9 , 12). Our data, however, indicate that this is not the case; we found no evidence that responses to K^+ in hypertensive animals or men are greater than those in normotensives. On the contrary, if we consider the significant relationship between IR and ΔR and plot the 95% confidence intervals for responses in the control normotensive patients (Fig. 1), one-third of the hypertensive subjects actually appear to have markedly attenuated responses to the highest dose level of K^+. Our conclusion is further supported by covariance analysis which indicates that responses in the hypertensive men as a group are significantly lower than those in the normotensive men. It is noteworthy that we analyzed our data from renal hypertensive animals in a similar manner and arrived at similar conclusions (9, 10).

In using covariance analysis we have assumed that regression coefficients in the two groups were homogeneous; our data lead us to conclude that this assumption was valid. We have additional evidence that suggests that the regression of vasodilator responses on IR is independent of the source of variation in resistance (28): In the forelimbs of dogs we measured vascular responses to intrabrachial arterial infusions of methacholine while producing stepwise increases in limb initial vascular resistance by several maneuvers: hemorrhage, local nerve stimulation, and local infusion of angiotensin II. In these dogs we found that the regression of limb response on IR was homogeneous for all methods used to alter resistance.

Our finding of attenuated responses to K^+ in essential hypertensive men cannot be attributed to differences between the hypertensive and normotensive groups in age, body weight, limb volume, limb resting blood flows, blood hematocrit levels or serum concentrations of potassium, sodium, calcium, or magnesium. With one exception, the hypertensive subjects had not received therapy for 1 mo before study, so it is unlikely that differences in responses can be attributed to the effects of antihypertensive drugs. Two of the hypertensive subjects, however, were receiving digitoxin at the time of the study. Digitalis might decrease vascular Na^+-K^+-ATPase activity and thus attenuate responses to K^+. In this regard responses in one of the subjects on digitalis (R. S.) were markedly attenuated, but responses in the other subject (A. G. L.) fell well within the normal range. In view of the normal responses in A. G. L., it seems unlikely that the markedly attenuated responses in R. S. can be attributed to digitalis effect.

It is also unlikely that the attenuated responses to K^+ represented nonspecific abnormalities in vascular responses in the hypertensive patients, attributable, for example, to structural changes in the vascular bed. Regarding structural changes, arterial hypertrophy (29) should increase vascular responses to vasoactive agents in a nonspecific manner. However, we found no evidence for enhanced responses to K^+ in essential hypertensives, observing, in contrast, attenuated K^+ responses. On the other hand, reduction of numbers of arterioles in the vascular bed (30) might conceivably decrease vascular responses to vasoactive agents. We do not believe that this latter explanation accounts for our present observations, because in many of these same hypertensive men, using similar techniques, we have also studied limb vascular responses to intrabrachial arterial infusions of solutions containing magnesium (12) or calcium (31). In contrast to our findings with K^+, we found no evidence for attenuated vasodilator responses to magnesium or attenuated vasoconstrictor responses to calcium, using similar methods of analysis. Furthermore, in hypertensive dogs (9), we observed limb vascular responses to a number of vasoactive agents (K^+, Mg^{++}, Ca^{++}, methacholine, angiotensin II, and plasma hyper- or hypo-osmolality) and found the abnormality in the K^+ response to be unique.

It is possible that our patients may have had a degree of renal hypertension superimposed on their essential hypertension. Thus, these essential hypertensives might respond to K^+ similarly to renal hypertensive animals. To investigate this possibility, we performed additional studies on five hypertensive patients with markedly attenuated responses (low responders) and compared them with similar studies done on other hypertensives with responses falling within the normal range (normal responders). Although there was a trend for the low responders to have more severe hypertensive disease, longer duration of hypertension, and higher PRA, none of these differences were statistically significant, there being considerable overlap between the two groups. Mean serum K^+ concentrations in the two groups were identical, and there were no significant differences in creatinine clearance, and urine Na^+ and K^+ excretions. Furthermore, symptoms of renal disease such as nocturia

were no more prevalent in the low responders. Thus we failed to find real evidence to suggest that the low responders had any more renal dysfunction than did the other hypertensives. These results argue against the possibility that the attenuated responses in the hypertensive group as a whole are attributable to occult renal hypertension (32). Nevertheless, we do not feel that we have excluded this possibility, which requires further study.

The very fact that we identified a group of low responders and a group of normal responders within our hypertensives suggests heterogeneity of disease mechanisms. It is noteworthy that, if data from the six low responders are excluded from our statistical analyses, we are no longer able to demonstrate any significant difference between responses to K^+ in normotensives and hypertensives. Thus it is entirely possible that only certain essential hypertensives have these attenuated responses to K^+.

In another study we found no evidence for attenuation of vascular responses to K^+ in genetically hypertensive rats of the New Zealand strain (10). Genetically hypertensive rats have been considered to be the closest animal model of essential hypertension in man (33), but our findings may indicate basic differences in disease mechanisms. On the other hand, disease mechanisms in the genetically hypertensive rats may be similar to those in the essential hypertensive men we categorized as normal responders. The normal responses in genetically hypertensive rats, however, make it unlikely that the attenuated responses to K^+ we have observed in rats, dogs, and men can be attributed to the effects of the elevated intravascular pressures. Rather, it appears to us that these abnormalities may reflect causative disease processes.

Our present observations allow us to extend our hypothesis of a defect in cellular Na^+-K^+ATPase enzyme systems underlying hypertension to include a proportion of men with essential hypertension. In this regard abnormalities in vascular muscle cell electrolyte metabolism may constitute a "common denominator" in several forms of hypertension, as we suggested several years ago (34). In renal hypertension such abnormalities might conceivably be the effects of decreased excretion and therefore abnormally elevated body levels of substances which inhibit Na^+-K^+-activated ATPase, such as methylguanidine (35, 36), which, interestingly, is known to evoke vasoconstriction (37) and to elevate blood pressure (38). In essential hypertensive men such enzyme (or pump) abnormalities might be attributable to genetic-induced defects. If so, identification of such defects could lead to the development of specific therapy. In this regard it is interesting that Limas and Cohn (39) have recently reported that several antihypertensive agents, including hydralazine and diazoxide, appear to evoke vasodilation by stimulating Na^+-K^+-ATPase of vascular smooth muscle.

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