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Relationship of Sodium Retention and Induction of Hypertensive Arterial Necrosis in Rabbits[1] (41331)

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Abstract. During the first 15 days of one-kidney, one-wrapped (1K1W) hypertension in rabbits, retention of sodium occurred compared with essentially normotensive 2K1W control rabbits (1K1W, 30 ± 9 meq/15 days vs 2K1W, −6 ± 15 meq/15 days, $P < 0.02$). Most of the sodium retention occurred between the fifth and eighth days of the hypertensive period (3.7 ± 0.9 meq/day vs control period, 0.8 ± 0.9 meq/day, $P < 0.02$). Sodium retention occurred even though sodium intakes were reduced (hypertensive period, 8.7 ± 1.0 meq/day vs control period, 16.3 ± 0.9 meq/day, $P < 0.001$), serum sodium and potassium levels remained normal, and no potassium retention occurred. Positive sodium balances of individual 1K1W rabbits for the first 8 days of the hypertensive period correlated directly with the degree of arterial necrosis and with the degree of cardiac enlargement ($P < 0.05$). Change in voluntary dietary sodium intake for the entire hypertensive period correlated directly with the elevation in blood pressure (ΔBP vs ΔNa intake, $P < 0.01$). Consequently, reduction in sodium excretion due to decreased intake moderated 1K1W hypertension (ΔBP vs ΔNa Ex, $P < 0.01$) but was not related to the degree of cardiovascular disease. This study indicates that in the induction of 1K1W hypertension: (1) sodium retention occurs in a setting of reduced sodium intake; (2) development of arterial disease appears to be related to mechanisms of sodium retention; whereas (3) elevation of blood pressure occurs after sodium retention has occurred and is related to the total sodium intake and excretion.

The early and midinduction phase of single kidney, silk-and-turpentine perinephritis hypertension in rabbits, a variant of one-kidney, one-wrapped (1K1W) hypertension, is characterized by a gradual elevation in blood pressure, accompanied by widespread necrotic, proliferative arterial lesions and other features of accelerated or malignant hypertension (1–3). Previous studies have shown that the arterial disease and hypertension in this model are separable but interrelated phenomena (1, 4). The arterial disease occurs only if contralateral nephrectomy (CN) is performed during the exudative phase of unilateral perinephritis, while CN after the resolution of exudative perinephritis results in a more rapid increase in blood pressure without arterial necrosis (1, 4). Recent investigations have documented that plasma renin activity (PRA) is reduced in this model (5, 6). Immunization against angiotensin II (AII) does not reduce the elevation of blood pressure (7, 8). In this form of hypertension, responses to intravenous injections of AII are enhanced, and short-term infusions of an AII antagonist and a converting enzyme (CE) blocker do not reduce the blood pressure (6). These findings suggest that this type of experimental hypertension is not sustained by AII-mediated vasoconstriction. However, the degree of vascular disease developing in individual 1K1W rabbits is related to decreased serum CE activity and to prolongation of responses to intravenous injections of bradykinin (5, 6). Thus, components of the kallikrein–kinin system rather than components of the renin–angiotensin system may be participating in the induction of 1K1W arterial disease.

Many forms of low renin hypertension are sodium dependent (9). Our own observations have suggested that during the low renin phase of 1K1W hypertension food intake is reduced, but (i) the highest blood pressures appear to occur in 1K1W rabbits with the greatest food intake and (ii) the

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degree of arterial disease does not appear to be related to either blood pressure (5) or food intake. Consequently, we postulated that renal sodium excretion is altered during the low-renin phase of 1K1W hypertension and that the arterial necrosis may be independent of total sodium handled but related to sodium retention which occurs due to reduced renal sodium excretory capacity. The present experiment is designed specifically to address the following queries about sodium metabolism during the induction of 1K1W hypertension: (i) Can sodium retention occur in a setting of reduced sodium intake? (ii) Is the development of arterial necrosis related to mechanisms of sodium retention? and (iii) Is blood pressure elevation related to sodium intake and/or excretion? Accordingly, a detailed study of continuous sodium balance, monitored daily, was conducted through a control period (steady state), after both renal manipulations and into the mid induction phase of 1K1W hypertension. Since chronic treatment with the CE blocker teprotide lowers blood pressure in this model without altering the degree of arterial disease (5, 6), a group of teprotide-treated rabbits was included in the study. If arterial disease is related to sodium retention and not to the degree of elevation of blood pressure, then sodium retention of treated and untreated 1K1W rabbits should be similar.

Materials and Methods. *Surgical preparations.* Young male, New Zealand white rabbits (Charles Gilreath, Monroe, Ga.), 3.0 to 4.0 kg, were anesthetized with sodium pentobarbitol supplemented with lidocaine locally. Left silk-and-turpentine perinephritis (PN) was produced as previously described (1, 10). Seven days later, a right nephrectomy (RN) produced the 1K1W preparation or a sham, when the right kidney was exposed and replaced, produced a 2K1W control preparation. A third preparation was produced by performing only right nephrectomy (RN-only).

Experimental design. These experiments utilized a matched-set design of nine untreated 1K1W preparations, nine teprotide-treated (SQ, 20,881, Beckman Instruments, Palo Alto, Calif.; 1 mg/kg im, t.i.d.) 1K1W preparations (1K1W-T) (6), and seven 2K1W preparations. The five RN-only rabbits were done as a separate experiment. Rabbits surviving the entire experiment, i.e., 15 days after RN, were as follows: nine 1K1W, eight 1K1W-T (one teprotide-treated rabbit died 8 days after RN), seven 2K1W, and five RN-only preparations.

The rabbits were maintained in our laboratory until they appeared to be acclimated and in a consistent state of food intake. Daily metabolism studies were then initiated 4 days prior to the first surgical procedure to obtain an estimate of "steady state" sodium, potassium, and fluid balances and were continued during the 22 days of the experiment, i.e., for 26 consecutive days.

At the end of the experiment, the remaining kidney(s) was(were) surgically removed and the rabbits were killed by exsanguination under pentobarbitol anesthesia. The hearts and decapsulated kidneys were weighed. The cardiac and kidney indices were determined by dividing the respective organ weights by the weight of the carcass, as previously defined (1). The degree of hypertension-associated arterial disease was determined by a standard microscopic examination of hematoxylin and eosin-stained slides prepared from selected tissues fixed in 10% imidazole-buffered formalin, pH 7.4, as previously described (1, 2, 5).

Blood pressure. Indirect blood pressures were monitored daily on the central ear artery using a modification of the Grant–Rothchild capsule in a fashion that gives an approximation of the diastolic blood pressure (6, 11, 12). In addition, direct blood pressures were obtained on unanesthetized rabbits retained upright in rabbit restrainers (Plas-Lab, Lansing, Mich.) by cannulation of a central ear artery in the control period and on the final day of the experiment (Statham pressure transducer P23Dc, Grass Model 5 polygraph). Blood pressure measurements were obtained after at least 10 min of observation in a quiet room, when blood pressure had stabilized, and are the mean of a further 5-min observation.

Sodium, potassium, and fluid balances. Rabbits were placed in metabolism cages

and were maintained on standard Purina Rabbit Chow (approximately 0.32% (0.14 meq/g) sodium and 1.51% (0.39 meq/g) potassium, percentage ash) and tap water *ad libitum*. Daily intake of food was measured. The 24-hr urine volume was monitored. The 24-hr feces collection was dried at 150°C for 24 hr and then weighed. Food or feces were ground in a Waring blender to a homogenous powder. A 2-g sample was wet ashed with 4 ml of 1:1 mixture of concentrated HNO_3 and concentrated H_2SO_4 for 30 min and appropriately diluted. Sodium and potassium concentrations were determined using a flame photometer (Beckman Klina Flame). Daily sodium and potassium balances were calculated from daily intake, urinary and fecal excretions. Since metabolic studies in rabbits may suffer from losses, especially of excretory material, the quality of the data we obtained was evaluated by comparing mean daily intakes and excretions of sodium for 3- or 4-day periods for the 1K1W group. A direct, linear relationship was found ($r_{33} = 0.822$, $P < 0.001$).

Serum sodium and potassium concentrations were determined by flame photometery in the control period, at RN and in 4-day intervals thereafter.

Statistical analyses. Grouped data were analyzed using paired or, where appropriate, unpaired Student's *t* tests. Curve fitting was calculated by the method of least squares. A value of $P < 0.05$ was considered significant. Results were expressed as mean ± standard error (M ± SEM).

Results. *Blood pressure.* Control direct diastolic blood pressure was 67 ± 2 mm Hg. Hypertension developed in both groups of 1K1W rabbits (Table 1). Final mean direct diastolic blood pressure on the 15th day after RN in the untreated 1K1W group was significantly increased ($P < 0.05$ vs control). Hypertension was moderated in the teprotide-treated group ($P < 0.05$ vs untreated 1K1W; $P < 0.05$ vs control). On the other hand, final mean direct diastolic blood pressure of the 2K1W group was only slightly but significantly elevated ($P < 0.05$ vs control).

Cardiovascular disease. Cardiac enlargement. Cardiac indices were increased

TABLE I. FINAL DIASTOLIC BLOOD PRESSURES, TOTAL ELECTROLYTE BALANCES FOR EXPERIMENTAL PERIOD, AND ANATOMICAL FINDINGS

Experimental group	Final diastolic blood pressure, direct (mm Hg)	Cumulative balance for experimental (hypertensive) period, Days 1–15 after second operation, meq/15 days		Change in body weight (g) final control	Left kidney weight (g)	Left kidney index ($\times 10^3$)	Cardiac index ($\times 10^3$)	Arterial lesions
		Sodium[a]	Potassium[b]					
1K1W	112 ± 4*	30.4 ± 8.8‡§	−21.7 ± 12.1	−400 ± 70*‡§	11.7 ± 0.5‡	4.9 ± 0.3‡	4.8 ± 0.3‡§	168 ± 43‡§
1K1W-T	98 ± 6*†	32.9 ± 8.2‡§	−37.4 ± 19.7	−490 ± 120*‡§	11.8 ± 0.8	5.1 ± 0.3‡	4.4 ± 0.2§	190 ± 55‡§
2K1W	80 ± 3*†	−5.5 ± 14.6	−54.4 ± 35.9	−140 ± 40*	9.4 ± 0.8	3.7 ± 0.3	3.8 ± 0.2§	0
RN-only	70 ± 1†	−7.8 ± 12.4	2.4 ± 24.5	−130 ± 70	12.0 ± 1.4	4.5 ± 0.4	3.1 ± 0.1	0

Note. Abbreviations as in text. Control blood pressure 67 ± 2 mm Hg.

[a] Note that cumulative sodium retention occurred in both 1K1W groups during a period of considerable weight loss, i.e., about 13% from control.

[b] No significant cumulative retention or loss of potassium occurred in any group.

* $P < 0.05$ relative to control value.

† $P < 0.05$ relative to 1K1W value.

‡ $P < 0.05$ relative to 2K1W value.

§ $P < 0.05$ relative to RN-only value.

in both 1K1W groups; $P < 0.05$ vs the RN-only group. The cardiac indices of the 2K1W group were also increased ($P < 0.05$ vs the RN-only group) but to a lesser degree than those of 1K1W groups ($P < 0.05$). Notably, cardiac indices in the 1K1W rabbits did not correlate with either final direct blood pressure or changes in blood pressure, but correlated directly with the number of arterial lesions developing in all 1K1W rabbits ($r_{14} = 0.579, P < 0.02$; linear).

Necrotic proliferative arterial disease. This occurred in both treated and untreated 1K1W rabbits. The mean number of arterial lesions in all 1K1W rabbits was 180 ± 37, and no difference was noted between the two 1K1W groups (Table I). No arterial lesions developed in the 2K1W or RN-only rabbits.

Sodium and potassium balance. Intake, output, and balances of sodium and potassium were essentially the same (Table I) in the treated and untreated 1K1W groups; the data were, therefore, presented together (Fig. 1). Daily sodium studies for the control period ("steady state") and the experimental (hypertensive) period are shown as means of 3- and 4-day intervals. The data for the 2K1W control group are similarly shown. During the 7-day period between the renal manipulations sodium intake and excretion decreased markedly but returned to "steady state" levels prior to the second surgical procedure, and no significant retention or loss of sodium occurred. Changes in sodium intake, output, and balance after the second surgical procedure are discussed below. Changes in intakes and outputs of potassium closely paralleled those for sodium, however, no significant retention or loss of potassium was noted (Table I). Although all groups of rabbits that underwent kidney wrapping showed in the experimental period mean cumulative losses of potassium which probably in part reflect their weight loss, their potassium balances were not significantly different from the RN-only group. Therefore, increase in blood pressure that occurred in rabbits with wrapped kidneys cannot be attributed to a cumulative loss of potassium.

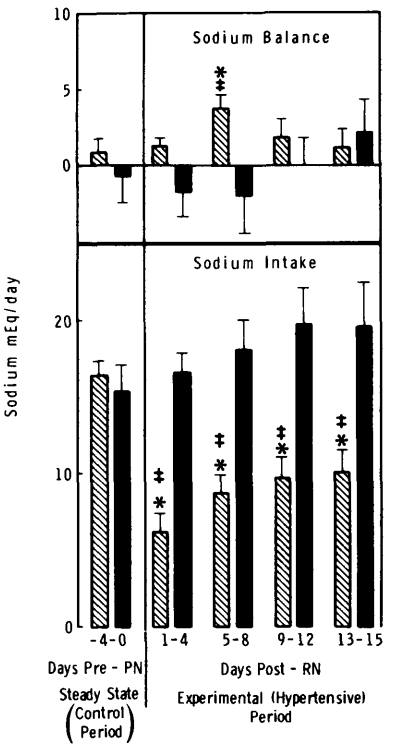

FIG. 1. Sodium balances (upper panel) and sodium intakes (lower panel) for all 1K1W hypertensive rabbits (hatched bars) and 2K1W control rabbits (solid bars). Mean daily sodium outputs are intakes minus balances. The hypertensive 1K1W rabbits showed significant sodium retention (positive balance) between days 5 and 8 post-RN while sodium intake was significantly reduced. In contrast, the control 2K1W rabbits did not show significant sodium retention even though sodium intake was at "steady state" levels and significantly greater than that of the 1K1W group. *$P < 0.05$ relative to control ("steady state") period; ‡ $P < 0.05$ relative to 2K1W control rabbits.

From these studies the following were documented in 1K1W hypertensive rabbits:

1. Sodium retention occurs in a setting of reduced sodium intake. Reductions in intake and output of sodium (Fig. 1) and potassium occurred in the period of development of the hypertension after RN. In fact, sodium intake for the entire 15-day hypertensive period was less than control (8.7 ± 1.0 meq/day vs 16.3 ± 0.9 meq/day, $P < 0.001$). In this period of reduced sodium intake, retention of sodium oc-

curred (Table I) principally in the 4- to 8-day period after RN (Fig. 1). Sodium retention occurred while serum sodium and potassium levels were normal (Na:138 ± 2 meq/liter, Day 4 after RN vs 138 ± 2 meq/liter, control) (K:4.6 ± 0.2 meq/liter, Day 4 after RN vs 4.8 ± 0.2 meq/liter, control). There was no potassium retention depsite significant weight loss (Table I). In contrast following sham nephrectomy in 2K1W rabbits, no change in intake, output, or retention of sodium (Fig. 1) or potassium was noted. Thus, reduction in *ad libitum* dietary sodium intake did not obviate sodium retention during the early phase of 1K1W hypertension.

2. *Cardiovascular disease is related to sodium retention.* During the early phase of 1K1W hypertension (Days 5–8 after RN) when most of the sodium retention occurred, the sodium balances of individual 1K1W rabbits correlated directly (r_{15} = 0.539, $P < 0.05$) with the number of arterial lesions induced. This relationship was also significant for the entire early phase of the experiment (Days 1–8 after RN) (Fig. 2a). A similar relationship between cardiac enlargement and sodium balance (r_{15} = 0.553, $P < 0.05$) was also apparent at this time. Thus, those 1K1W rabbits which retained the most sodium developed the greatest degree of cardiovascular disease.

3. *Blood pressure elevation is related to sodium intake and excretion.* In the midinduction phase (Days 9–15 after RN) of 1K1W hypertension, after most of the sodium retention had already occurred, the degree of elevation of blood pressure correlated directly with the change in sodium intake from control (r_{14} = 0.623, $P < 0.01$) and with the change in sodium excretion from control (Fig. 3). In addition, sodium retention of individual rabbits correlated inversely with the final direct blood pressure (Fig. 2b) and those rabbits which retained less sodium in the midinduction phase became more hypertensive.

Left kidney weight and left kidney indices of the 1K1W rabbits were significantly greater than those of 2K1W rabbits (Table I). The weight of the enlarged wrapped kidneys of the 1K1W and 1K1W-T rabbits and the mean daily urine volume on the final three experimental days correlated directly with the final direct diastolic blood pressures (r_{14} = 0.528, $P < 0.05$ and r_{14} = 0.703, $P < 0.005$, respectively). Thus, 1K1W rabbits with the largest kidneys and the greatest excretion of sodium and fluid developed the highest blood pressure.

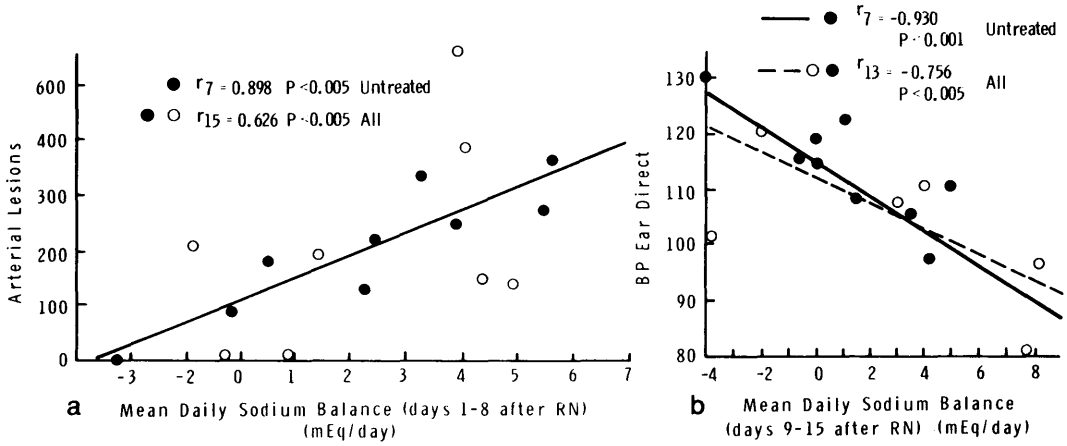

FIG. 2. (a) Relationship of mean daily sodium balances in the early induction phase of 1K1W hypertension to the number of arterial lesions found at autopsy (left panel). Arterial lesions also correlated with cardiac indices (see text). (b) Relationship of mean daily sodium balances in the midinduction phase of 1K1W hypertension to final direct blood pressures obtained in the central ear artery (right panel).

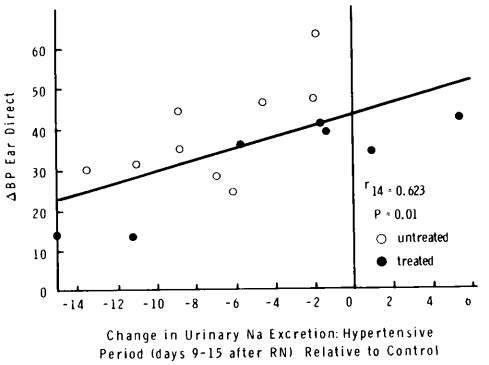

FIG. 3. Relationship of change of urinary sodium excretion from control to change in blood pressure from control.

Discussion. The principal findings of this study are (i) that sodium retention occurred early in acute 1K1W hypertension and (ii) that the degree of sodium retention during the early induction phase, i.e., the first 8 days, correlated directly with both the number of arterial lesions and the degree of cardiac enlargement that occurred. Sodium retention occurred despite a marked reduction of both sodium intake and body weight, while serum sodium and potassium levels remained normal. During the period of sodium retention, potassium retention did not occur. We infer from the findings that retention of sodium is due to loss of renal excretory capacity. Consequently, sodium retention appears to be an essential feature of the pathogenic mechanism that induces cardiovascular disease in this model of renal hypertension.

A concept that vascular sodium metabolism plays an essential role in the genesis of hypertension-associated cardiovascular alterations is supported by other studies that have shown (i) increased sodium and water content in rabbit aortic explants cultured in media supplemented with serum from 1K1W dogs (13); (ii) depressed function of the ouabain-sensitive sodium–potassium pump in blood vessels from 1K1W dogs (14); and (iii) increased water and sodium content in the femoral veins of 1K1W dogs (15). The present study extends these findings by showing a direct relationship between sodium retention and the induction of malignant 1K1W cardiovascular disease.

Sodium retention has also been demonstrated in high-renin forms of experimental one-kidney hypertension. In two of four dogs with thoracic vena caval constriction in which one-kidney, one-clipped hypertension was subsequently induced, marked sodium retention and ascites formation accompanied the development of malignant hypertension (16).

The data shown here also extend that obtained from other models of experimental hypertension where retention of sodium precedes the development of malignant hypertension which usually occurs in a period of natriuresis. Arterial and arteriolar disease occur in rats with marked DOCA-salt hypertension where sodium and water retention precedes the development of malignant arterial disease which is accompanied by negative sodium balance, decreased body weight, decreased blood pressure, and hemoconcentration (17). In the two-kidney, one-clip model of Goldblatt hypertension in rats natriuresis, fluid loss and hemoconcentration developed about the same time that vascular lesions of malignant hypertensions appeared in the unclipped kidney. It was postulated that an increase in blood pressure resulted in salt and water losses triggering the onset of the malignant phase (18). In our study, the use of a matched 1K1W and 2K1W experimental design has permitted the demonstration that transient retention of sodium in the early phase of this cardiovascular disease is related to the degrees of arterial necrosis and of cardiac enlargement which subsequently develop.

An additional important finding of the present study pertains to sodium handling in the midinduction phase, i.e., Days 9 to 15, after most of the sodium retention has already occurred and most of the arterial necrosis has already been induced. At this time, sustained elevations of blood pressure were first manifested. Changes in both sodium intake and excretion correlated in a direct linear fashion with increases in blood pressure. The weight of the wrapped kidney and the volume of urine in the 3-day period prior to sacrifice also correlated directly

with the final blood pressure levels. Thus, those rabbits with the highest blood pressures had the highest sodium intakes, excreted the largest portion of their dietary sodium and developed the greatest renal enlargement. These findings suggest that moderate reductions in sodium intake will reduce blood pressure elevation and are consistent with the concept that pressure natriuresis and renal hypertrophy are mechanisms by which sodium retention is moderated in 1K1W rabbits. Tobian (19) has suggested that a similar mechanism occurs in several forms of experimental and spontaneous hypertension where the kidney retains sodium and water until "escape" begins. At this point, no further sodium and water are retained, but the general level of body sodium and water is slightly elevated. Over a long period of time this produces hypertension in the susceptible animal.

Chronic treatment with the CE blocker teprotide after the production of PN and through the induction phase significantly reduced the degree of 1K1W hypertension that developed. However, no appreciable differences in either the intake, excretion, or balance of sodium or potassium relative to untreated hypertensive rabbits were noted. Chronic treatment with CE blockers moderates other forms of normal to low renin or volume-expanded hypertension without affecting sodium metabolism (20–25). For example, the moderation of hypertension in spontaneously hypertensive rats (SHRs) and rats with angiotensin-salt hypertension is not associated with diuresis, natriuresis, or kaliuresis (20, 21, 24). The CE blocker captropril does not moderate hypertension in SHRs after bilateral nephrectomy (20, 25) or in rabbits with renoprival hypertension (23). A complex mechanism, possibly mediated by the kidney, has been postulated to result in the antihypertensive effect of CE blockers in those forms of renin-suppressed and/or volume-expanded hypertension where natriuresis and diuresis are not induced by CE blockade (23, 24, 26).

Finally, while reduction in total sodium handled appeared to reduce the blood pressure elevations occurring in acute 1K1W hypertension, reductions in dietary sodium intake within the ranges occurring in these experiments did not show a clear tendency to moderate the amount of vascular disease. Nevertheless, two of three rabbits that developed little or no arterial disease had "unphysiologically" low sodium intakes. Clearly, the hypothesis that restriction of sodium intake may reduce the arterial disease and produce a renin-mediated acute 1K1W hypertension as seen in one-kidney, one-clipped hypertension in sodium-depleted rats (27) must be tested.

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