Plasma endothelin-1 and big endothelin-1 levels in women with pre-eclampsia

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To examine a possible role for endothelin-1 (ET-1) and conversion of big ET-1 to ET-1 in the pathophysiology of pre-eclampsia, we measured plasma levels of ET-1 and big ET-1 in 16 women with pre-eclampsia in the third trimester and compared them with those in 11 age-matched normotensive pregnant women and in 10 age-matched pregnant women with chronic hypertension in the third trimester. The plasma concentrations of ET-1 and big ET-1 in the normotensive pregnant women were significantly lower than those in 16 non-pregnant women with a higher molar ratio of big ET-1 to ET-1 in the former group. The plasma concentrations of ET-1 and big ET-1 in the women with pre-eclampsia, on the other hand, were significantly higher than those in the normotensive pregnant women and the molar ratio of big ET-1 to ET-1 in the former group was less than that in the latter group. In sharp contrast, plasma ET-1 and big ET-1 levels in the pregnant women with chronic hypertension were not significantly different from those in the normotensive pregnant women. When examined after delivery, elevated plasma ET-1 and big ET-1 in the women with pre-eclampsia declined, with restoration of normal blood pressure, to the levels in the normotensive women after parturition. There were no significant differences of the levels of ET-1 and big ET-1 in umbilical venous plasma and simultaneously drawn maternal plasma at cesarean section between normotensive pregnant women and women with pre-eclampsia, respectively. These results suggest that normal pregnancy is associated with decreased plasma concentrations of ET-1 with reduced conversion of big ET-1 to ET-1 in maternal vascular endothelial cells. The derangement of this regulatory system plays an important role in the pathophysiology of pre-eclampsia.

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An increasing body of evidence indicates that the vascular endothelium plays an important role in the regulation of vascular tone and regional blood flow by the production of both vasodilators and vasoconstrictors (1). Endothelin (ET) is an endothelium-derived peptide that possesses the most potent vasoconstrictor activity of naturally occurring pressor substances known (2). Infusion of ET into experimental animals markedly increases vascular resistance and decreases renal perfusion and glomerular filtration (3, 4). We have shown previously that, of the three isopeptides, endothelin-1 (ET-1) is the major molecular form of ET present in human plasma (5). Endothelin-1 is produced from big ET-1, an intermediate generated from proendothelin, by an as yet unidentified converting enzyme presented within the vascular endothelial cells or blood vessels (6). Plasma ET-1 levels are elevated in certain pathological conditions (7–11), whereas the conversion of big ET-1 to ET-1 is reduced in diabetes mellitus (12), suggesting a possible role for ET-1 and the activity of its converting enzyme in the pathophysiology of human diseases.

Pre-eclampsia is characterized by plasma volume contraction and generalized vasoconstriction, and is associated with increased sensitivity of the vasculature to endogenous pressor substances (13–15). This contrasts with normal pregnancy, where the vasculature is rather resistant to vasoressors. Although the underlying mechanism remains unknown, maternal vascular endothelial dysfunction with resultant impaired synthesis of vasodilators or excessive production of vasoconstrictors may be a central pathogenic feature of pre-eclampsia (15, 16). In accordance with this view, we have shown in our preliminary report (17) that plasma ET-1 levels are elevated in women with pre-eclampsia, which may support the pathophysiological significance of ET-1 in pre-eclampsia. However, whether change in conversion of big ET-1 to ET-1 may be related to the pathogenesis in women with pre-eclampsia is unknown. To answer the questions, we examined plasma levels of ET-1 and big ET-1 in patients with this disorder in the present study.

Materials and methods

Subjects

The study consisted of 16 nulliparous patients with pre-eclampsia, aged between 21 and 30 years (27 ± 3 years, mean ± sd), in the third trimester of pregnancy.
patients compared of collected women containing these levels \( (p < 0.01) \) albumin in history over the period. The mean systolic and diastolic pressures of the patients were \( 161 \pm 13 \) and \( 103 \pm 13 \) mmHg, respectively. All of the patients had edema, proteinuria of \( \geq 2 \) (using a dip stick on a catheterized urine sample) and no evidence of overt renal failure, with plasma creatinine levels similar to normal controls. The mean of serum albumin levels was \( 31 \pm 5 \) g/l. None of the patients had pre-existing hypertension or renal, hepatic of heart disease. The severity of pre-eclampsia in the women with a diastolic blood pressure of \( < 110 \) mmHg, a systolic blood pressure of \( < 160 \) mmHg and proteinuria of \( \leq 1 \) was classified as mild to moderate, whereas in those with higher diastolic and systolic blood pressures and a proteinuria of \( \geq 2 \) pre-eclampsia was defined as severe.

We also studied 10 women with chronic hypertension (class I in the WHO classification), aged between 21 and 31 years (\( 30 \pm 5 \) years), in the third trimester of pregnancy (32.6 \( \pm 2.1 \) weeks). The mean systolic and diastolic blood pressures in the patients were 156 \( \pm 9 \) and 92 \( \pm 18 \) mmHg, respectively. There was no significant difference in the mean arterial blood pressure, which was calculated by adding one-third of the pulse pressure to the diastolic blood pressure of both groups (122 \( \pm 12 \) vs 113 \( \pm 13 \) mmHg). The mean of the serum albumin levels was \( 33 \pm 5 \) g/l, which was not significantly different from that in women with pre-eclampsia.

Two control groups consisted of 27 women, aged between 21 and 33 years, who were randomly selected over the same period. The first consisted of 11 women in the third trimester of pregnancy (32.5 \( \pm 0.9 \) weeks), while the second consisted of 16 healthy non-pregnant women. All of them had normal blood pressure and no history of hypertension or renal, hepatic or heart disease. The mean of the serum albumin levels (\( 31 \pm 7 \) g/l) in the former group was not significantly different from those in women with pre-eclampsia or in women with chronic hypertension. In contrast, the mean of the serum albumin in the latter group (46 \( \pm 4 \) g/l) was significantly \( (p < 0.01) \) higher than that in each group. Uric acid levels in all groups were not estimated. None of the women in any of the groups at the time of study was in labor or taking any medication, cigarettes or illicit drugs.

Blood samples were collected by venipuncture from these subjects in the sitting position into chilled tubes containing disodium ethylenediaminetetraacetic acid (1 g/l) and aprotinin (500 mU/l).

In seven normotensive pregnant women and in six women with pre-eclampsia, umbilical venous blood was collected at the time of cesarean section before the onset of labor and their ET-1 and big ET-1 concentrations were compared in the two groups. The former group of patients was delivered by cesarean section because of transverse lie or breech presentation. The Apgar scores in the former group were 8 \( \pm 2 \) at 1 min and 9 \( \pm 1 \) at 5 min, whereas those in the latter group were 8 \( \pm 2 \) and 8 \( \pm 2 \), respectively. There was no significant difference between the two groups. The cord pH was not recorded.

The umbilical cord was clamped after delivery and blood drawn from the umbilical vein was collected into chilled tubes containing disodium ethylenediaminetetraacetic acid and aprotinin. Blood was quickly centrifuged at \( 4^\circ \)C and plasma and amniotic fluid were stored at \( -20^\circ \)C until assayed.

**Determinations of ET-1 and big ET-1**

Plasma ET-1 and big ET-1 concentrations were measured by two different sandwich-type enzyme immunoassays (EIAs) \( (19, 20) \) after separation of ET from plasma by affinity chromatography on agarose-linked ET-1 monoclonal antibody. The details of the extraction and EIAs were described previously \( (5) \). In brief, a 2-ml aliquot of plasma, to which an equal volume of phosphate-buffered saline (PBS) (\( \mathrm{pH} 7.0 \)) and 500 mU/l aprotinin had been added previously, was applied to the anti-ET-1-agarose column (total volume 0.1 ml). The column was washed with 2 ml of PBS and eluted with 0.8 ml of 1 M acetic acid containing 1 g/l bovine serum albumin. The eluates were lyophilized and reconstituted with 0.45 ml of the assay buffer, and 0.1-ml aliquots were subjected in duplicate to each EIA. The reagents for EIAs were kindly supplied by Takeda Chemical Industries, Ltd. (Osaka, Japan). The EIA for ET-1 equally reacted with ET-2, but not with big ET-1 or ET-3.

As little, if any, ET-2 is present in human plasma \( (5) \), immunoreactive ET measured by this EIA was assigned to ET-1. The EIA for big ET-1, on the other hand, did not show a significant cross-reactivity with other ET peptides. The recoveries of ET-1 and big ET-1 were 78.3 \( \pm 2.6 \% \) (mean \( \pm \) SD, \( \mathrm{N} = 8 \)) and 75.3 \( \pm 4.1 \% \) (\( \mathrm{N} = 8 \)), respectively, and the sensitivities of the EIAs for ET-1 and big ET-1 were 0.14 and 0.08 pmol/l, respectively. The coefficients of variation determined in the EIAs for ET-1 averaged 8.1% for intra-assay error and 13.5% for interassay error, respectively and those in the EIA for big ET-1 averaged 6.8% for intra-assay error and 12.6% for interassay error, respectively. Plasma concentrations of ET-1 and big ET-1 in the present study were not corrected for recoveries.

**Statistical analyses**

Values in the text and tables are shown as the mean \( \pm \) SD unless otherwise specified. Paired or unpaired Student’s \( t \)-test and ANOVA were used for statistical evaluation. If data were not distributed normally, non-parametric tests were done (Wilcoxon’s two-sample test). Values of \( p < 0.05 \) were considered to be significant.
Results

Plasma ET-1 and big ET-1 levels of the women in four different groups are shown in Fig. 1. When compared to the non-pregnant women, plasma ET-1 levels were low in all of the normotensive pregnant women. The mean (±sd) plasma concentration of ET-1 in the normotensive pregnant women (0.25 ± 0.04 pmol/l) was significantly (p<0.01) lower than in the non-pregnant women (0.60 ± 0.06 pmol/l). The mean plasma concentration of ET-1 in the women with pre-eclampsia (0.75 ± 0.28 pmol/l), on the other hand, was significantly (p<0.01) higher than in the normotensive pregnant women. There was no overlap in plasma ET-1 levels in individual women in both groups. In contrast, plasma ET-1 levels in the pregnant women with chronic hypertension (0.40 ± 0.12 pmol/l) were not significantly different from those in the normotensive pregnant women. Similarly, the mean plasma concentration of big ET-1 in the normotensive pregnant women (0.99 ± 0.21 pmol/l) was significantly (p<0.01) lower than in the non-pregnant women (1.49 ± 0.15 pmol/l). The mean plasma big ET-1 concentration in the women with pre-eclampsia (1.87 ± 0.62 pmol/l) was significantly (p<0.01) higher than in the normotensive pregnant women or in the non-pregnant women, while the mean plasma big ET-1 in the pregnant women with chronic hypertension (1.40 ± 0.49 pmol/l) was not significantly different from that in the normotensive pregnant women. No correlation between maternal mean blood pressure and plasma ET-1 level (r = −0.26, p > 0.05) or big ET-1 level (r = 0.006, p > 0.05) was observed in the women with pre-eclampsia. When plasma ET-1 concentrations in individual subjects in four groups were pooled and compared with simultaneously measured plasma big ET-1 concentrations, a significant (p<0.05) correlation between the two variables was observed, but there was no high correlation (r = 0.66).

Mean (±sd) molar ratios of plasma big ET-1 to ET-1 in the four different groups of women are shown in Table 1. The mean big ET-1 to ET-1 ratio in the normotensive pregnant women was significantly higher than in the non-pregnant women. The mean ratio in the women with pre-eclampsia was significantly lower than in the normotensive pregnant women. There was no significant difference between the mean ratios of big ET-1 to ET-1 in the women with chronic hypertension and that in the normotensive pregnant women.

![Graph](image_url)

**Fig. 1.** Plasma levels of endothelin-1 (ET-1) (●) and big ET-1 (○) in women with pre-eclampsia, pregnant women with chronic hypertension, normotensive pregnant women and normotensive non-pregnant women. Horizontal bars indicate the mean concentrations of ET-1 and big ET-1 for each patient group.
Table 1. Mean (+±sd) molar ratios of plasma big endothelin (ET-1) to ET-1 in non-pregnant women, normotensive pregnant women, women with pre-eclampsia and women with chronic hypertension.

<table>
<thead>
<tr>
<th>Groups of subjects</th>
<th>Number of subjects</th>
<th>Plasma big ET-1 to ET-1 ratios</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-pregnant women</td>
<td>16</td>
<td>2.5 ±0.3</td>
</tr>
<tr>
<td>Normotensive pregnant women</td>
<td>11</td>
<td>4.1 ±1.0*</td>
</tr>
<tr>
<td>Women with pre-eclampsia</td>
<td>11</td>
<td>3.0 ±0.8*</td>
</tr>
<tr>
<td>Women with chronic hypertension</td>
<td>8</td>
<td>3.5 ±1.3</td>
</tr>
</tbody>
</table>

*a p<0.01 vs non-pregnant women.

*b p <0.01 vs normotensive pregnant women.

All 11 normotensive pregnant women and seven women with pre-eclampsia were examined again within 1 week (5 ± 1 days, mean ±sd) after delivery (Fig. 2). The mean plasma big ET-1 concentration in the normotensive pregnant women (1.46 ±0.25 pmol/l) rose significantly (p<0.01) after delivery and reached the levels in non-pregnant women. Plasma ET-1 levels also increased significantly (p<0.01) (0.42 ±0.10 pmol/l), although the mean concentration was lower than in the non-pregnant women. They resulted in a significant (p<0.01) reduction in the mean ratio of big ET-1 to ET-1 (3.6 ±0.8), which is higher than in the non-pregnant women. In contrast, plasma ET-1 levels decreased significantly (p<0.01) after delivery, with restoration of normal blood pressure, in the women with pre-eclampsia (0.41 ±0.14 pmol/l), which was not different from those in the non-pregnant women. The mean of plasma big ET-1 concentrations also decreased significantly (p<0.05) to the levels (1.69 ±0.78 pmol/l) not distinguishable from those in the non-pregnant women. The mean ratio of big ET-1 to ET-1 (3.7 ±1.5) in the women with pre-eclampsia was increased more significantly (p<0.01) than that before delivery, which was not significantly different from that in normotensive pregnant women.

Table 2 shows concentrations of ET-1 and big ET-1 and ratios of big ET-1 to ET-1 in maternal venous plasma and in umbilical venous plasma collected at the time of cesarean section in seven women with pre-eclampsia and in six normotensive women. The mean maternal plasma ET-1 concentration in the women with pre-eclampsia was significantly higher than in the normotensive women, consistent with the findings observed before cesarean section (Fig. 1). Similarly, the mean maternal plasma big ET-1 was higher in the women with pre-eclampsia, although the difference was not statistically significant, and the mean ratio of big ET-1 to ET-1 in the former group was significantly lower than in the latter group. Concentrations of ET-1 in umbilical venous plasma were higher than in maternal venous plasma in both the women with pre-eclampsia and the normotensive pregnant women. Less markedly, big ET-1 levels in umbilical venous plasma and in amniotic fluid were higher than in maternal venous plasma in both groups, which resulted in a significant reduction in big ET-1 to ET-1 ratios. The reduced ratio of big ET-1 to ET-1 was significantly (p<0.01) lower than that in non-pregnant women. There were no significant differences in concentrations of ET-1 and big ET-1 and ratios of big ET-1 to ET-1 in umbilical venous plasma in the two groups.

![Fig. 2. Changes in plasma mean (+±sd) levels of endothelin-1 (ET-1) and big ET-1 after delivery in seven women with pre-eclampsia (■) and 11 normotensive pregnant women (□). * p<0.01 for difference between the two groups.](image-url)
Table 2. Mean (±sd) endothelin-1 (ET-1) and big ET-1 concentrations and molar ratios of plasma big ET-1 to ET-1 in maternal and umbilical venous plasma collected at the time of cesarean section in normotensive pregnant women and women with pre-eclampsia.

<table>
<thead>
<tr>
<th>Groups of subjects</th>
<th>ET-1 (pmol/l)</th>
<th>Big ET-1 (pmol/l)</th>
<th>Big ET-1 to ET-1 ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normotensive pregnant women (N = 6)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maternal venous plasma</td>
<td>0.53 ± 0.16</td>
<td>1.82 ± 0.49</td>
<td>3.5 ± 0.8</td>
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<td>Umbilical venous plasma</td>
<td>2.54 ± 1.28a</td>
<td>4.05 ± 2.46a</td>
<td>1.7 ± 0.8ac</td>
</tr>
<tr>
<td>Women with pre-eclampsia (N = 7)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maternal venous plasma</td>
<td>0.88 ± 0.42b</td>
<td>1.92 ± 0.69</td>
<td>2.8 ± 1.0b</td>
</tr>
<tr>
<td>Umbilical venous plasma</td>
<td>2.83 ± 0.96a</td>
<td>4.25 ± 0.79a</td>
<td>1.6 ± 0.4a</td>
</tr>
</tbody>
</table>

* p < 0.01 vs maternal venous plasma.
** p < 0.01 vs normotensive pregnant women.
*** p < 0.01 vs non-pregnant women.

Discussion

One of the fundamental hemodynamic changes that occurs in the maternal circulation during pregnancy is a reduction in peripheral vascular resistance by, as yet, unknown mechanisms (13–15). Blood pressure does not usually rise in normal pregnancy because an increase in cardiac output is compensated by a decrease in peripheral vascular resistance. The present study demonstrates that plasma levels of ET-1 and big ET-1 are low in normal pregnant women in the third trimester, which increase after delivery. Women with normal pregnancy have an expanded plasma volume, which circulates through the vascular system, and the plasma volume in normal pregnant women is maintained at a low level by the release of vasodilator factors, such as prostaglandins, nitric oxide, and endothelium-derived relaxing factor (16, 17). The reduction in plasma ET-1 levels could not be explained by the dilutional effect because the biologically active hormones in plasma are not diluted or concentrated simply by plasma volume (22), as indicated in the normal blood levels of free thyroxine and free triiodothyronine in the third trimester (23, 24); also, circulating ET-1 and big ET-1 do not bind with plasma albumin (5) and thus may have biological activity (11). Accordingly, lowered ET-1 levels in the circulation may reflect decreased production and secretion of this vasoconstrictor peptide in the endothelial cells. A reduction in peripheral vascular resistance during pregnancy, therefore, may be explained at least in part by decreased ET-1 at the endothelial interface that is directly involved in the regulation of vascular tone.

Of interest in this regard is that a decrease in plasma ET-1 levels was more pronounced than a decrease in big ET-1 in normal pregnant women, as evidenced by higher molar ratios of plasma big ET-1 to ET-1 than in non-pregnant women. One of the mechanisms underlying decreased plasma ET-1 levels in pregnancy may be the diminished cleavage of big ET-1 to produce ET-1 by a converting enzyme present in the endothelial cells. As reported in patients with diabetes mellitus (12).

Whether plasma ET-1 levels change during pregnancy is a matter of controversy. In contrast with our results, Mastrogiannis et al. (25) reported that plasma ET-1 levels in normal pregnant women were not different from those in non-pregnant women. Clark et al. (26) found that plasma ET-1 levels tended to rise in late gestation. Conversely, Schiff et al. (27) reported that normotensive pregnant women in the third trimester had slightly but significantly lower ET-1 levels than non-pregnant women, which is consistent with our finding. Although the exact causes responsible for these diverse results are unknown at present, one of the possible explanations may reside in the specificity of ET-1 assays used in their studies. In two of these three studies, the ET-1 RIA kits obtained from Amersham (Amersham International, Amersham, UK) were employed. When we analyzed human plasma extracts by reversed-phase high-performance liquid chromatography with RIA of resultant fractions using the ET-1 RIA kits from Amersham, we found multiple peaks of immunoreactive ET in more polar fractions than those corresponding to ET-1, ET-2, ET-3 or big ET-1, which was not detected by the EIAs used in the present study (5). Thus, decreased plasma ET-1 levels during normal pregnancy may have been masked in previous studies by the existence of unidentified materials in plasma that react in the ET-1 RIA systems of some sources.

When compared to normal pregnant women, plasma levels of ET-1 were elevated in women with pre-eclampsia. Elevated plasma ET-1 may not be consequent to impaired renal function (7), because our patients with pre-eclampsia had no evidence of overt renal failure and had plasma creatinine concentrations similar to normal controls. In addition, plasma volume may be reduced in women with pre-eclampsia (13–15), although plasma albumin levels in this study are similar to those in normotensive pregnant women, which may have resulted in part, from loss of albumin from kidney. The reduced plasma volume, however, may not contribute to the elevated plasma ET-1 for the same reason described above (22). No relation between the elevated plasma ET-1 concentrations and mean blood pressure may be explained by the fact that the patients studied had similar levels of blood pressure with similar clinical severity, in contrast with our finding in a patient with disseminated intravascular coagulation (11). The result
is consistent with our preliminary study (17) and the report of Taylor et al. (28), which was confirmed recently by other investigators (25–27, 29). Furthermore plasma big ET-1 levels also were elevated, although less markedly, resulting in lower molar ratios of plasma big ET-1 to ET-1 than in normal pregnant women. This suggests that increased plasma ET-1 levels in women with pre-eclampsia are partly due to accelerated conversion of big ET-1 to ET-1 in vascular endothelial cells. No high correlation between plasma levels of ET-1 and big ET-1 in any of the groups may be explained in part by the alterations in the conversion of big ET-1 to ET-1.

After delivery, plasma levels of both ET-1 and big ET-1 decreased, with normalization of blood pressure, to the levels in non-pregnant women and there was no significant difference in the ratio of big ET-1 to ET-1 between normotensive pregnant women and women with pre-eclampsia. Women with chronic hypertension, on the other hand, had plasma ET-1 and big ET-1 levels and ratios of big ET-1 to ET-1 that were not distinguishable from those in normal pregnant women. The evidence also supports the fact that plasma ET-1 and the conversion of big ET-1 to ET-1 are involved in the pathophysiology of pre-eclampsia.

Concentrations of ET-1 and big ET-1 in umbilical venous plasma collected at the time of cesarean section were higher than in simultaneously taken maternal venous plasma in both women with pre-eclampsia and normotensive pregnant women, whereas the mean ratio of big ET-1 to ET-1 in umbilical venous plasma was lower than in maternal venous plasma in the two groups. The findings indicate that there may be an increased conversion of big ET-1 to ET-1 in placental tissue. There was no significant difference in umbilical venous plasma ET-1 and big ET-1 levels or in the ratios of big ET-1 to ET-1 of both groups, although the mean maternal plasma ET-1 concentration in women with pre-eclampsia was significantly higher than in normotensive pregnant women and the mean ratio of big ET-1 to ET-1 in the former group was significantly lower than in the latter group. The findings are not explained by fetal distress, which may influence the levels of ET-1 (30) because the Apgar scores are not different in the two groups. In view of this observation, the possibility that elevated maternal plasma ET-1 and big ET-1 levels in women with pre-eclampsia is due to the increased production of ET peptides with accelerated activity of their converting enzymes in placental tissue (25) may not be likely.

In conclusion, all our data presented here support the view that ET-1 may play an important role in the control of vascular tone in normal pregnancy and that the derangement of this regulatory system may lead to vasospasm and hypertension associated with pre-eclampsia. The changes in the production of ET-1 may be due, at least in part, to changes in the conversion of big ET-1 to ET-1 by the converting enzyme that cleaves big ET-1 to liberate ET-1. It may be argued, however, that increased plasma ET-1 and big ET-1 levels in pre-eclampsia are secondary to the events that initiate this syndrome rather than playing a primary role in the pathogenesis (28). Although this possibility could not be ruled out by the present study, it does not negate the pathophysiological significance of ET-1 and the conversion of big ET-1 to ET-1 in pre-eclampsia. Excessive production or leakage of ET-1 from injured vascular cells may aggravate the disease process by causing progressive vasospasm and by facilitating the intravascular formation of microthrombi with resultant ischemic end-organ damage. This may be true particularly in states of diminished vasodilatory prostaglandin production, such as pre-eclampsia (15), because ET-1 activity is shown to interact with prostacyclin (31). The precise mechanism underlying the decreased production of ET-1 with reduced conversion of big ET-1 to ET-1 during normal pregnancy and its reversal in pre-eclampsia remains to be investigated.

References

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