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Peripheral blood concentrations of TGFβ1, IGF-1 and bFGF and remodelling of the left ventricle and blood vessels in hypertensive patients

Beata Kieć-Wilk[1], Katarzyna Stolarz-Skrzypek[2], Agnieszka Śliwa[1], Anna Zdzienicka[1], Kalina Kawecka-Jaszcz[2]

[1]Chair of Clinical Biochemistry, Jagiellonian University Medical College, Krakow, Poland
[2]1st Department of Cardiology and Hypertension, Jagiellonian University Medical College, Krakow, Poland

Abstract

Background: Remodelling process is associated with activity of such substances as transforming growth factor β1 (TGFβ1), basic fibroblast growth factor (bFGF, FGF2), or insulin like growth factor-1 (IGF-1). In the course of hypertension the remodelling of blood vessels and heart muscle takes place. Studies performed on animal models as well as clinical trials on aetiology of left ventricular hypertrophy (LVH), documented elevated level of both mRNA and proteins of TGFβ1 and IGF-1.

Aim: To analyse the correlation between cytokine levels and vascular and LV remodelling.

Methods: One hundred seven patients with essential hypertension (age 50 ± 10 years) as well as 50 healthy volunteers participated in the study. Blood pressure was measured in the doctor's office as well as using the ABPM method. The LVH was diagnosed by echocardiographic examination, while ultrasound diagnostic was used to analyse the blood vessels remodelling measured as carotid intima–media thickness. Based on echocardiography results hypertensive patients were divided into two groups — with or without LVH. Peripheral blood concentration of analysed cytokines was measured using Enzyme-Linked Immunosorbent Assay (ELISA). The results were compared with data obtained from control group of normotensive participants.

Results: Values of single measurements of growth factors levels did not show significant differences between analysed groups ($p = 0.322$), and they did not correlate with the blood pressure levels. The tendency to negative correlation between parameters of diastolic LV function and plasma concentrations of IGF-1 and TGF was found. The value of IMT also did not show significant correlation with TGFβ1, bFGF and IGF-1 in all investigated groups.

Conclusions: The obtained results point to the limited usefulness of single measurements of TGFβ1, bFGF as well as IGF-1 blood concentrations, as the potential prognostic factors of the remodelling of blood vessels and cardiac muscle in patients with essential hypertension.

Key words: bFGF, essential hypertension, growth factors, IGF-1, intima–media thickness, left ventricular hypertrophy, TGFβ1

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INTRODUCTION

Transforming growth factor β1 (TGFβ1), basic fibroblast growth factor (bFGF, FGF2) and insulin like growth factor-1 (IGF-1) are regulators of growth, cell proliferation and development [1–3]. Previous studies have confirmed the role of cytokines and growth factors in the processes of the blood vessel and cardiac remodelling [4–6]. The observations on animal models as well as in hypertensive patients with left ventricular hypertrophy (LVH) documented the presence of increased mRNA as well as protein levels of TGFβ1 and IGF-1 [7, 8].

Address for correspondence:
dr n. med. Beata Kieć-Wilk, Chair of Clinical Biochemistry, Jagiellonian University Medical College, ul. Kopernika 15a, 31–501 Kraków, Poland,
tel: +48 12 421 87 92, e-mail: mbkiec@gmail.com
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Although the role of TGFβ signalling pathway and bFGF in the development of heart hypertrophy was highlighted by transgenic animal studies [9, 10], the clinical studies investigating the relationship between cardiac hypertrophy and blood levels of cytokines and growth factors produced inconsistent results [11, 12]. Increased mRNA levels of TGFβ1 and IGF-1 in cardiomyocytes of patients with idiopathic hypertrophic cardiomyopathy suggested the importance of these substances in the regulation of cardiac hypertrophy [13, 14], however involvement of TGFβ1, bFGF and IGF-1 in the regulation of LVH development remain an issue of major controversy [11]. The observations on the role of cytokins as well as growth factors in pathogenesis of blood vessels remodelling also did not give one, simple answer. There is a theory about protective role of cytokines stabilising atherosclerotic plug or the reparative function of TGFβ1, on the other hand there are reports showing the pro-inflammatory activity of these factors, promoting restenosis after angioplastic treatment [15].

Enzyme-Linked Immunosorbent Assay (ELISA) is the recommended, suitable assay for the measurement of cytokines and growth factors in peripheral blood [16]. This method is both highly sensitive and specific [17].

The aim of this study was to compare the levels of TGFβ1, bFGF and IGF-1 in peripheral blood with the parameters of LV structure as well as intima–media thickness (IMT) of the carotid artery in hypertensive patients and control volunteers.

METHODS

Patients

One hundred fifty seven subjects (52% female, 48% male) were recruited to participate in the study. The patient group included 107 subjects with moderate hypertension (the duration of hypertension was up to 10 years), treated with the combined antihypertensive therapy. The control group (n = 50) consisted of age- and sex-matched healthy volunteers. The exclusion criteria were as follows: secondary hypertension, obesity (BMI > 30 kg/m^2), diabetes, endocrinological disorders, heart failure, arrhythmias, coronary heart disease, cardiomyopathy, kidney disease, chronic lung disease, auto-immunological disease, cancer and pregnancy.

The study was approved by the Jagiellonian University Ethics Committee.

Procedures

The blood pressure was measured in the doctor's office according to the ESC/ESH guidelines [18]. A 24-hour ambulatory blood pressure monitoring (ABPM; SpaceLabs 90207, Redmond, WA, USA) was also performed. An echocardiographic M-mode and 2D examination (Hewlett-Packard, SONOS 5500) was used to analyse the morphology and function of the LV. The LVH was defined as LV mass index (LVMI) > 125 g/m^2 in men and > 110 g/m^2 in women [19]. The IMT was measured in the common carotid artery, in the bulb of the carotid artery and in the internal carotid artery, and was used as the parameter of vessel wall remodelling (Hewlett-Packard, Sonos-5500, probe 13.5 MHz) [19]. The IMT was expressed as the mean of three measurements taken in each region of interest.

Biochemical analysis

The TGFβ1, bFGF and IGF-1 levels were measured in venous blood obtained after overnight fasting. Results were expressed as the mean of results from triplicates of each sample. For the TGFβ1 analysis 5 mL of blood was taken (without using a tourniquet) on EDTA. The blood sample was immediately placed on ice. The plasma was spun for 30 min in 1000 xg and later 10 min at 10 000 xg to remove platelets (which contain a large amount of TGF) to obtain the platelet poor plasma (PPP). The activation of TGFβ1 in PPP was obtained by acidification of PPP with 2.5 N acetic acid/10 urea and later pH was adjusted up to 7.2–7.6 using 2.7 N NaOH/1M HEPES. The analysis was done by ELISA following the Human TGF-β1 Immunoassay protocol (Quantikine, R&D Systems), method sensitivity was 7.0 pg/mL.

Blood samples for the bFGF measurements were taken into tubes containing sodium citrate according to the protocol of Human FGF basic Immunoassay (Quantikine HS, R&D Systems). Sensitivity of this method was 0.2 pg/mL. For the IGF-1 measurement blood was collected into a tube without anticoagulant. The IGF-1 in serum was measured by ELISA according to a standard protocol (Human IGF-I Immunoassay, Quantikine, R&D Systems). The sensitivity of this method was 0.026 ng/mL. The inter- and intra-assay errors were less than 5%.

Statistical methods

Statistical analysis was performed with the Statistica 6.0 PL for Windows from Statsoft. Results are presented as mean ± SD or numbers and percentages. The χ^2 test was used for comparison of proportions and unpaired t-test for comparison of quantitative variables. The differences between variables in the investigated groups were compared by analysis of variance (ANOVA), and the correlations between variables was checked by regression analysis. Levels of statistical significance were set at $p < 0.05$.

RESULTS

The hypertensive patients were divided according to the presence of LVH into the LVH (+) (n = 52) and LVH (–) (n = 55) group. Ultrasound analysis of carotid arteries showed significantly increased IMT in hypertensive patients with LVH compared to other groups [p = 0.002 for control, p = 0.034 for LVH (–)] (Fig. 1).

Single measurements of TGFβ1, IGF-1 and bFGF levels did not show any differences between the groups (p = 0.322) (Fig. 2). The mean IGF blood concentration measured was:

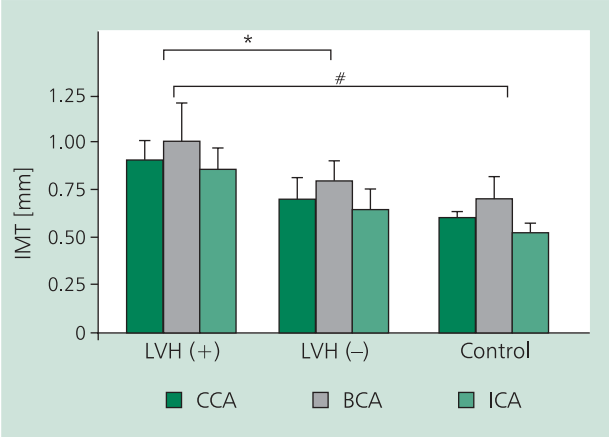

Figure 1. Comparision of the intima-media thickness in the studied groups; IMT — intima-media thickness; BCA — bulb of carotid artery; CCA — common carotid artery; ICA — internal carotid artery; LVH (+) and LVH (–) — group of hypertensive patients with LVH and without LVH; *p < 0.05 *vs* LVH (–), #p < 0.05 *vs* Controls

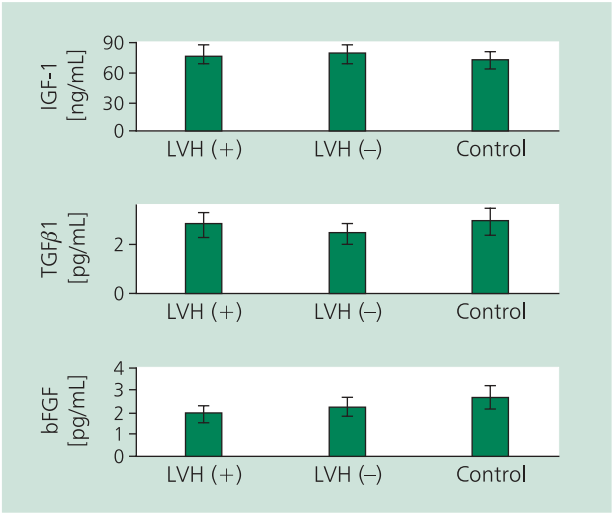

Figure 2. Comparison of the levels of TGFβ1, bFGF and IGF-1 in the studied groups. Abbreviations as in Figure 1

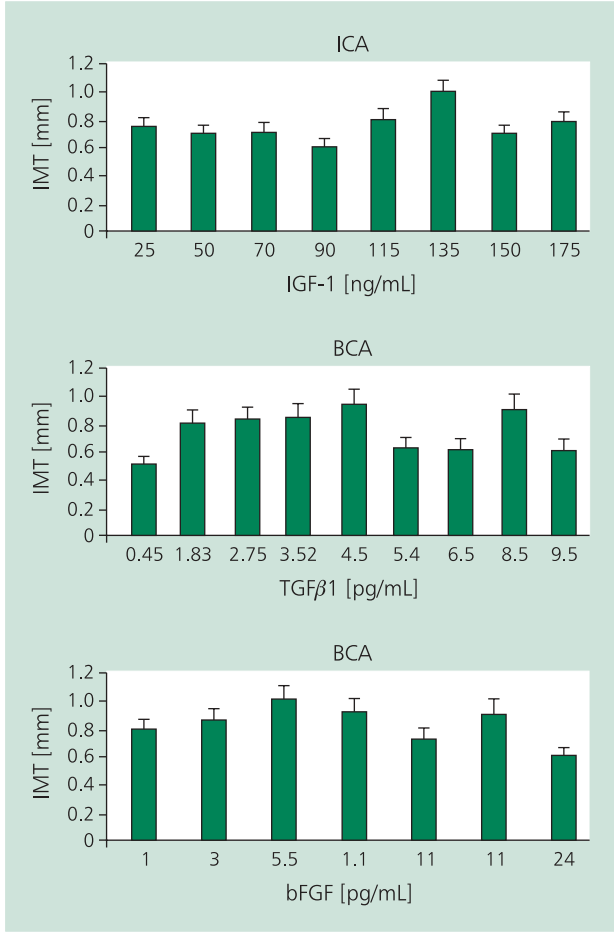

Figure 3. Relationship between TGFβ1, bFGF and IGF-1 levels and intima–media thickness (IMT) parameters in three investigated groups. Abbreviations as in Figure 1

in control group 72.3 ng/mL; in group LVH (+) 78.5 ng/mL and in LVH (–) 78 ng/mL. The TGFβ1 level was respectively: 2.85 pg/ml in controls, 2.74 pg/mL in the LVH (+) group and 2.38 pg/ml in the LVH (–) group. The bFGF mean concentration was 2.63 pg/mL in control group; 1.91 pg/mL in LVH (+) and 2.21 pg/mL in LVH (–).

Additional analysis of the investigated factors (TGFβ1, bFGF and IGF-1) in controls and hypertensive patients, independently to the presence/absence of LVH, did not show any significant correlations. The ultrasound measurements of carotid IMT did not show significant correlation with TGFβ1, bFGF and IGF-1 blood levels (Fig. 3). Regression analysis did not revealed significant correlation between TGFβ1, bFGF, and IGF-1 levels in peripheral blood and blood pressure, either measured in the office or monitored with ABPM (Table 1).

The analysis of LV function showed a tendency toward a negative correlation between the parameters of diastolic dysfunction (E/A ratio and IVRT) and blood levels of IGF-1 and between the E wave deceleration time and blood levels of TGFβ1 (Table 2).

DISCUSSION

Among numerous factors that influence vascular wall remodelling and the process of LVH in the course of hypertension, the activity of different cytokines and growth factors have been demonstrated [5, 7, 20]. Our results confirmed the lack of correlation between the plasma levels of TGFβ1, bFGF and IGF-1 and the LV remodelling in the course of hypertension. These results are in concordance with other reports describing the lack of association between the cytokine serum level and LV mass in hypertensive patients [21].

Table 1. The correlation between systolic (SBP) and diastolic (DBP) blood pressure values and the TGFβ1, bFGF and IGF-1 levels in peripheral blood of hypertensive patients (with and without LVH) and controls.

Office blood pressure level

Blood pressure	Factor	Coefficient of line inclination	P
SBP [mm Hg]	TGF [pg/mL]	0.057	0.943
	bFGF [pg/mL]	–0.532	0.254
	IGF-1 [ng/mL]	–0.029	0.326
DBP [mm Hg]	TGF [pg/mL]	–0.135	0.789
	bFGF [pg/mL]	–0.733	0.091
	IGF-1 [ng/mL]	–0.045	0.153

Ambulatory blood pressure monitoring

Parameter	Factor	Coefficient of line inclination	P	Parameter	Factor	Coefficient of line inclination	P
SBP 24 h [mm Hg]	TGF [pg/mL]	–0.148	0.067	DBP 24 h [mm Hg]	TGF [pg/mL]	–0.241	0.053
	bFGF [pg/mL]	0.045	0.591		bFGF [pg/mL]	–0.019	0.818
	IGF-1 [ng/mL]	0.006	0.943		IGF-1 [ng/mL]	–0.049	0.961
SBP day [mm Hg]	TGF [pg/mL]	–0.138	0.206	DBP day [mm Hg]	TGF [pg/mL]	–0.112	0.165
	bFGF [pg/mL]	0.002	0.982		bFGF [pg/mL]	–0.039	0.843
	IGF-1 [ng/mL]	–0.017	0.843		IGF-1 [ng/mL]	–0.064	0.791
SBP night [mm Hg]	TGF [pg/mL]	–0.108	0.102	DBP night [mm Hg]	TGF [pg/mL]	–0.119	0.087
	bFGF [pg/mL]	–0.001	0.995		bFGF [pg/mL]	–0.004	0.101
	IGF-1 [ng/mL]	–0.043	0.862		IGF-1 [ng/mL]	–0.040	0.630

SBP 24 h — mean level of SBP during 24 h; DBP 24 h — mean level of DBP during 24 h; SBP day — mean level of SBP measured during the day (6am–10pm); DBP day — mean level of DBP measured during the day (6am–10pm); SBP night — mean level of SBP measured during the night (10pm–6am); DBP night — mean level of DBP measured during the night (10pm–6am)

Table 2. Influence of TGFβ1, bFGF and IGF-1 level on the left ventricle parameters in all investigated groups: LVH (+), LVH (–) and control

Parameter	Factor	Coefficient of line inclination	P	Parameter	Factor	Coefficient of line inclination	P
LVMI [g/m^2]	TGF [pg/mL]	–0.013	0.876	IVRT [ms]	TGF [pg/mL]	–0.085	0.758
	bFGF [pg/mL]	–0.127	0.189		bFGF [pg/mL]	0.002	0.581
	IGF-1 [ng/mL]	–0.015	0.983		IGF-1 [ng/mL]	0.035	0.147
IVSD [mm]	TGF [pg/mL]	–0.018	0.823	E [cm/s]	TGF [pg/mL]	–0.128	0.112
	bFGF [pg/mL]	–0.103	0.202		bFGF [pg/mL]	0.005	0.832
	IGF-1 [ng/mL]	0.003	0.973		IGF-1 [ng/mL]	–0.063	0.661
PWD [mm]	TGF [pg/mL]	–0.067	0.415	A [cm/s]	TGF [pg/mL]	0.072	0.505
	bFGF [pg/mL]	–0.126	0.130		bFGF [pg/mL]	–0.039	0.753
	IGF-1 [ng/mL]	–0.003	0.973		IGF-1 [ng/mL]	–0.168	0.128
E/A	TGF [pg/mL]	–0.114	0.725	decE [ms]	TGF [pg/mL]	0.146	0.064
	bFGF [pg/mL]	0.001	0.993		bFGF [pg/mL]	0.028	0.919
	IGF-1 [ng/mL]	–0.120	0.117		IGF-1 [ng/mL]	0.057	0.416

LVMI — left ventricular mass index; IVSD — inter-ventricular septum in diastole; IVRT — intra-ventricular relaxation time; PWD — posterior wall in diastole; E, A — wave E and wave A parameters of left ventricle relaxation; decE — deceleration of wave E

The cardiovascular remodelling in hypertension has been analysed for several years [5, 21, 22]. In our study considerable attention was paid to the recruitment and homogeneity of the groups. The antihypertensive medication was an important difference between the controls and the hypertensive patients, but the treatment could not be discontinued for ethical reasons.

Our study did not show any significant relationship between investigated factors and blood vessels structure. The presented results are in agreement with previous clinical observations which did not find any correlation between IMT value and IGF-1 level [23, 24].

The role of TGFβ1, as well as IGF-1 in the development of heart muscle hypertrophy has been confirmed by several *in vitro* studies [25, 26]. In an *in vivo* model increased mRNA and protein levels of TGFβ1 and of bFGF in cardiomyocytes of hypertrophied heart have been demonstrated [2, 27]. Only of non-significant tendency towards a correlation between the LV diastolic dysfunction and the studied cytokines was observed. These findings argue for the local, intramuscular role of generated TGFβ1, and IGF-1 in the pathogenesis of cardiovascular wall remodelling [19, 28]. The impaired relaxation of the LV precedes the development of LVH in hypertensive patients [29]. There exists a single report about the possible beneficial effect of IGF-1 for diastolic relaxation [30]. The correlation between overproduction of TGFβ1 and impaired filling of the LV in obese and overweight hypertensive patients was reported [11]. However, such a correlation did not reach significance in hypertensive patients with normal body mass index [11], which is in line with the results obtained in our study.

Our results do not exclude the local role of TGFβ1, bFGF and IGF-1 in the pathogenesis of the hypertension-associated vessel wall remodelling or LVH. It has been demonstrated that growth factors act mainly in the area of their production [19]. The blood levels obtained by single measurements may not reflect the local concentration of cytokine in the target organ. Both experimental and clinical studies failed to document the correlation between TGFβ1, bFGF and IGF-1 blood levels and tissue remodelling in the course of hypertension [31]. However, it may be speculated that monitoring the level of these factors in the early stages of hypertension performed individually may be useful for the early detection of decreased relaxation of LV musculature, which precedes the development of LVH [29].

CONCLUSIONS

Our observations bring into question the importance of the single measurements of TGFβ1, bFGF and IGF-1 levels in peripheral blood as the predictive factors of cardiovascular remodelling in the course of hypertension.

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Stężenie czynników TGFβ1, IGF-1 i bFGF we krwi obwodowej a przebudowa lewej komory i naczyń tętniczych u pacjentów z nadciśnieniem tętniczym

Beata Kieć-Wilk[1], Katarzyna Stolarz-Skrzypek[2], Agnieszka Śliwa[1], Anna Zdzienicka[1], Kalina Kawecka-Jaszcz[2]

[1]Katedra Biochemii Klinicznej, *Collegium Medicum*, Uniwersytet Jagielloński, Kraków
[2]I Klinika Kardiologii i Nadciśnienia Tętniczego, *Collegium Medicum*, Uniwersytet Jagielloński, Kraków

Streszczenie

Wstęp: Przebudowa tkanek wiąże się z produkcją takich czynników, jak TGFβ1 (transforming growth factor β1), bFGF (basic fibroblast growth factor, FGF2) czy IGF-1 (insulin-like growth factor-1). W przebiegu nadciśnienia tętniczego dochodzi do przebudowy naczyń i serca. Badania przeprowadzone na modelach zwierzęcych oraz próby kliniczne nad przerostem ściany lewej komory (LVH) w przebiegu nadciśnienia tętniczego potwierdziły podwyższone stężenie mRNA oraz białka TGFβ1 i IGF-1.

Cel: Celem niniejszej pracy była ocena związku stężeń TGFβ1, bFGF oraz IGF-1, mierzonych we krwi obwodowej, z parametrami struktury lewej komory oraz z wartościami grubości kompleksu intima–media (IMT), wskaźnika przebudowy ścian naczyń u pacjentów z nadciśnieniem tętniczym, u których rozwinęły się (lub nie) zmiany narządowe, oraz u osób zdrowych z prawidłowym ciśnieniem tętniczym.

Metody: W badaniu uczestniczyło 107 pacjentów z nadciśnieniem tętniczym (w wieku 50 ± 10 lat) oraz 50 zdrowych ochotników dobranych pod względem płci i wieku. Pomiary ciśnienia tętniczego przeprowadzono w gabinecie lekarskim oraz wykonano 24-godzinny nieinwazyjny pomiar ciśnienia tętniczego (ABPM). Przerost lewej komory rozpoznawano na podstawie badania echokardiograficznego, a diagnostyka ultrasonograficzna obrazowała przebudowę naczyń na podstawie wartości IMT. Uwzględniając wyniki badania echokardiograficznego pacjentów z nadciśnieniem podzielono na dwie grupy — z LVH i bez LVH. Stężenie we krwi obwodowej badanych cytokin mierzono przy użyciu metody ELISA (Enzyme-Linked Immunosorbent Asay).

Wyniki: Stężenia czynników wzrostu w pojedynczym pomiarze nie różniły się istotnie między badanymi grupami ($p = 0{,}322$); nie korelowały także z wartościami ciśnienia tętniczego. Zaobserwowano tendencję do negatywnej korelacji pomiędzy parametrami funkcji rozkurczowej lewej komory a stężeniami IGF-1 i TGF w surowicy krwi. Wartość IMT w badanych grupach również nie wykazała istotnego związku ze stężeniem TGFβ1, bFGF oraz IGF-1.

Wnioski: Uzyskane wyniki wskazują na ograniczoną przydatność diagnostyczną pojedynczego pomiaru stężeń TGFβ1, bFGF oraz IGF-1 w surowicy krwi obwodowej jako czynnika prognostycznego przebudowy serca oraz ścian naczyń u pacjentów z nadciśnieniem, a przez to w stratyfikacji ryzyka osób z nadciśnieniem tętniczym.

Słowa kluczowe: bFGF, czynniki wzrostu, IGF-1, IMT, przerost lewej komory, nadciśnienie tętnicze, TGFβ1

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Adres do korespondencji:
dr n. med. Beata Kieć-Wilk, Katedra Biochemii Klinicznej, *Collegium Medicum*, Uniwersytet Jagielloński, ul. Kopernika 15a, 31–501 Kraków, tel: +48 12 421 87 92, e-mail: mbkiec@gmail.com
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