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Association of Increased Plasma Cardiotrophin-1 With Inappropriate Left Ventricular Mass in Essential Hypertension

Begoña López, José M. Castellano, Arantxa González, Joaquín Barba, Javier Díez

Abstract—Inappropriate left ventricular mass is present when the value of left ventricular mass exceeds individual needs to compensate hemodynamic load imposed by increased blood pressure. The goal of this study was to investigate whether plasma concentration of cardiotrophin-1, a cytokine that induces exaggerated hypertrophy in cardiomyocytes with hypertensive phenotype, is related to inappropriate left ventricular mass in patients with essential hypertension. The study was performed in 118 patients with never-treated hypertension and without prevalent cardiac disease. The left ventricular mass prediction from stroke work (systolic blood pressure × Doppler stroke volume), sex, and height (in meters^2.7) was derived. An observed left ventricular mass/predicted left ventricular mass value >128% defined inappropriate left ventricular mass. Plasma cardiotrophin-1 was measured by an enzyme-linked immunosorbent assay. The studies were repeated in a group of 45 patients after 1 year of antihypertensive treatment. At baseline 67 and 51 patients presented with appropriate and inappropriate left ventricular mass, respectively. Plasma cardiotrophin-1 was higher (P < 0.001) in patients with inappropriate mass than in patients with appropriate mass and normotensive controls. A direct correlation was found between cardiotrophin-1 and observed left ventricular mass/predicted left ventricular mass ratio (r = 0.330, P < 0.001) in all hypertensive patients. After treatment, plasma cardiotrophin-1 decreased and increased in patients in which inappropriate left ventricular mass regressed and persisted, respectively, despite a similar reduction of blood pressure in the 2 subgroups of patients. Albeit descriptive in nature, these results suggest the hypothesis that an excess of cardiotrophin-1 may contribute to inappropriate left ventricular growth in hypertensive patients. (Hypertension. 2007;50:977-983.)

Key Words: hypertension, left ventricular echocardiography

The term inappropriate left ventricular mass (iLVM) has been applied to conditions in which the observed level of LVM exceeds the theoretical value predicted by sex, body size, and stroke work.1–3 iLVM is associated with LV concentric geometry, and systolic and diastolic dysfunction, even in the absence of traditionally defined LV hypertrophy (LVH).4–6 In addition, iLVM appears to be a marker of adverse cardiovascular prognosis independent of LVH.1,7 Recent data suggest that changes in the appropriateness of LVM from baseline to follow-up during treatment may predict a subsequent cardiovascular event in hypertensive patients.8

Cardiotrophin-1 (CT-1) is a member of the interleukin (IL)-6 superfamily,9 which induces cardiomyocyte growth.10 Of interest, we have shown recently that CT-1 exerts exaggerated growth responses in cardiomyocytes from adult spontaneously hypertensive rats (SHR) compared with cardiomyocytes from adult Wistar rats.11 Other studies have shown that CT-1 expression is abnormally increased in the hypertrophied left ventricle of hypertensive rats.11–13 Recently, it has been reported that plasma CT-1 is increased in hypertensive patients, namely in those with LVH.14,15 Furthermore, an association has been found between treatment-induced decrease of plasma CT-1 and LVH regression in hypertensive patients.16

It has been proposed that the process that yields iLVM can be mediated by cytokines among other nonhemodynamic factors.17 Thus, we have hypothesized that CT-1 may be abnormally upregulated in hypertensive patients with iLVM. To test this hypothesis, plasma CT-1 was determined in normotensive subjects and never treated hypertensive patients with either appropriate LVM (aLVM) or iLVM. In addition, the relationship of plasma CT-1 with iLVM was further analyzed in a subgroup of hypertensive patients after 1 year of antihypertensive treatment. Methods

Subjects
All subjects gave written informed consent to participate in the study and the institutional review committee approved the study protocol.
The study conformed to the principles of the Helsinki Declaration. The study population consisted of 118 hypertensive patients with sitting systolic and sitting diastolic blood pressure of more than 139 and 89 mm Hg, respectively. All patients had appropriate clinical and laboratory evaluation to exclude secondary hypertension and none of them had received previous treatment with antihypertensive drugs. Other cardiac diseases associated with LVH (eg, hypertrophic cardiomyopathy and aortic stenosis) were excluded on echocardiography. No patient exhibited clinical manifestations of ischemic heart disease or heart failure.

Fifty-six from the 118 initially enrolled patients agreed to receive antihypertensive treatment prescribed by their family doctors in accordance with the 2003 European Society of Hypertension–European Society of Cardiology guidelines and to continue the study. The family doctors were blind to the presence or absence of iLVM in their patients. Forty-five of these patients reached 1 year of follow-up and were considered eligible for complete medical examination, including echocardiography and biochemical determinations.

A group of 31 normotensive subjects (23 men and 8 women; mean age, 55 years; range, 40 to 68 years) were used as control subjects for biochemical studies. These controls were subjects without iLVM and without clinically proven cardiac disease.

Assessment of LVM and Function

Two-dimensional echocardiographic imaging, targeted M-mode recordings, and Doppler ultrasound measurements were obtained in each patient as previously reported. The LVM was calculated in accordance with the Penn convention (LVM = 1.04 [(intraventricular septal thickness (IVST)+ posterior wall thickness (PWT) + LV internal diameter) / 2]− LV internal diameter)2−13.6) and normalized by height2.2 LVH was defined by sex-specific partition values, as LVM index (LVMI) exceeded 50% and 55% for men and 46.7 g/m2.7 for women.2 Relative wall thickness (RWT) was calculated as PWT/LV internal radius. LV concentric geometry was defined as RWT ≥ 0.44.

LV end-diastolic volume (LVEDV) was calculated using Teichholz formula. Stroke volume was generated from Doppler interrogation of transaortic flow at the aortic annular level and aortic cross-sectional area. Stroke work (SW) was therefore computed using systolic blood pressure, as previously reported.2 An equation to predict compensatory LVM [predicted LVM = 55.37 + 6.64 X height(2)−0.65 X SW−18.07 X sex, where male gender is 1 and female gender is 2] was used in accordance with de Simone et al.2 The value of LVM directly measured from echocardiograms was divided by that predicted by the above equation and LVM was expressed as a percent of predicted (Δ%LVM), representing the excess relative to the “compensatory” value (ie, 100% of predicted). iLVM was defined as >128% of the predicted value (ie, Δ%LVM >128%).

LV systolic function was estimated at the chamber level, by computation of ejection fraction (EF) from Doppler stroke volume divided by LVEDV, and at the midwall as midwall fractional shortening (MWS) as both absolute and corrected for circumferential end-systolic stress (ESS).20 Systolic dysfunction was defined as EF <50% and >30%,21 or as ESS-corrected MWS <89.2%.22

The following pulsed Doppler measurements of the mitral inflow were obtained: maximum early transmitral velocity in diastole (Vₑ), maximum late transmital velocity in diastole (Vₐ), the deceleration time of the early mitral filling wave (DT), and isovolumic relaxation time (IVRT). As a normal Vₑ/Vₐ ratio is strongly dependent on age and heart rate, its raw value was normalized by the following equation:

\[ \frac{Vₑ}{Vₐ}\text{adj} = \frac{Vₑ}{Vₐ} + 0.0199 \times (\text{age} - 50) + \frac{0.0082 \times (\text{heart rate} - 75)}{0.0082 \times (\text{heart rate} - 75)} \]

A value of Vₑ/Vₐ adj (< 0.66) or a value of IVRT greater than 100 ms or a value of DT greater than 220 ms were used to identify abnormal LV relaxation.23

Measurement of Plasma CT-1 and Serum Amino-Terminal Pro-Brain Natriuretic Peptide (NT-proBNP)

Blood samples were taken at 08:30 hour with all the subjects being in fasting conditions. Plasma CT-1 was measured by an enzyme-linked immunosorbent assay (ELISA) as previously reported.14 The assay and intraassay coefficients of variations were 6.9 and 7.4%, respectively. The sensitivity was 2.9 fmol of CT-1/mL. The upper limit for plasma CT-1 values measured in controls was of 41 fmol/mL NT-proBNP was measured in serum samples by ELISA according to Karl et al.23 The interassay and intraassay coefficients of variation were lower than 2%.

Statistical Analysis

The differences between the 2 subgroups of untreated hypertensives at baseline and between the subgroups of treated hypertensives after treatment were tested by a Student t test for unpaired data once normality was demonstrated (Shapiro–Wilks test); otherwise, a nonparametric test (Mann–Whitney U test) was used. To analyze the differences between the normotensive group and the 2 subgroups of untreated hypertensive patients at baseline, a 1-way analysis of variance followed by a Student—Newman–Keuls test was performed once normality was checked (Shapiro–Wilks test); otherwise, the nonparametric Kruskal–Wallis test followed by a Mann–Whitney U test (adjusting the α-level for Bonferroni inequality) was used. Differences between hypertensives before and after treatment were tested by a Student t test for paired data once normality was demonstrated (Shapiro–Wilks test); otherwise, a nonparametric test (Wilcoxon test) was used. Categorical variables were analyzed by the chi-square (χ²) Fisher exact test when necessary. Plasma CT-1 was normalized by logarithmic transformation for the correlational analysis. Correlations were estimated by Spearman correlation coefficients. Partial correlation coefficients were calculated after adjustment for potential confounding factors. Values are expressed as mean±SEM. A value of P <0.05 was considered statistically significant.

Results

Baseline Clinical and Echocardiographic Characteristics

Hypertensive patients were divided into 2 subgroups according to the presence (n =51) or absence (n =67) of iLVM at baseline. Table 1 shows the clinical and echocardiographic parameters assessed in the 2 subgroups of patients. No differences in blood pressure were found between the 2 subgroups of patients. Body mass index, LVM, LVMId, RWT, and LVEDV were higher in hypertensives with iLVM than in hypertensives with aLVM. LVH was present in 39% and 76% of patients with aLVM and iLVM, respectively, this difference being statistically significant (P <0.001). The prevalence of concentric LV geometry was higher (P <0.01) in patients with aLVM (63%) than in patients with iLVM (36%).

ESS was higher and ESS-corrected MWS and EF were lower in hypertensives with iLVM than in hypertensives with aLVM. Whereas the Vₑ/Vₐ adj ratio was diminished in hypertensives with iLVM compared with hypertensives with aLVM, no significant differences in either DT or IVRT were observed between the 2 subgroups of patients.

The observed LVM/predicted LVM ratio was inversely correlated with ESS-corrected MWS (r =0.530, P <0.001; Figure 1A) and EF (r =0.368, P <0.005; Figure 1B) in all hypertensives. In addition, significant associations were found between iLVM and myocardial systolic dysfunction (χ² =10.29, P <0.001) and LV systolic dysfunction (χ² =5.44, P <0.05).
Hyperontes compared with normotensives (Figure 2). Plasma CT-1 was significantly increased in the whole group (P \( \leq 0.05 \)) in all hypertensives. No associations were found between observed LVM/predicted LVM ratio and parameters assessing diastolic function.

### Baseline Plasma CT-1 and NT-proBNP

Plasma CT-1 was significantly increased in the whole group of hypertensives (data not shown) and in each subgroup of hypertensives compared with normotensives (Figure 2). Furthermore, CT-1 was higher in hypertensives with iLVM than in hypertensives with aLVM (Figure 2).

Figure 1. Inverse correlations between the baseline observed left ventricular mass/predicted left ventricular mass (oLVM/pLVM) ratio and baseline circumferential end-systolic stress-corrected midwall fractional shortening (ESS-corrected MWS) (y = -28.17x + 126.82; left panel), and baseline ejection fraction (EF) (y = -10.18x + 75.24) (right panel) in all untreated hypertensives.

Figure 2. Baseline plasma concentration of cardiotrophin-1 (CT-1) in normotensives, untreated hypertensives with appropriate left ventricular mass (HT-aLVM), and untreated hypertensives with inappropriate LVM (HT-iLVM). Bars represent mean±SEM.

Plasma CT-1 directly correlated with the observed LVM/predicted LVM ratio (r = 0.330, P < 0.01; Figure 3) and with LVM (r = 0.483, P < 0.001) in all hypertensives. The correlation between CT-1 and the observed LVM/predicted LVM ratio remained significant when we excluded the influence of body mass index (r = 0.322, P < 0.005), LVEDV (r = 0.318, P < 0.001), MWS (r = 0.394, P < 0.001), ESS (r = 0.383, P < 0.001), ESS-corrected MWS (r = 0.371, P < 0.001), EF (r = 0.385, P < 0.001), Vt/Vadj (r = 0.369, P < 0.001), and concentric LVH (r = 0.287, P < 0.05) in partial correlation analysis.

Significant associations were found between abnormally high CT-1 and the presence of iLVM (\( \chi^2 = 4.08, P < 0.05 \)), myocardial systolic dysfunction (\( \chi^2 = 3.49, P < 0.05 \)), LV systolic dysfunction (\( \chi^2 = 5.62, P < 0.05 \)), and abnormal LV relaxation, ie, prolonged IVRT (\( \chi^2 = 4.07, P < 0.05 \)) in all hypertensives.

No significant differences were found in the values of NT-proBNP between the whole group of hypertensives and the group of normotensives (61 ± 9 versus 56 ± 7 pg/mL), and between hypertensives with aLVM and hypertensives with iTVM (66 ± 11 versus 55 ± 8 pg/mL).

### Findings After Treatment

After 1 year of antihypertensive treatment the patients were classified in 4 subgroups: patients with baseline aLVM in which aLVM persisted (n = 14, subgroup 1) or in which aLVM developed de novo (n = 2, subgroup 2) after treatment, and patients with baseline iTVM in which iTVM regressed...
Whereas systolic blood pressure was lower in subgroup 4 than in subgroup 1, no differences in diastolic blood pressure were observed among the 3 subgroups of patients. The heart rate was lower in subgroup 4 than in subgroups 1 and 3. The LVMI was higher in subgroup 4 than in subgroups 1 and 3. Although the ESS-corrected MWS did tend to be lower in subgroup 4 than in subgroups 1 and 3, the differences did not reach statistical significance. The EF was lower in subgroup 4 than in subgroups 1 and 3. Although the \( V_t/V_{adj} \) did tend to be lower in subgroups 3 and 4 than in subgroup 1, the differences did not reach statistical significance. No significant differences in NT-proBNP were observed among the three subgroups of hypertensives (data not shown).

As shown in Figure 4, values of plasma CT-1 remained unchanged after treatment in subgroup 1, decreased by 21% after treatment in subgroup 3, and increased by 31% after treatment in subgroup 4. Thus, final values of CT-1 were higher in subgroup 4 than in subgroups 1 and 3. A direct correlation \( (r=0.452, P<0.01) \) was found between final values of plasma CT-1 and final values of the observed LVMI/predicted LVM ratio in all treated hypertensives (Figure 5). In addition, an association was found between decrease of plasma CT-1 to normal values and reduction of the observed LVMI/predicted LVM ratio to normal values in all treated hypertensives \( (\chi^2=4.08, P<0.05) \).

**Discussion**

The main findings of this study are as follows: (1) CT-1 is associated with iLVM in patients with essential hypertension; and (2) CT-1 is associated with systolic and diastolic dysfunction in hypertensive patients.

As stated by de Simone G et al,17 the biological process that yields iLVM is probably linked to the protracted activity over time of biological mediators of LVH, such as proto-oncogenes and other growth factors, neurohormones, and cytokines, inducing structural modifications that initially compensate imposed overload but eventually change the structure and function of LV myocardial tissue. In this regard, although weak, the correlation found between CT-1 and the observed LVMI/predicted LVM ratio and its independence from concentric LVH suggest that CT-1 may be one of the cytokines involved in the development of iLVM. Furthermore, the observation that CT-1 was increased in those treated patients in which iLVM persisted despite normalization of blood pressure with treatment adds support to the above possibility.

Some experimental and clinical observations suggest that CT-1 may contribute to exaggerated LV growth in hypertensive patients. We have shown recently that hypertrophy induced by CT-1 is higher in cardiomyocytes from adult SHR than in cardiomyocytes from adult normotensive Wistar rats and that an exaggerated expression of myocardial CT-1 is temporally associated with cardiomyocyte hypertrophy during the development of LVH in adult SHR.11 On the other hand, an association between LVH and high plasma levels of CT-1 has been reported in hypertensive patients.14,15 Furthermore, reversion of LVH and diminution of plasma levels of CT-1 are associated in treated hypertensive patients.16

The associations of CT-1 with ESS-corrected MWS and EF here reported suggest that CT-1 can be involved in

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**Figure 3.** Direct correlation between baseline plasma cardiac tropin-1 (CT-1) and baseline observed left ventricular mass/predicted left ventricular mass (oLVM/pLVM) ratio \( (y=0.002x+1.16) \) in all untreated hypertensives.

(n=20, subgroup 3) or persisted (n=9, subgroup 4) after treatment. Because of the low number of patients in subgroup 2, only the final data assessed in patients from the remaining subgroups are presented in Table 2. Whereas most patients in subgroups 1 and 3 (82% and 94%, respectively) received the angiotensin type II receptor blocker losartan with or without hydrochlorothiazide as treatment, most patients (78%) in subgroup 4 were treated with the \( \beta \)-blocker atenolol with or without hydrochlorothiazide, these differences being statistically significant \( (\chi^2=5.89, P<0.05) \).

**Table 2.** Main Clinical, Echocardiographic, and Biochemical Parameters Assessed After Antihypertensive Treatment in Hypertensive Patients Classified in Accordance With the Response of Left Ventricular Mass to Treatment

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Persisted aLVM</th>
<th>Regressed iLVM</th>
<th>Persisted iLVM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Losartan, n</td>
<td>11</td>
<td>19</td>
<td>2</td>
</tr>
<tr>
<td>Atenolol, n</td>
<td>3</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td>Hydrochlorothiazide, n</td>
<td>5</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>147±5</td>
<td>138±3</td>
<td>127±5†</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>87±2</td>
<td>84±2</td>
<td>83±2</td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>66±3</td>
<td>68±3</td>
<td>50±2‡</td>
</tr>
<tr>
<td>LVMI, g/h²⁷</td>
<td>48.6±3.3</td>
<td>48.6±3.3</td>
<td>58.3±3.5∥</td>
</tr>
<tr>
<td>RWT</td>
<td>0.40±0.02</td>
<td>0.42±0.01</td>
<td>0.45±0.02</td>
</tr>
<tr>
<td>oLVM/pLVM ratio</td>
<td>1.03±0.05</td>
<td>1.02±0.04</td>
<td>1.49±0.06‡</td>
</tr>
<tr>
<td>ESS-corrected MWS, %</td>
<td>94.5±3.2</td>
<td>92.1±2.8</td>
<td>85.6±4.3</td>
</tr>
<tr>
<td>EF, %</td>
<td>63.5±1.3</td>
<td>63.8±1.3</td>
<td>58.4±2.1∥</td>
</tr>
<tr>
<td>( V_t/V_{adj} )</td>
<td>1.02±0.09</td>
<td>0.93±0.04</td>
<td>0.92±0.08</td>
</tr>
</tbody>
</table>

aLVM indicates appropriate left ventricular mass; iLVM, inappropriate LVMI; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; LVMI, LVMI index; RWT, relative wall thickness; oLVM/pLVM, observed LVMI/predicted LVM; ESS, circumferential end-systolic stress; MWS, mid-wall fractional shortening; EF, ejection fraction; \( V_t \), maximum early transmitral velocity in diastole; \( V_e \), maximum late transmitral velocity in diastole.

\*P<0.05 for the distribution of antihypertensive medications among groups; †P<0.001 compared with the subgroup of patients in which persisted aLVM; ‡P<0.001, §P<0.01, ||P<0.05, compared with the other 2 subgroups of hypertensives.
systolic dysfunction present in hypertensive patients, namely those with iLVM. Several experimental and clinical observations support this possibility. We found recently enhanced ERK5 activation by CT-1 in cardiomyocytes from SHR compared with cells from Wistar rats. Interestingly, it has been shown that cardiac-specific overexpression of activated ERK5 in transgenic mice resulted in contractile heart failure. It has been reported in heart tissues reconstituted from neonatal rat cardiomyocytes that long-term exposure to CT-1 significantly depressed basal force of contraction and the inotropic response to Ca++ and isoprenaline, thus suggesting that a chronic excess of the cytokine may induce ineffective force generation by the cardiac muscle. Finally, CT-1 has been reported to be increased in the myocardium and plasma of heart failure patients in relation to the severity of LV systolic dysfunction.

The question arises as to the mechanisms determining the excess of CT-1 in hypertensive patients with iLVM. Our finding that ESS was higher in hypertensives with iLVM than in hypertensives with aLVM suggests a role for mechanical afterload. This is supported by previous experiments showing that myocardial CT-1 release is stimulated by ventricular stretch/pressure. Nevertheless, nonhemodynamic factors may be also involved in upregulation of CT-1. For example, data from studies with isolated cardiomyocyte and cardiac fibroblast clearly demonstrate that CT-1 synthesis and release results from the action of angiotensin II through the AT1 receptor. In this regard, we report here that treatment with losartan was associated with reduction in plasma CT-1 in those hypertensives with high baseline values of the cytokine and in which iLVM regressed after treatment. The finding that CT-1 increases in hypertensive patients receiving atenolol as treatment in which iLVM persisted is difficult to interpret. Norepinephrine has been shown to induce CT-1 in cardiac cells both at the mRNA and protein level. However, because no data are available on the involvement of the α-or the β-adrenergic receptor in such stimulation, no prediction on the effect of β-blockers on plasma CT-1 can be made.

Elevated circulating NT-proBNP levels have been found associated with LVH and cardiac dysfunction in population studies and hence this peptide has been proposed as a marker of hypertrophy and dysfunction whatever is the underlying cardiac condition. However, our results demonstrate that, in contrast to CT-1, no association exists between NT-proBNP and iLVM in hypertensive patients either at baseline or after treatment. Thus, the possibility exists that plasma CT-1 is a more sensitive and specific biomarker than NT-proBNP for detection of the inappropriateness of LVM and LV dysfunction in hypertension.

Limitations of the Study
First, the baseline study involved a relatively small number of hypertensive patients. However they were all never-treated patients which allowed us to exclude any influence of the antihypertensive treatment on the appropriateness of LVM. Second, the interventional study was a nonrandomized, open-label, pilot study involving few patients and heterogeneous treatment, but because of the nature of the hypothesis under investigation this design is adequate. Third, although it has been shown that the human heart secretes CT-1 via the coronary sinus into the peripheral circulation, given the earlier evidence showing that CT-1 mRNA is expressed in other organs, there may be additional potential sources of
circuiting CT-1. Fourth, the correlation between CT-1 and the observed LVM/predicted LVM ratio was weak, which means that a small fraction of variability of this parameter is explained by CT-1. However, additional partial correlation analysis showed that correcting for other parameters does not weaken this correlation. This reinforces the possibility that CT-1 plays a modest but direct role on the development of iLVM in hypertensive patients and probably in its response to the antihypertensive treatment. Finally, our findings do not necessarily conflict with previous experiments demonstrating survival effects of CT-1 on cardiomyocytes submitted to acute stress conditions.37,38 In the short run, CT-1 obviously helps to preserve myocardial integrity; in the long run, however, it may induce both abnormal growth and dysfunction of the LV myocardium.

Perspectives
The present study supports the hypothesis that a chronic excess of CT-1 in association with other hemodynamic and nonhemodynamic factors may contribute to inappropriate LV growth and dysfunction in essential hypertension. Thus, beside an ECG or an echocardiogram, the measurement of plasma CT-1 could be an additional useful tool in the initial cardiac assessment of hypertensive patients. In particular, it might have clinical relevance in identifying those patients with iLVM and asymptomatic cardiac dysfunction which may be prone to progress to heart failure and other cardiovascular complications. However, before CT-1 is introduced in clinical practice, data are needed from a large cohort of patients with respect to its sensitivity and specificity, as well as its positive and negative predictive value in the detection and regression of iLVM.

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Disclosures
None.

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