Evidence for Heritability of Non-modulating Essential Hypertension

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We have previously described a subset of subjects with essential hypertension who fail to appropriately modulate renal vascular and adrenal reactivity with changes in dietary sodium and in response to infused angiotensin II (Ang II). In this paper, we studied these responses in 13 unselected hypertensive subjects in whom the family history of hypertension had been carefully detailed. Nine of these 13 subjects had a positive family history (FH^+) for hypertension and had significantly smaller decrements in renal blood flow with Ang II infusion than the four subjects who had a negative family history (FH^-) (-84 ± 16 ml/min/1.73 m^2 for FH^+ vs. -149 ml/min/1.73 m^2 for FH^-, $p=0.024$). These FH^+ subjects also showed smaller increases in renal blood flow with increases in dietary sodium than FH^- subjects (7 ± 10 ml/min/1.73 m^2 vs. 72 ± 24 ml/min/1.73 m^2, respectively; $p=0.014$). When classified as modulators or non-modulators by previously established criteria, all seven non-modulators were FH^+, and seven of nine FH^+ subjects were non-modulators. This association between non-modulation and family history of hypertension is significant ($p=0.021$). To further clarify the association between non-modulation and family history of hypertension, we have studied the renal blood flow response to Ang II in 31 hypertensive siblings from 14 sibships. Twenty-five of these 31 subjects (81%) behaved as non-modulators ($p=0.008$ compared with expected value in an unselected hypertensive population). Additionally, strong concordance of non-modulation between sibling pairs was observed ($p=0.004$). These findings indicate that a high proportion of FH^+ subjects are non-modulators and that non-modulation shows familial aggregation. These observations together strongly suggest that non-modulation is a heritable trait. Furthermore, the high prevalence of non-modulation in FH^+ subjects further suggests that this trait may be one of the most important heritable factors in essential hypertension. (*Hypertension* 1989;13:884–889)

Despite enormous effort, the primary abnormalities responsible for essential hypertension remain unknown. Given the panoply of regulatory systems that are activated with alterations in blood pressure, it is not surprising that a host of physiological abnormalities have been described in hypertensive patients. Which, if any, of these abnormalities is primary is difficult, if not impossible, to determine from purely physiological analysis. In contrast, identification of an altered gene or gene product that precisely cosegregates with hypertension or a physiological abnormality that causes hypertension in hypertensive kindreds would clearly establish this altered gene as primary. Once identified, one could then determine how this genetic alteration changes normal physiology to produce hypertension.

Such an approach presumes that hypertension is at least in part a heritable trait. Studies of the variation in blood pressure both within large populations[1–6] and between monozygotic versus dizygotic twins[7] have clearly established that a large proportion of phenotypic variation in blood pressure is genetically determined. The nature of these blood pressure–determining genes, however, has remained elusive. This is largely a consequence of the polygenic inheritance of this variability in blood pressure,[3–6] which prevents the use of blood pressure alone as a true genetic marker and also prevents the presumption of any degree of homogeneity in the inherited abnormalities in hypertensive individuals.

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Consequently, identifying the genes responsible for hypertension will require identification of discrete physiological characteristics in hypertensive patients that are causal to the development of hypertension and inherited as single genes.

Over the last several years, we have identified a number of related abnormalities in a subset of patients with essential hypertension.[8–16] These patients are a subgroup of hypertensive patients with normal or elevated plasma renin activity and comprise roughly 44% of the more than 350 patients with essential hypertension we have studied. These patients are unique in that, unlike normal individuals or other hypertensive patients, they fail to appropriately modulate adrenal and renal vascular responsiveness to angiotensin II (Ang II) on low and high salt diets. The hallmarks of these patients, who we refer to as non-modulators, include the failure to appropriately increase renal blood flow with increases in dietary sodium and the failure to appropriately decrease renal blood flow in response to infused Ang II while on high sodium diet. These abnormalities are not fixed lesions, a consequence of longstanding hypertension, since 1) they are present in patients under age 30 who have only recently developed hypertension[9] and 2) these abnormalities are reversible by converting enzyme inhibitors.[11,12] These findings have led us to suggest that these related abnormalities could be primary and contribute to the pathogenesis of hypertension. We have previously shown that non-modulators show diminished sodium clearance and greater volume expansion on high sodium diets than modulators[16]; additionally, we have speculated that the blunted aldosterone response on low salt diets seen in non-modulators could result in inappropriately high Ang II levels and increased vascular tone.[13]

Several lines of evidence suggest that non-modulation may be heritable. First, the abnormalities were initially observed in patients eating defined diets on a metabolic ward; therefore, many potential environmental variables were eliminated. Secondly, we have observed several characteristics of the non-modulator phenotype in young normotensive offspring of hypertensive individuals.[15]

If non-modulation is indeed heritable and contributes substantially to the pathogenesis of hypertension in affected individuals, we would expect the following to be true: 1) Non-modulators should predominantly have positive family histories (FH^+) of hypertension and should infrequently have negative family histories (FH^-) of hypertension. 2) Hypertensive siblings of non-modulators should predominantly be non-modulators (i.e., non-modulation should show familial aggregation). Finally, if non-modulation is heritable and contributes substantially to the pathogenesis of hypertension in the general hypertensive population, a high proportion of hypertensive individuals who are FH^+ should be non-modulators.

In this study we demonstrate that 1) non-modulators are predominately FH^+ for hypertension, 2) hypertensive individuals who are FH^+ are predominantly non-modulators, and 3) non-modulation shows familial aggregation. These findings support the hypothesis that non-modulation is heritable and contributes substantially to the heritable variability in blood pressure.

Patients and Methods

Patient Populations

Patients were studied at the General Clinical Research Center (GCRC) at either Brigham and Women's Hospital in Boston, or the University of Utah in Salt Lake City. In Boston, hypertensive subjects were defined as FH^+ if they had at least one sibling or parent who developed essential hypertension before age 60. To avoid bias, the family history was in all cases obtained after completion of the study by individuals who were unaware of study results. In Utah, hypertensive subjects were selected for having a positive family history of hypertension, which was defined as having at least one sibling who developed hypertension before age 60. Subjects were defined as FH^- if there was no hypertension in either parent or any sibling before age 60. In all cases, histories were confirmed by direct examination of family members or by obtaining records from the subject's physician.

All subjects taking antihypertensive medications discontinued them at least 3 weeks before study. In Boston, subjects were studied on isocaloric, isovolumic low sodium (10 meq/day) and high sodium (200 meq/day) diets administered as inpatients at the GCRC as described previously.[9] In Salt Lake City, subjects were prescribed diets designed to approximate 200 meq Na^+/day for 3 days before study. They were then admitted to the GCRC overnight. In all subjects, sodium excretion was assessed by 24-hour urine collection obtained the day before study. All subjects were studied at 8:00 AM while recumbent after an overnight fast. Renal blood flow was determined by *p*-aminohippuric acid infusion, both before (−10 minutes and at start of Ang II infusion) and during Ang II infusion at 3 ng/kg/min (measured after a 45-minute infusion) as described previously.[9] In previous studies normotensive control subjects and modulating hypertensive subjects have shown decrements in renal blood flow greater than 120 ml/min/1.73 m^2 in response to a 3 ng Ang II infusion.[9] We have defined non-modulation in the present study as a decrement less than 120 ml/min/1.73 m^2 in response to the 3 ng Ang II infusion.

Statistical analysis included use of *t* test and χ^2 analysis where appropriate.

Research protocols were approved by the human subjects committees at both institutions. All subjects provided informed consent before enrollment into the study.

Results

Association Between Non-modulation and a Positive Family History for Hypertension

In our prior studies,[8–16] we have shown that non-modulators have smaller decrements in renal

TABLE 1. Clinical and Study Parameters of Subjects With Positive Family History and Negative Family History for Hypertension

Variable	FH^+ (n=9)	FH^- (n=4)	p
Age (yr)	56±2.3	52±6.6	0.46
Male:female	8:1	3:1	1.0
Weight (kg)	84±5	78±7	0.32
Duration of hypertension (yrs)	12.3±3.5	14±4.0	0.70
Systolic blood pressure (mm Hg)	148±6	138±4	0.34
Diastolic blood pressure (mm Hg)	93±4	93±5	0.91
Creatinine clearance (ml/min)	109±12	120±19	0.64
U_{Na} (10 meq Na diet)	22.1±11	15±1	0.59
U_{Na} (200 meq Na diet)	176±30	183±21	0.87
Basal RBF 10 meq Na diet (ml/min/1.73 m^2)	441±27	459±41	0.73
Basal RBF 200 meq Na diet (ml/min/1.73 m^2)	448±38	530±34	0.21
ΔRBF with change in diet (ml/min/1.73 m^2)	7.3±10.3	71.5±23.8	0.014*
ΔRBF with Ang II infusion (ml/min/1.73 m^2)	−84±16	−149±10	0.024*

Values are mean±SEM. All measurements were obtained during admission to the General Clinical Research Center. FH^+, positive family history for hypertension; FH^-, negative family history for hypertension; U_{Na}, 24-hour urinary sodium; RBF, renal blood flow; ΔRBF, change in renal blood flow; Ang II, angiotensin II.
*$p<0.05$.

blood flow in response to Ang II while on high salt diets and have smaller increases in renal blood flow when changed from low to high salt diets. In Boston we studied 13 hypertensive subjects without prior knowledge of their family histories; nine subjects were FH^+, and four subjects were FH^-. Table 1 shows that these two groups were similar with respect to age, gender, blood pressure, duration of hypertension, and sodium excretion. Despite these similarities, there were significant differences between these two groups with respect to change in renal blood flow in response to Ang II on high sodium diet (Figure 1; FH^+ −84±16 ml/min/1.73 m^2, FH^- −149±10 ml/min/1.73 m^2; p=0.024). Furthermore, the mean response to Ang II in FH^+ subjects was virtually identical to that previously determined for non-modulators[9] (−84±16 vs. −84±11). Seven of nine FH^+ subjects were classified as non-modulators by their renal blood flow response to Ang II while none of the four FH^- subjects were classified as non-modulators. Conversely, seven of seven non-modulators were FH^+ whereas only two of six modulators were FH^+ (Figure 1). This association between family history and non-modulation is significant (p=0.021 by Fisher's exact test).

Similarly, the change in renal blood flow on shifting from low to high salt diet was significantly different in the two groups (p=0.014; Table 1). Eight of nine FH^+ subjects had less than 30 cc increases in renal blood flow, a characteristic of non-modulation. In contrast, all four FH^- patients had increases of more than 30 cc. The frequency distribution of responses in FH^+ and FH^- subjects is again highly similar to that seen in patients sorted according to their renal blood flow response to Ang II (Figure 2).

These studies establish that the response of renal blood flow to either changes in dietary sodium or exogenous Ang II is strongly influenced by the presence of a family history of hypertension.

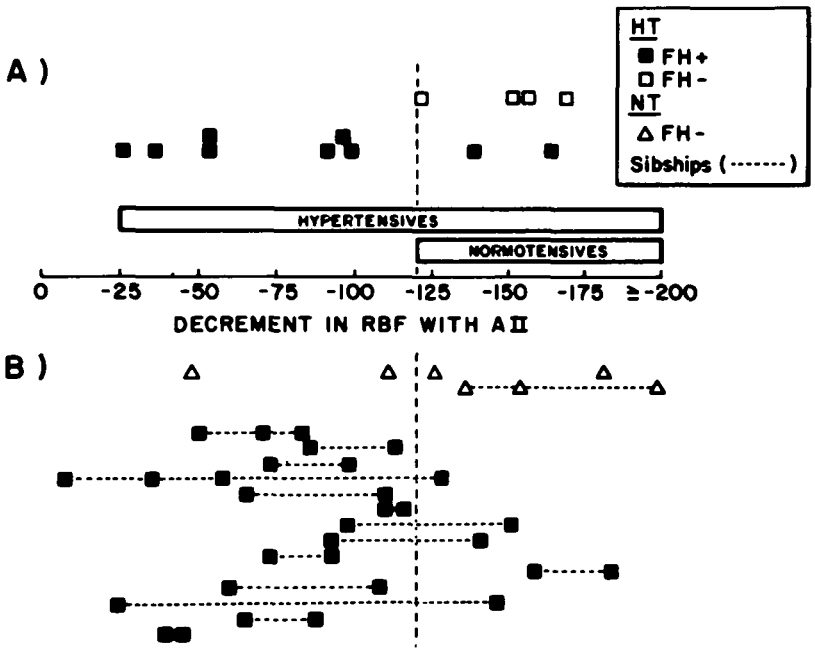

FIGURE 1. *Data summary of renal blood flow (RBF) response to angiotensin II (A II) in subjects with positive family history (FH^+) and negative family history (FH^-) for hypertension. Change in renal blood flow (ml/min/1.73 m^2) in response to A II infusion (3 ng/kg/min) in individual subjects on high sodium diets is shown. Range of responses of normotensive (NT) individuals and unselected hypertensive (HT) individuals[9] is shown for comparison.* Panel A, *subjects studied in Boston.* Panel B, *subjects studied in Utah. Subjects connected by dotted lines are siblings.*

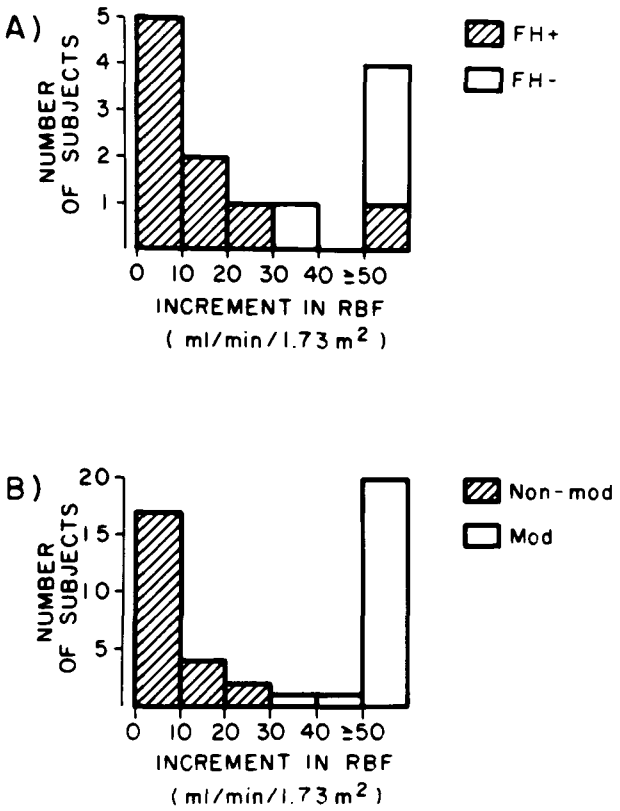

FIGURE 2. *Graphs showing frequency distribution of the change in renal blood flow (RBF) with change in dietary sodium in subjects with positive family history (FH^+) and negative family history (FH^-) for hypertension.* Panel A, *change in basal RBF (ml/min/1.73 m²) with shift in dietary sodium from 10 to 200 meq/day is shown for FH^+ and FH^- subjects.* Panel B, *change in RBF with shift in dietary sodium is shown for an unselected hypertensive population. Individuals have been classified as modulators (Mod) or non-modulators (Non-mod) based on their RBF response to angiotensin II. (Adapted from data in Reference 16).*

Familial Aggregation of Non-modulation

To determine whether non-modulation is prevalent and shows familial aggregation in hypertensive siblings, we studied a group of normotensive FH^- subjects and demonstrated that the renal blood flow response to Ang II in Utah in normal subjects was comparable with the response seen in normal subjects in Boston (−137±19 ml/min/1.73 m² vs. −174±11 ml/min/1.73 m², respectively; $p=0.13$; Figure 1). We then studied the renal blood flow response to Ang II in 31 hypertensive subjects in 14 sibships. The baseline clinical characteristics of these subjects were similar to those of the Boston subjects (Table 2). The mean blood pressures of these hypertensive subjects on admission to the GCRC were relatively low, probably reflecting recent discontinuation of antihypertensive medications. The hypertensive FH^+ subjects again showed a significantly smaller decrement in renal blood flow than control subjects (mean −90±7 ml/min/1.73 m² for FH^+, mean −137±19 ml/min/1.73 m² for FH^-, $p=0.013$).

TABLE 2. **Clinical and Study Parameters of Hypertensive Siblings**

Variable	Mean±SEM ($n=31$)
Age (yr)	47±1
Male:female	19:12
Weight (kg)	88±3
Duration of hypertension (yr)	6±1
Systolic blood pressure (mm Hg)	136±2
Diastolic blood presure (mm Hg)	86±2
Serum creatinine (mg/dl)	0.94±0.04
U_{Na} 200 meq diet (meq/day)	216±14
Basal RBF (ml/min/1.73 m²)	480±16
ΔRBF Ang II (ml/min/1.73 m²)	−90±7

Measurements were obtained during admission to the General Clinical Research Center. U_{Na}, urinary sodium; RBF, renal blood flow; ΔRBF, change in RBF; Ang II, angiotensin II.

Furthermore, the mean response to Ang II for these FH^+ subjects was indistinguishable from that for the FH^+ patients studied in Boston (−90±7 vs. −84±12, $p=0.67$).

Twenty-five of 31 of these FH^+ subjects (81%) behaved as non-modulators; this percentage was far greater than the expected 44% of the general hypertensive population ($p=0.008$). Furthermore, there is familial aggregation of non-modulation, manifest in the high concordance of non-modulation in hypertensive sibling pairs. Hypertensive sibling pairs are far more likely to both be non-modulators and far less likely to both be modulators than would be expected from the frequency of non-modulation (44%) in the general hypertensive population (Table 3, $p=0.004$).

These findings thus confirm that selecting hypertensive subjects who are FH^+ preferentially selects for non-modulators and indicates strong familial aggregation of non-modulation.

Discussion

We have shown that the renal blood flow response to Ang II and to changes in sodium intake are markedly different between individuals who are FH^+ and FH^- for hypertension. Individuals who are FH^+ respond predominantly as non-modulators. These data are substantial: seven of nine FH^+ subjects in Boston and 25 of 31 FH^+ subjects in Salt Lake City were non-modulators as defined by renal blood flow response to Ang II on high sodium diet.

TABLE 3. **Concordance of Non-modulation in Hypertensive Sibships**

	Both non-modulators	One non-modulator	No non-modulators
Sibling pairs	14	6	1
Expected	4	10	7

Expected frequencies in random pairs of hypertensive subjects are calculated based on a prevalence of non-modulation of 44% in the general hypertensive population.
$p=0.004$, Pearson's χ^2 analysis.

The similar prevalence of non-modulation in FH^+ subjects in these two centers, as well as the virtually identical mean reduction in renal blood flow in the two groups, indicates the consistency of this relation. Additionally, all seven non-modulators in the unselected Boston group were FH^+. These findings indicate that the vast majority of non-modulators are FH^+.

In contrast, we have studied only four hypertensive individuals with documented negative family histories. Nonetheless, these FH^- subjects were all modulators and as a group were significantly different from the FH^+ subjects in renal blood flow response to Ang II (Table 1; Figure 1). Clearly, it will be necessary to study a larger group of FH^- hypertensive subjects to extend and confirm these results.

Non-modulators, as defined by renal blood flow response to Ang II, fail to appropriately increase renal blood flow when switched from low to high sodium diets. We have shown that sorting subjects on the basis of family history divides them into groups that either change renal blood flow normally (FH^-) or abnormally (FH^+) with changes in dietary sodium with 12 of 13 subjects being properly categorized on the basis of family history alone (Figure 2). Interestingly, the one misclassified subject (FH^+ but with change in renal blood flow like a modulator) also behaved as a modulator with the Ang II infusion, with a decrement in renal blood flow of -168 ml/min/1.73 m^2 in response to Ang II. Thus, this individual, although FH^+, behaves as a modulator by both tests.

Finally, we have shown that the abnormal decrement in renal blood flow in response to Ang II seen in non-modulators aggregates in families, with strong correlations between siblings.

We therefore now have substantial evidence indicating the heritability of non-modulation: 1) non-modulation can be found in young normotensive offspring of hypertensive subjects; 2) non-modulation is observed in patients eating defined isocaloric, isovolumic diets on a metabolic ward, which eliminates many potential environmental influences; 3)non-modulation is selectively found in subjects who are FH^+ for hypertension; and 4) non-modulation aggregates in families. Additionally, we have recently observed non-modulation in successive generations of hypertensive kindreds (data not shown).

The simplest explanation of these findings is that non-modulation is a genetically transmitted trait. We think alternative explanations of these findings, namely that they are the consequence of shared environment, are unlikely. Although it is possible that such hypothetical environmental factors could outlast a 2-week GCRC admission, could persist indefinitely after siblings move apart, and could conceivably produce this particular abnormality in renal hemodynamics, we find the genetic hypothesis more likely.

If non-modulation is indeed inherited, several crucial questions must be answered if this trait is to be used as a genetic marker to find the altered gene responsible for the trait. The first question is whether non-modulation is determined by monogenic or polygenic inheritance. If the inheritance is polygenic, this trait will not be useful in genetic mapping studies. The best evidence that this trait is not produced by polygenic inheritance lies in the frequency distribution of parameters that define this phenotype. The frequency distribution of four of these parameters appears to be bimodal in the hypertensive population and cleanly separates non-modulators from modulators. These parameters are 1) change in renal blood flow when shifted from low to high sodium diet, 2) aldosterone secretion rate with acute volume depletion, 3) increment in aldosterone secretion in response to Ang II while on a low sodium diet, and 4) time required for saline infusion to suppress plasma renin activity.[14] Such bimodality is the hallmark of a trait produced by single gene inheritance and is unlike the continuous distribution one would expect for polygenic inheritance.

If monogenic inheritance of non-modulation is correct, autosomal dominant transmission appears to be the most likely mode of transmission. The evidence supporting this contention includes 1) the high frequency with which non-modulators have hypertensive (and in a few documented cases, non-modulating) parents, 2) the high observed prevalence of two or more non-modulators in a single sibship, and 3) no evidence of a sex bias in non-modulators to suggest linkage to the X chromosome.

The best means by which to establish the mode of inheritance of non-modulation is pedigree analysis, analyzing how this trait segregates in successive generations of large kindreds. We have initiated these studies. Such analysis will conclusively establish the mode of inheritance of non-modulation. Furthermore, these investigations will indicate whether the expression of the trait is dependent in any fashion on age, blood pressure, or gender. Such questions are crucial if non-modulation is to ultimately be used as a genetic marker in linkage studies.

Not all FH^+ subjects in this study proved to be non-modulators. Similarly, the concordance of non-modulation in siblings was not perfect. These results should not be surprising. As mentioned, epidemiological studies have shown that many genes contribute to the pathogenesis of essential hypertension. Consequently, there are undoubtedly other heritable traits that contribute to hypertension in both non-modulator and modulator kindreds. These other heritable traits could easily account for the 20% of FH^+ subjects who are modulators.

With this in mind, the very high prevalence of non-modulation in FH^+ hypertensive subjects and its low prevalence in FH^- hypertensive and normotensive subjects is remarkable. These findings are what one would expect if 1) non-modulation is commonly inherited and rarely not inherited, 2) non-modulation results in hypertension in a high

proportion of affected individuals, and 3) non-modulation is one of the most prevalent inherited traits that contributes to essential hypertension. In contrast, if non-modulation were sporadic in the population, one would not expect non-modulation to segregate between FH^+ and FH^- subjects, and there should be no familial aggregation of the trait. Similarly, if only a small proportion of non-modulators developed hypertension, one would expect more non-modulators to be FH^- for hypertension, and non-modulators might be common in the normotensive population. Finally, and most importantly, if other inherited traits were much more common than non-modulation in the hypertensive population, one would expect only a small fraction of FH^+ subjects to be non-modulators. The observation that 80% of FH^+ subjects are non-modulators thus suggests that this trait is one of the most important heritable traits in essential hypertension.

Several other phenotypes that may predispose subjects to hypertension have been shown to be genetically determined. Among these, red blood cell Na^+-Li^+ countertransport[17–20] and urinary kallikrein levels[21] have shown major gene effects. Our results suggest that non-modulation may also show evidence of inheritance by a major gene. In addition, it appears that Na^+-Li^+ countertransport and non-modulation are independent genetic systems since there is imperfect concordance between these phenotypes in individual subjects (M. Canessa and G. H. Williams, unpublished observations). A link between non-modulation and urinary kallikreins would be plausible since both involve renal vascular tone. Such studies are in progress. Thus, it is anticipated that by identifying genetically determined traits that predispose individuals to hypertension, one will be able to combine clinical, physiological, and molecular genetics to identify the primary abnormalities that together result in the hypertensive phenotype.

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