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Myocardial dysfunction in treated adult hypopituitarism: a possible explanation for increased cardiovascular mortality

Manjit Shahi, Salem A Beshyah, David Hackett, Patrick S Sharp, Desmond G Johnston, Rodney A Foale

Abstract

***Objective*—To assess cardiac structure and function in patients with treated hypopituitarism and to determine their relation to the degree of growth hormone deficiency and body composition pattern.**

***Design*—26 patients with treated hypopituitarism were studied by cross sectional and Doppler echocardiography and by exercise testing. The results were analysed and their relation to the degree of growth hormone deficiency and body composition determined.**

***Setting*—All tests were performed in the department of cardiology and the unit of metabolic medicine at a tertiary referral centre.**

***Patients*—Patients with hypopituitarism referred for endocrine assessment.**

***Main outcome measures*—Left ventricular mass, left ventricular diastolic function, and exercise capacity in patients with hypopituitarism and their relation to growth hormone deficiency.**

***Results*—Mean (SD) serum concentration of insulin-like growth factor 1 (IGE-1), a measure of growth hormone deficiency, was 82·4 (45) μg/l. Lean body mass calculated by measuring total body potassium was 50 (9) kg. All patients had a normal left ventricular mass index and a normal left ventricular ejection fraction. Eight patients had abnormal left ventricular diastolic function. There was a significant correlation between IGF-1 and left ventricular mass ($r = 0·45$, $p < 0·02$). Lean body mass was also significantly correlated with left ventricular mass ($r = 0·78$, $p < 0·0001$) and left ventricular diastolic function ($r = -0·63$, $p < 0·01$). The mean exercise duration was 8·6 (3·6) minutes. There was a significant correlation between serum IGF-1 and the rate-pressure product on exercise ($r = 0·47$, $p < 0·01$). Seven patients had planar ST segment depression > 0·1 mV during exercise testing. In five of these patients there was rapid resolution of ST segment depression immediately after exercise. Two patients developed considerable ST segment depression, and subsequent coronary angiography showed normal coronary arteries. Exercise-induced ST segment depression was not related to the severity or duration of growth hormone deficiency or serum cholesterol concentration.**

***Conclusions*—This study suggests that left ventricular mass and the rate-pressure product are related to the degree of growth hormone deficiency, that left ventricular diastolic dysfunction is frequently seen in hypopituitarism, and that these patients may have ischaemic-like ST segment changes during exercise testing. These findings may explain the increased cardiovascular mortality in patients with hypopituitarism and may also have implications for growth hormone replacement therapy in adults.**

Clinical Department of Cardiology, St Mary's Hospital, London
M Shahi
D Hackett
R A Foale

Unit of Metabolic Medicine, St Mary's Hospital, London
S A Beshyah
P S Sharp
D G Johnston

Correspondence to
Dr Manjit Shahi, Clinical Department of Cardiology, St Mary's Hospital, Praed Street, London W2 1NY.

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Patients who develop hypopituitarism in adulthood have conventionally received replacement therapy with thyroxine, cortisone, and sex hormones but not growth hormone. This has in part been because of the limited availability of growth hormone and the belief that growth hormone has no important action once final linear growth has been achieved.[1] However, growth hormone has now been made available in essentially unlimited amounts and in a pure synthetic form by genetic engineering techniques. Also, recent evidence has suggested that the increased cardiovascular mortality, in particular a high incidence of myocardial infarction and heart failure, seen in patients with treated hypopituitarism may be due to growth hormone deficiency.[2]

Growth hormone is known to be a potent agent affecting anabolism and lipolysis. Adults with growth hormone deficiency are known to have an altered body composition with excess body fat and decreased lean body mass.[3] This form of change in body composition has been previously shown to be associated with an increased risk of cardiovascular disease in symptom free individuals.[4,5] In addition, growth hormone seems to be important in the regulation of plasma lipids, with deficiency of growth hormone often causing hypercholesterolaemia.[6,7]

The aim of the present study was to assess cardiac structure and function in patients with treated hypopituitarism and to determine their relation to the degree of growth hormone deficiency and body composition pattern.

Patients and methods

PATIENTS

Patients recruited into the study had documented hypopituitarism mostly resulting from pituitary or parapituitary tumours treated surgically, with radiotherapy, or with both. All

had been on hormonal replacement therapy with thyroxine and adrenal and sex steroids, if appropriate, for at least one year. Optimal substitution with thyroxine and adrenal steroids were defined as a total serum thyroxine (T4) within the normal reference range and at least one plasma cortisol value > 350 nmol/l during the day. In addition, all patients were severely deficient in growth hormone, defined as a growth hormone response of < 5 mU/l during an insulin induced hypoglycaemia test (serum glucose < 2·2 mmol/l) or, if hypoglycaemia was contraindicated, a growth hormone response of < 5 mU/l in response to 50 μg oral clonidine. No patient had previously received growth hormone replacement.

METABOLIC ASSESSMENT

Lean body mass was calculated from total body potassium[8] which was measured in a whole-body potassium-40 counter (MRC Cyclotron Unit, Hammersmith Hospital). Serum insulin-like growth hormone factor (IGF-1), a measure of growth hormone deficiency, was measured by radioimmunoassay.[9] The mean value of IGF-1 in our laboratory in 40 healthy volunteers was 215 (40) μg/l.

ECHOCARDIOGRAPHY

Each patient was examined in the left lateral supine position by cross sectional and Doppler echocardiography with a phased array sector scanner (General Electric Pass 11, 3·5 MHz transducer) in a standardised examination protocol.[10] Left ventricular septal and posterior wall thickness, and cavity dimensions were measured from the parasternal left ventricular short axis projections at the chordae and papillary muscle junction by cross sectionally guided M mode echocardiography. Left ventricular mass was determined by an area × length method which has been previously been validated in humans[11] with all measurements taken at end diastole and at end expiration. Two echocardiographic views are required to make this calculation: a parasternal short axis view of the left ventricle at the papillary muscle tip level to determine the area of the myocardium and an apical four chamber view that maximises the distance from the mitral valve annulus to the left ventricular apex to determine the length of the ventricle (fig 1). The following formula was used to calculate left ventricular mass: LV mass = $1{\cdot}04\,(5/6\,A_1xl_1 - 5/6\,A_2xl_2)$ where A_1 and A_2 represent the epicardial and endocardial areas respectively (measured by planimetry) and l_1 and l_2 represent the length of the left ventricle from mital annulus to epicardial and endocardial borders respectively. Left ventricular mass index was determined by dividing the left ventricular mass by the patient's body surface area ($S = M^{0{\cdot}425} \times H^{0{\cdot}725} \times 71{\cdot}84$, where S = body surface area (cm^2), M = body mass (kg), and H = height (cm)).

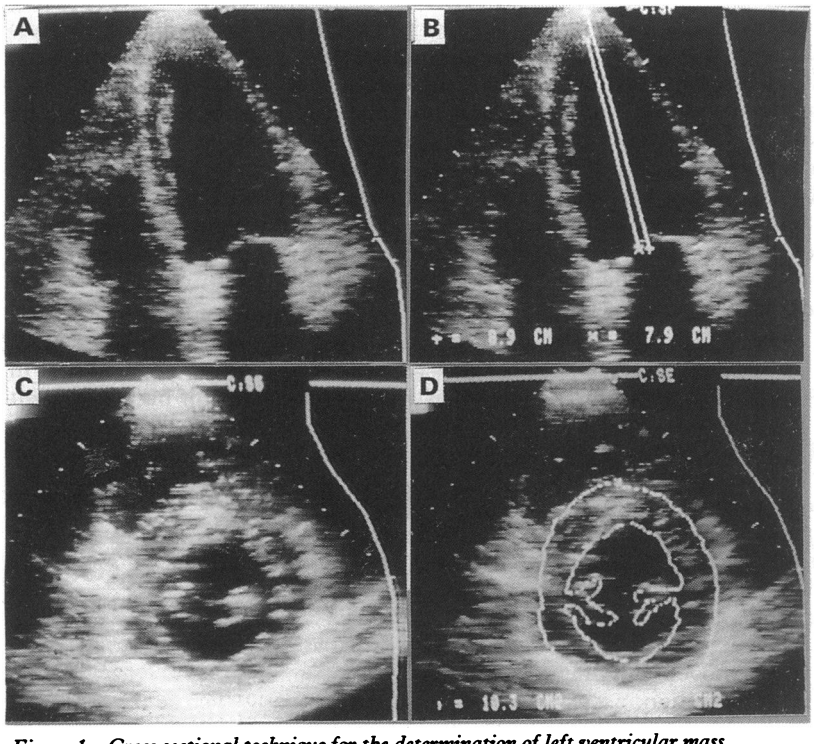

Figure 1 Cross sectional technique for the determination of left ventricular mass. (A) Apical four chamber view, (B) length of left ventricle from mitral annulus to epicardial and endocardial borders, (C) parasternal short axis view, (D) epicardial and endocardial areas measured by planimetry. See text for method of calculation.

DOPPLER STUDIES

Pulsed Doppler examination of transmitral flow was recorded from the apical four chamber view with reference to the cross sectional echocardiographic image. The sample volume was positioned between the mitral annulus and the tips of the mitral leaflets with the position adjusted to maintain the sample volume at an angle as near parallel to transmitral flow as possible by using the audible signal and spectral velocity display. When the maximum transmitral velocity for the early filling wave was detected, we recorded the velocity profile at 50 mm/s with the patient in passive end expiration. The peak flow velocities of the early and atrial waves were measured from the three consecutive cardiac cycles that showed the highest measurable velocity profiles.

The isovolumic relaxation time (IVRT) was measured from the apical five chamber view by placing the continuous wave Doppler beam between the mitral and aortic valve junction. The interval between the end of the aortic velocity envelope and the onset of the early filling wave was taken to represent the isovolumic relaxation time. Abnormal left ventricular diastolic function was defined as follows: IVRT > 82 ms and E/A ratio < 1·5 between the ages of 20 and 29; IVRT > 92 ms and E/A ratio < 1·4 between the ages of 30 and 49; IVRT > 100 ms and E/A ratio < 0·8 between the ages of 50 and 59.[12 13]

EXERCISE ASSESSMENT

Symptom-limited, graded multistage treadmill exercise testing according to Bruce's standard protocol[14] was performed by all patients in a temperature and humidity controlled environment with standard safety precautions. Heart rate and blood pressure were measured at the end of each stage of the protocol and exercise was stopped by symptoms such as leg weakness, shortness of breath, or exhaustion. Data

Table 1 Patient details

Patient	Sex	Age (yr)	BMI (kg/m²)	DOH (yr)	Cholesterol (mmol/l)	Triglyceride (mmol/l)	Diagnosis	Replacement* therapy
1	M	34	26·6	15	8·67	2·0	Cushing's	A, B, C
2	M	59	26·2	28	7·78	3·1	CP	A, B, C, D
3	M	47	28·2	5	9·02	3·4	CP	A, B, C, D
4	M	64	25·0	9	6·09	1·2	Prolactinoma	A, B, C
5	M	59	25·7	9	7·94	1·3	Prolactinoma	A, C
6	M	52	26·0	3	5·92	3·9	Cushing's	A, B
7	M	27	19·4	6	7·41	1·2	Pinealoma	A, B, C
8	M	45	29·9	3	6·09	1·7	NFA	A, B, C
9	M	59	29·5	20	5·37	0·9	NFA	A, B, C
10	M	50	33·8	6	3·35	1·0	Prolactinoma	B, C
11	M	44	32·4	4	8·64	1·1	NFA	A
12	M	41	33·5	2	4·93	1·1	Prolactinoma	C
13	M	63	33·9	1	9·37	1·2	NFA	A, B, C
14	F	53	25·1	21	10·0	1·9	CP	A, B, D
15	F	59	27·5	15	10·0	1·9	NFA	A, B, E
16	F	57	29·7	1	5·72	0·6	NFA	A, B
17	F	47	29·1	16	7·63	1·7	Cushing's	A, B
18	F	26	21·8	3	7·79	1·4	CP	A, B, D, E
19	F	38	30·5	3	6·90	1·0	Cushing's	A, E
20	F	41	32·1	6	4·67	1·3	Prolactinoma	A, B, D
21	F	44	31·1	3	9·00	9·2	Prolactinoma	A, B, D, E
22	F	53	26·3	6	5·60	1·1	Meningioma	A, B
23	F	49	23·5	4	7·60	1·9	NFA	A, B, D
24	F	43	32·7	3	6·28	1·8	Prolactinoma	D
25	F	27	26·5	4	5·20	1·3	CP	D
26	F	41	19·9	3	6·64	0·7	NFA	B

BMI, body mass index; DOH, duration of hypopituitarism; CP, craniopharyngeoma; NFA, non-functioning adenoma.
*A, thyroxine; B, adrenal steroids; C, testosterone; D, desmopressin; E, oestrogen/progesterone.

from the exercise tests were analysed by computer assisted methods to give exercise time, workload, heart rate × systolic blood pressure product at peak exercise, and extent of electrocardiographic ST segment change. The level of the ST segment 0·08 s after the J point was measured in each lead using an average beat every one minute and only planar ST segment depression > 0·1 mV was considered to be abnormal. ST segment depression found by the average beat analysis was confirmed on the actual electrocardiogram by manual measurement.

Results

PATIENT CHARACTERISTICS

Twenty six patients (13 men and 13 women) with confirmed hypopituitarism were recruited into the study during the period December 1989–January 1991. All patients attended the endocrinology clinic in our hospital. The mean (SD) age was 46 (11) years (range 26–64 years). Table 1 shows the primary diagnosis, duration of hypopituitarism, duration of hormone replacement therapy, and other patient details. The lean body mass and body fat were 50 (9) kg (range 38–64 kg) and 30 (11) kg (range 11–55 kg) respectively. The degree of growth hormone deficiency, assessed by serum concentration of insulin-like growth factor (IGF-1) was 82 (45) μg/l (range 21–221 μg/l). There was a significant positive correlation between IGF-1 and lean body mass in our patients ($r = 0·5$; $p < 0·01$). No patient had a previous history of ischaemic heart disease, peripheral vascular disease, or hypertension except for one patient with Cushing's disease (patient 6) whose blood pressure had been raised before his pituitary tumour was removed but then returned to normal after the operation.

ECHOCARDIOGRAPHIC AND DOPPLER CHARACTERISTICS

All patients had a normal left ventricular ejection fraction (67 (8)%) and a normal left ventricular mass index (men 101 (17) g/m² range 76–132 g/m²; women 84 (20) g/m² range 56–119 g/m²) but the distribution was skewed towards the lower end of the normal range (skew 0·25). Patients who had Cushing's disease did not have higher left ventricular mass indexes. Table 2 shows the other echocardiographic and Doppler characteristics. Compared with the age related reference values established by previous investigators,[13 14] thirteen patients (50%) had an abnormally prolonged isovolumic relaxation time (112 (15) ms) and eight (31%) had both an increased isovolumic relaxation time (103 (8) ms) and evidence of abnormal left ventricular filling (E/A ratio 1·06 (0·25) table 3). There was significant correlation between left ventricular mass and serum IGF-1 ($r = 0·45$; $p < 0·02$). Left ventricular mass and left ventricular filling were related to lean body mass ($r = 0·78$ $p < 0·0001$; $r = -0·63$ $p < 0·001$) (figure 2A–C). There was no relation between left ventricular mass and duration of hypopituitarism.

EXERCISE ASSESSMENTS

The mean exercise duration during the Bruce protocol was 8·6 (3·6) minutes. The exercise test was terminated because of leg weakness in seven patients, by shortness of breath in eight

Table 2 Echocardiographic and Doppler characteristics of study patients

Variable	Mean (SD)	Range
LV septum (cms)	0·85 (0·2)	0·5–1·1
LV posterior wall (cms)	0·84 (0·2)	0·6–1·1
LV internal diameter (cms)	4·82 (0·4)	4·1–5·6
LV mass (male) (g)	212 (49)	138–323
LV mass (female) (g)	148 (42)	92–231
IVRT (ms)	103 (16)	72–140
E (cm/s)	64 (13)	38–87
A (cm/s)	55 (10)	36–71
E/A ratio	1·18 (0·31)	0·74–1·94

LV, left ventricle; IVRT, isovolumic relaxation time; E, early filling velocity; A, atrial filling velocity.

Table 3 Details of patients with abnormal left ventricular diastolic function

Patient	Age (yr)	Heart rate	IVRT (ms)	E (cm/s)	A (cm/s)	E/A	Max ST depression on exercise (mV)
1	34	70	108	66	48	1·37	None
3	47	65	96	66	58	1·15	0·22
7	27	77	92	78	62	1·26	0·13
8	45	69	111	49	62	0·8	0·19
9	59	78	108	39	51	0·77	None
11	44	63	94	72	61	1·17	None
12	41	74	112	48	65	0·74	None
18	26	73	104	75	59	1·25	None

IVRT, isovolumic relaxation time; E, early filling velocity; A, atrial filling velocity.

patients, and by exhaustion in 11 patients. No patient developed chest pain during exercise. A significant correlation was seen between serum IGF-1 and the rate-pressure product (systolic blood pressure × heart rate) at peak exercise ($r = 0{\cdot}47$; $p < 0{\cdot}01$; fig 2D) but not with exercise duration ($r = 0{\cdot}1$; p = NS). Baseline electrocardiograms were normal in all patients except for patients 8 and 15 who had minor ST segment abnormalities in the lateral chest leads. Seven patients developed planar ST segment depression > 0·1 mV during exercise testing (maximum ST segment depression in these seven patients was 0·18 (0·03) mV). In five of these patients the ST segment depression occurred at a high workload with immediate resolution after exercise. Two patients developed ST segment depression after a few minutes of exercise with slow resolution during the post-exercise period. Subsequent coronary angiography showed no abnormality of the epicardial coronary arteries. Exercise-induced ST segment depression was not related to the severity or duration of growth hormone deficiency or to serum cholesterol concentration. Three of these seven patients also had abnormal left ventricular diastolic function.

Discussion

The principal findings of this study were firstly that in patients with treated hypopituitarism but without growth hormone replacement therapy the left ventricular mass and maximum cardiac work achieved on exercise were inversely related to the degree of growth hormone deficiency. Second, left ventricular diastolic dysfunction seems to be a frequent finding in these patients and furthermore these patients often have ischaemia-like ST segment changes during exercise testing.

All of the patients in this study had a normal left ventricular mass index with a trend towards the lower end of the normal range. The relation between left ventricular mass and body weight/lean body weight seen in this study is similar to that reported in healthy individuals.[15] However, the relation between left ventricular mass and the degree of growth hormone deficiency is surprising, because it suggests that growth hormone may still be necessary for the maintenenace of cardiac size in adulthood. Growth hormone administration in adult rats increased left ventricular mass in proportion to the observed increase in body weight.[16] In humans, however, four months of growth hormone replacement therapy given to growth hormone deficient adults had no significant effect on left ventricular mass.[17] It is possible, however, that left ventricular mass may increase with longer term replacement therapy. Whether our measurements of left ventricular mass are indeed "normal" for these patients is open to debate; however, the inverse relation between the degree of growth hormone deficiency and peak cardiac work on exercise (rate-pressure product) suggests that the exercise capacity of the heart is impaired in hypopituitarism. Nonetheless, the mechanism for exercise

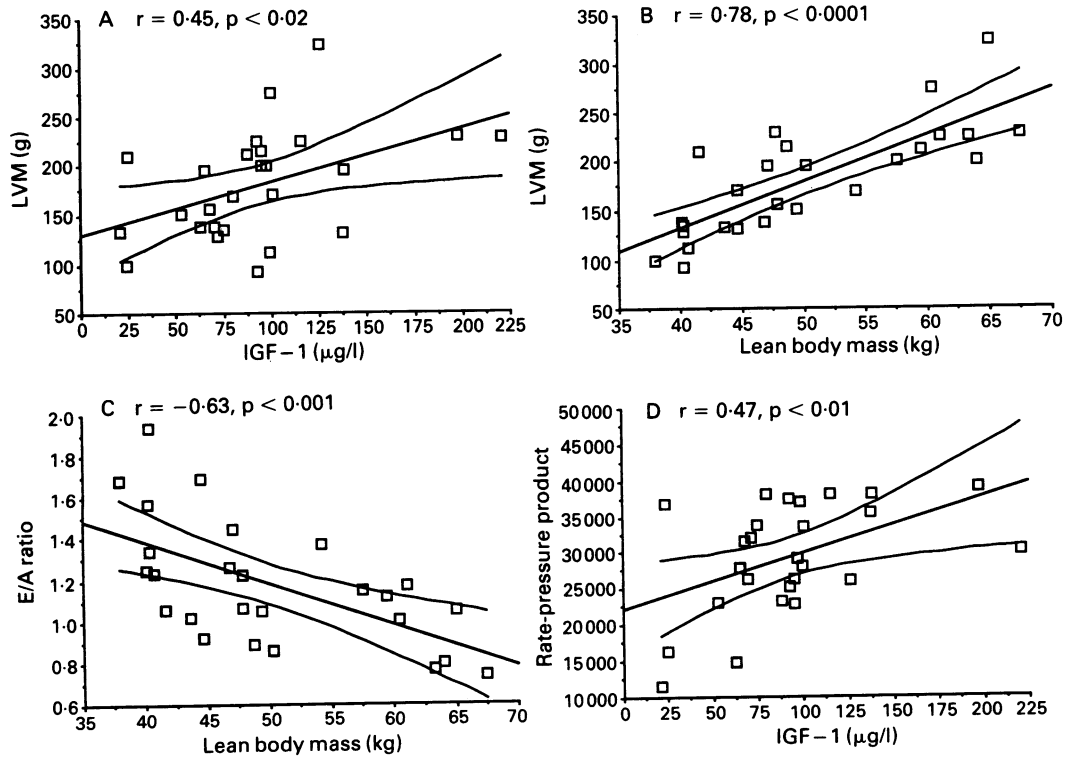

Figure 2 (A) Relation between serum IGF-1 and left ventricular mass (LVM), (B) relation between lean body mass and LVM, (C) relation between lean body mass and left ventricular filling (E/A ratio), (D) relation between serum IGF-1 and the rate-pressure product. The regression line and its 95% confidence limits are shown for each scattergram.

limitation in this patient population is complex and probably relates to a combination of peripheral muscle atrophy, deconditioning, and changes in cardiac function. In the present study, only seven of the 26 patients had their exercise test stopped because of leg weakness while the rest were stopped by shortness of breath or extreme exhaustion.

The frequent finding that abnormalities of left ventricular diastolic function in the presence of normal left ventricular systolic function in patients with hypopituitarism has not been described before. It has been suggested that these abnormalities are a possible precursor of left ventricular systolic failure and may be the earliest manifestations of cardiac failure.[18] These abnormalities may explain the increased incidence of heart failure in patients with hypopituitarism.[2] Whether growth hormone replacement therapy will improve this abnormality is not known. However, in healthy people growth hormone therapy increased myocardial contractility and cardiac output[19] and therefore it might be able to reverse the diastolic abnormalities observed in this study. Growth hormone therapy was shown to benefit one growth hormone deficient patient with severe cardiac failure.[20]

Nor has the increased incidence of ST segment depression on exercise, similar to that seen in patients with coronary artery disease, been reported before in patients with hypopituitarism. Most of these patients developed these abnormalities at a high workload; however, two patients did have ST segment depression at a low workload and subsequent coronary angiography was normal. Although these may have been false positive electrocardiographic responses to exercise testing, it may in light of the known increased cardiovascular mortality in these patients suggest that they have small coronary vessel disease or some undisclosed form of myocardial disease. McHenry and colleagues reported that symptom free patients who had not had coronary angiography had about a 40% chance of developing coronary artery disease over a 14 year period if they had an ischaemic-type response to exercise.[21] If the outcome were similar in our patients, with their additional risk of increased serum cholesterol, this could explain the increased incidence of myocardial infarction observed in patients with treated hypopituitarism.[2]

We cannot be certain that inadequate replacement therapy of other pituitary dependent hormones—for example, thyroxine, cortisol, and oestrogen therapy, was not the reason for the abnormal cardiac findings in our patients. However, all our patients had been euthyroid for at least one year and had thyroxine (T_4) concentrations within the normal range. Patients with Cushing's disease had been cured for at least three years and sex hormones were prescribed to all patients. In addition no patients had hypertension or diabetes mellitus.

Though we did not study age matched controls our criteria for abnormality were strictly defined and lay outside the 95% confidence intervals of the normal range reported by others.

In conclusion, we found that patients with treated hypopituitarism had abnormalities of cardiac structure and function that may explain the increased incidence of cardiovascular mortality observed in these patients. The relation with the degree of growth hormone deficiency may have implications for growth hormone replacement therapy in adults.

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