B. L. Herrmann[1]
K. Brandt-Mainz[2]
B. Saller[1]
C. Bruch[3]
H. Wieneke[3]
C. Kügler[4]
S. Ferdin[1]
S. Hahn[1]
R. Erbel[3]
A. Bockisch[2]
K. Mann[1]

Myocardial Perfusion Abnormalities in Patients with Active Acromegaly

Abstract

Cardiomyopathy is often seen in patients with a long history of acromegaly. In order to screen for perfusion abnormalities, patients with active acromegaly without evidence for coronary heart disease were examined by single photon emission computed tomography (SPECT). The study included a group of 11 strictly selected patients with active acromegaly (7 males and 4 females; age 51 ± 12 y [mean ± S.D.]) with elevated age-adjusted IGF-I levels (IGF-I 569 ± 193 µg/l; GH 31.2 ± 56.3 µg/l) compared to an age- and sex-matched non-acromegalic control group with comparable muscle mass index of the left ventricle (126 ± 41 active vs. 122 ± 33 g/m^2 control group) and body mass index (26.6 ± 2.7 vs. 27.0 ± 5.0 kg/m^2). To address this issue, myocardial perfusion was investigated by single photon emission computed tomography (SPECT) using a triple head gamma-camera. 70 MBq ^{201}TlCl was injected, and post-stress (from bicycle ergometer) images were obtained. Images were interpreted quantitatively by bull's eye polary map (16 regions of the left ventricle) and were compared to the control group. In the patients with active acromegaly, the mean nuclide uptake of the 16 regions of the left ventricle after bicycle stress examination was lower than in the control group (82.99 ± 2.85 active vs 85.48 ± 1.29 control group, $p < 0.01$). Nonhomogeneity of nuclide uptake was defined as the standard deviations of the 16 regions and was higher in patients with active acromegaly (11.11 ± 2.35 active vs. 8.77 ± 1.39 control group, $p < 0.01$). In conclusion, myocardial perfusion is impaired in patients with active acromegaly, thus representing an early stage of cardiac involvement in acromegaly that may be directly mediated by growth hormone excess.

Key words
Acromegaly · Impaired Myocardial Perfusion · Scintigraphy

Introduction

Patients with active acromegaly often suffer from cardiovascular complications such as cardiomyopathy, coronary heart disease and arrhythmias [1–7]. Cardiac abnormalities observed in growth hormone (GH) excess range from a hyperkinetic state and alterations of diastolic function during the early stages of disease to systolic cardiac dysfunction [8–10], which are mostly due to cardiac hypertrophy, overt cardiac failure, coronary heart disease, and ventricular arrhythmias. There are several lines of evidence that these cardiac impairments are predominantly caused by direct GH and insulin-like growth factor I (IGF-I) mediated effects on myocardial structure and function [11–13]. However, disturbances of the cardiovascular system in patients with acromegaly do not seem to be associated with myocardial neovascularization, as vascular endothelial growth factor (VEGF) [14–18], which is known to be linked to retinal ischemia-associated neoavascularization, is not increased in patients with ac-

Affiliation
[1] Division of Endocrinology, University of Essen, Germany
[2] Division of Nuclear Medicine, University of Essen, Germany
[3] Division of Cardiology, University of Essen, Germany
[4] Department of Angiology, University of Essen, Germany

Correspondence
B. L. Herrmann, M.D. · University of Essen · Center of Internal Medicine · Division of Endocrinology · Hufelandstr. 55 · 45122 Essen · Germany · Phone: +49 (201) 723-2821 · Fax: +49 (201) 723-5972 · E-Mail: burkhard.herrmann@uni-essen.de

Received 23 May 2002 · **Accepted after second revision** 14 October 2002

Bibliography
Horm Metab Res 2003; 35: 183–188 © Georg Thieme Verlag Stuttgart · New York · ISSN 0018-5043

romegaly according to previous observations [19]. Recently, endothelial dysfunction in the brachial artery has been reported in acromegalic patients [20,21], but less is known about disorders in perfusion of the myocardium.

Since the early 80's, single photon emission computed tomography (SPECT) has become an established method for verifying microvascular and macrovascular perfusion disorders in the myocardium [22,23]. The aim of the present study was to evaluate the impact of disease activity of acromegalic patients on myocardial perfusion abnormalities verified by single photon emission computed tomography (SPECT).

Patients and Methods

Patients

Eleven patients (7 males, 4 females; age range 38–67 y, mean age 51 ± 12 y; BMI 26.6 ± 2.7 kg/m^2, range 22.8–32.2) suffering from acromegaly were included in the study (Table **1**). Inclusion criteria for these strictly selected patients were active acromegaly, absence of diabetes mellitus, and normal or well-controlled blood pressure. There was no evidence for angina pectoris (CCS-grade I) or dyspnea (NYHA garde I) in any of these patients. In three of eleven patients, coronary artery disease was excluded by angiography. In all other acromegalic patients, there was no evidence for the presence of coronary heart disease judged by either stress ECG examination or single photon emission computed tomography (SPECT) in the myocardium. Holter detected ST-segment deviation, defined as ≥ 1 mm deviation from the baseline lasting ≥ 1 min separated by a minimum of 1min, was performed in ten of eleven patients; none of them had significant ST-segment deviation.

The diagnosis of acromegaly was made on the basis of physical examination, IGF-I and GH levels after an oral glucose load (75 g) following the consensus statement of criteria of acromegaly [24]. All of the patients had elevated IGF-I values (IGF-I 569 ± 193 µg/l, range 366–829; GH 31.2 ± 56.3 µg/l, range 1.4–189) outside the age-adjusted normal range of the IGF-I assay (25–39 y: 114–492 µg/l; 40–54 y: 90–360 µg/l; ≥ 55 y: 71–290 µg/l). Three patients were being treated with somatostatin analogues (1 with lanreotide [30 mg every 2 weeks i.m.], 2 with octreotide acetate [30 mg Sandostatin LAR® every 4 weeks i.m.)]. One patient was on cabergoline (Dostinex® 0.5 mg twice the week). 8 (73%) patients had undergone transsphenoidal surgery, two (18%) of these having additionally received pituitary radiation. The duration of disease was assumed to be the interval between the onset of clinical symptoms as judged by comparison of old photographs and the time of the study. Three patients had newly diagnosed acromegaly.

For every single patient, the following parameters were measured in the morning after an overnight fast: weight, height, BMI, systolic and diastolic blood pressure and lipid profile. Pituitary function was assessed by measuring the basal levels of free thyroxin, triiodothyronine, TSH, cortisol, testosterone or estradiol, FSH, LH, prolactin, GH and IGF-I. Seven of eleven patients (64%) had gonadotropin deficiency, 4/11 (36%) had ACTH-deficiency, 4/11 (36%) thyreotropin deficiency, and none of them had diabetes insipidus centralis. All patients with hypopituitarism had been receiving adequate substitution therapy at the time of the study at a stable dose for at least 6 months before study entry. Two patients were being treated with antihypertensive drugs; none of the eleven patients with active acromegaly had received any lipid-lowering or antidiabetic drugs. Ten of the eleven patients were non-smokers.

Control group

An age and sex-matched group of 11 patients (6 males, 5 females; mean age 49 ± 15 y, range 38–67; mean BMI 27.0 ± 5.0 kg/m^2, range 21.3–37.6) without coronary heart disease served as non-acromegalic controls for single photon emission computed tomography (SPECT). Significant coronary stenoses were excluded by coronary angiography. Clinical and echocardiography data are shown in Table **1**.

Thallium-201 chloride single photon emission computed tomography (SPECT)

^{201}TlCl myocardial SPECT was performed using a triple-head gamma camera (Siemens MultiSPECT 3, Hoffman Estates, IL) using a low-energy, high-resolution collimator. After an overnight fast, all patients underwent a stress bicycle test (max. heart frequence: 150 ± 16/min, range 128–183). At peak exercise during the bicycle stress test, 70 MBq ^{201}TlCl were injected intravenously. Stress images were obtained immediately after injection. All data were acquired in 93 projections over 360° (40 s/projection/image in a 64 × 64 matrix). The projection data were reconstructed by filtered back-projection with a Butterworth filter (cut-off 0.8 pix^{-1}, order 5). Short axis, horizontal and vertical long axis slices were generated after reconstruction without attenuation correction [25]. In each patient, the mean uptake of 16 segments of bull's eye polary map of the left ventricle (Fig. **3**) were analysed in stress and the standard deviation for each patient as a sign for intraindividual non-homogeneity was determined. The results were interpreted without knowledge of clinical data.

Echocardiographic examination

One-dimensional, two-dimensional and transthoracic Doppler echocardiography was performed using an ultrasound mechanical system equipped with 2.5 and 3.5 mHz transducers (Hewlett Packard Sonos 5500); images were stored on videotape for further analysis. Scans were obtained in the standard view in order to examine the aortic and mitral valves. We then obtained a derived M-mode recording of the left ventricle at a paper speed of 25 mm/s, having adjusted the transducer to obtain optimal recordings of the intraventricular septum and the left ventricular posterior wall. The M-mode scan at the level of the cordae tendineae was used to measure left ventricular end diastolic and end systolic dimensions, and the thickness of the interventricular septal wall and left ventricular posterior wall. Mean values from three cardiac cycles were used for calculation. From these values, we calculated muscle mass index of the left ventricle. Parameters of the diastolic and systolic function were also determined. Analysis of the echocardiograms was carried out without knowledge of the clinical and laboratory findings.

Brachial haemodynamics

All brachial haemodynamic studies were performed by an experienced vascular sonographer using an Elegra system (Siemens, Erlangen, Germany) with a 7.5-mHz linear array transducer. The studies were performed between 8:00 and 9:30 a.m. on fasting patients. To minimise external stimuli, all examinations were carried out in silence in a clinical research laboratory room. Blood pressure was obtained from the non-dominant arm using a sphygmomanometer three times during the study. Brachial artery diameter was measured from B-mode ultrasound images. In all studies, scans were obtained at rest and during reactive hyperaemia. The subjects lay quietly for 10min before the first scan. The brachial artery was scanned in longitudinal section 5 – 15 cm above the elbow. Depth and gain settings were set to optimize images of the lumen/arterial wall interface, and the operating parameters were not changed during the study. When a satisfactory transducer position was found, the position was marked on the skin and the arm remained in the same position throughout the study. All ultrasound scans were recorded on super-VHS tapes for off-line analysis. A resting scan was performed, and arterial flow velocity was measured in triplicate (Doppler angle $\alpha = 30 - 45^{\circ}$). Reactive hyperaemia was then induced. At first, suprasystolic composition of the brachial artery over 3 min was performed using an adult-size (12 × 44.5 cm) pneumatic tourniquet placed around the upper arm (proximal to the scanned part of the brachial artery). The pressure in the pneumatic tourniquet was individually adjusted to exceed systolic pressure by 30 mm Hg (up to 250 mm Hg at the most). Zero flow during suprasystolic compression was periodically assessed with the ultrasound probe. After 3 min, the pressure was suddenly released and reactive hyperaemia ensured. Subsequent scans were taken continuously between 40 and 180 s after cuff deflation. Since a shift in brachial artery position frequently occurs when the cuff is released, great care was taken to find an image of the largest lumen diameter (the centre of the artery). The first posthyperaemia scan was taken as early as possible – within the first 20 s after the cuff release. The flow-mediated dilation (FMD in %) was defined as the maximal percentage increase of the brachial diameter from baseline (at rest) to hyperaemia. Vascular resistances were calculated in the brachial artery as the max. systolic velocity – max. diastolic velocity/max. systolic velocity and pulsatility index as max. systolic velocity – enddiastolic velocity/mean velocity.

Hormone assays

Serum GH levels were determined by chemiluminescence immunometric assay (Nichols Institute Diagnostics GmbH, Bad Nauheim, Germany). The assay was calibrated against the WHO 1st international standard (80/505) for human GH. Normal range was ≤ 5 µg/l. Intra- and interassay coefficients of variation (CVs) for a low point of the standard curve were 5.4% and 7.9%, respectively. Plasma IGF-I concentrations were measured by immunoradiometric assay (Nichols Institute Diagnostics GmbH, Bad Nauheim, Germany). Age-adjusted normal range: 25 – 39 y: 114 – 492 µg/l; 40 – 54 y: 90 – 360 µg/l; ≥ 55 y: 71 – 290 µg/l. The assay was calibrated against the WHO 1st International Reference Reagent 87/518. Intra- and interassay CVs for low IGF-I concentrations were 2.4% and 5.2%, respectively. All other parameters were determined by routine methods.

Table **1** Clinical data of patients with active acromegaly and the control subjects

	Active (n = 11)	*Control group (n = 11)*	*p-value ns*
M/F	7/4	6/5	ns
Age (y)	51 ± 12	49 ± 15	ns
Body mass index (kg/m²)	26.6 ± 2.7	27.0 ± 5.0	ns
Left ventricle muscle mass index (g/m²)	126 ± 41	122 ± 33	ns
Intraventricular septum diameter (mm)	1.1 ± 0.28	1.1 ± 0.24	ns
Posterior wall thickness (mm)	0.95 ± 0.19	0.98 ± 0.24	ns
Ejection fraction (%)	62 ± 6	57 ± 9	ns
Cardiac index (l/min/m²)	2.1 ± 0.8	2.3 ± 0.8	ns
Systolic blood pressure (mm Hg)	134 ± 14	132 ± 12	ns
Diastolic blood pressure (mm Hg)	82 ± 8	75 ± 14	ns
Total cholesterol (mmol/l)	5.64 ± 1.48	6.32 ± 1.51	ns
LDL Cholesterol (mmol/l)	3.66 ± 1.3	3.85 ± 0.39	ns
HDL Cholesterol (mmol/l)	1.27 ± 0.42	1.17 ± 0.34	ns.
Triglycerides (mmol/l)	1.61 ± 0.80	2.15 ± 1.14	ns
Blood glucose (mmol/l)	5.38 ± 0.73	6.72 ± 2.07	ns

Statistical analyses

The data, if not marked otherwise, represent the mean ± standard deviation. Where distribution was skewed, the median was also determined. Data were tested statistically by the Wilcoxon U-test All tests were done two-tailed, p-values < 0.05 were considered statistically significant.

Results

Table **1** summarizes the important variables of acromegalic and control groups. Cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, fasting plasma glucose, systolic, and diastolic blood pressure did not differ significantly between the two groups. Echocardiography data showed no statistical differences concerning the left ventricle muscle mass, the intraventricular septum diameter, the posterior wall thickness and the ejection fraction (Table **1**). Cardiac index was normal and did not differ between the two groups.

Comparable values of body mass index and left ventricle muscle mass must be present in both groups to guarantee the same nuclide concentration in the myocardium after injection of thallium-201 chloride. Whenever the left ventricle could be divided into 33 regions to analyse the nuclide uptake, we analysed the myocardium without apex (16 regions) and base to minimise artefacts (Fig. **1**). In patients with active acromegaly, the mean counts of each region (nuclide uptake) of the left ventricle (Fig. **2**) was lower than in the control group (82.99 ± 2.85 active vs. 85.48 ± 1.29 control group, $p < 0.01$). Non-homogeneity of nuclide uptake was defined as the standard deviation of the 16 regions of the left ventricle of each patient. In the acromegalic group, the standard deviation (Fig. **3**) was higher than in the control group (11.11 ± 2.35 active vs. 8.77 ± 1.39 control group, $p < 0.01$). The counts and the non-homogeneity for nuclide up-

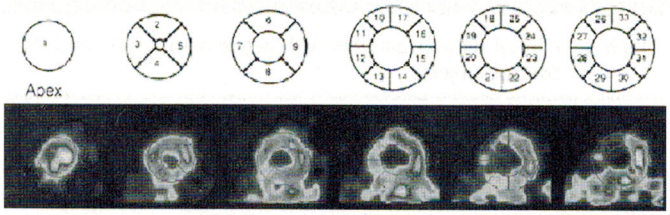

Fig. **1** Stress images of short-axis view and bull's-eye segmental polar-map analysis in a patient with active acromegaly. Images were obtained from the apex (left) to the base (right) of the left ventricle. The counts of nuclide distribution of thallium-201 chloride were analysed in 16 areas (area 2 – 17).

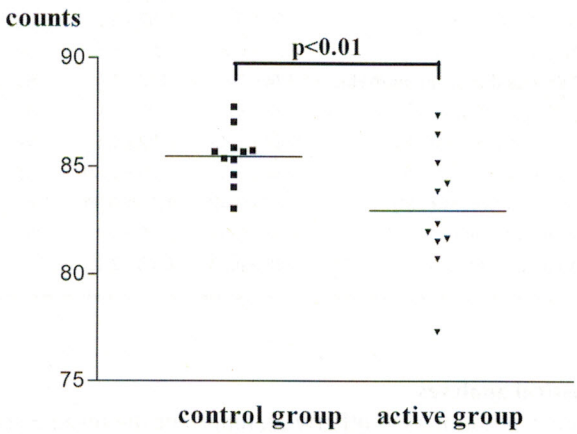

Fig. **2** Mean myocardial nuclide uptake (counts) of thallium-201 chloride of the left ventricle in patients with active acromegaly and a non-acromegalic control group without coronary heart disease.

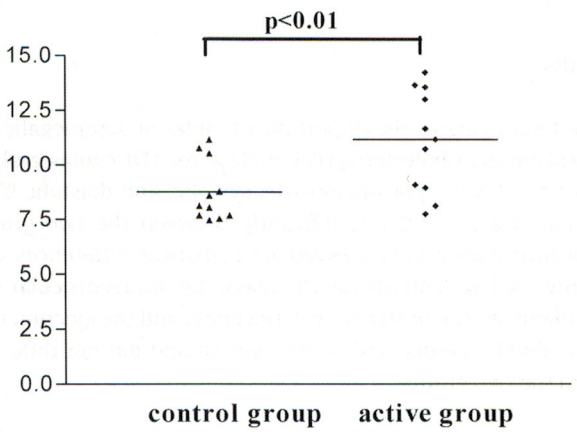

Fig. **3** Standard deviation as a parameter for inhomogeneous nuclide uptake with thallium-201 chloride of the left ventricle in patients with active acromegaly and a non-acromegalic control group without coronary heart disease.

take did not correlate to LVMMI. The mean total washout rate of thallium-201 chloride was calculated, and did not differ between the two groups (43 ± 10 active vs. 42 ± 11 % control group, p = ns). In two acromegalic patients with reduced washout rate (< 40 %), coronary artery disease was excluded by angiography.

In patients with active acromegaly, the mean diameter of the brachial artery at rest and after hyperaemia as well as the mean blood flow of the brachial artery at rest were higher than in the control group (Table **2**; p < 0.05). Endothelial dysfunction can be determined by flow-mediated dilation of the brachial artery [21]. In the present group, the flow-mediated dilation (FMD) did not differ between the two groups (3.3 ± 3.7 vs. 6.2 ± 7.0 %, p = ns). Moreover, the pulsatility index and the resistance index at rest was lower in patients with active acromegaly (Table **2**).

Table **2** Parameter of haemodynamics of the brachial artery

	Active	*Control group*	*p-value*
Mean diameter (mm) at rest	4.4 ± 0.3	3.6 ± 0.2	p < 0.05
With hyperaemia	4.5 ± 0.2	3.8 ± 0.1	p < 0.05
Mean blood flow (ml/min) at rest	101 ± 23	37 ± 4	p < 0.05
With hyperaemia	439 ± 137	278 ± 44	p = ns
Flow-mediated dilation (%)	3.2 ± 3.7	6.2 ± 7.0	p = ns
Peak velocity (cm/s) at rest	74 ± 7	66 ± 4	p = ns
With hyperaemia	139 ± 22	136 ± 10	p = ns
Pulsatility index at rest	4.9 ± 0.8	6.7 ± 0.3	p < 0.05
With hyperaemia	3.0 ± 1.0	1.6 ± 0.2	p = ns
Resistance index at rest	0.93 ± 0.03	0.99 ± 0.01	p < 0.05
With hyperaemia	0.73 ± 0.07	0.75 ± 0.04	p = ns

HOMA IR (homeostasis model assessment of insulin resistance [fasting insulin µU/ml × fasting plasma glucose mmol/l] / 22.5), a well-accepted parameter for determining insulin resistance [26 – 28], was reached in 9/11 patients and elevated in 7/9 patients (mean 3.03 ± 1.47, range 1.2 – 4.9), indicating an insulin-resistant state. The mean fasting insulin level was 12.5 ± 5.5 µU/ml (range 5.0 – 22.0). 2/9 patients were treated with somatostatin analogues. HOMA IR was not determined in controls.

Discussion

The coexistence of hypertension, diabetes mellitus, and dyslipoproteinaemia in acromegalic patients are important factors in the induction of progressive atherosclerosis and coronary artery disease [2, 29 – 32]. Cardiac involvement in unselected patients with acromegaly has been extensively investigated by echocardiography and radionuclide angiography study [33 – 36], but less is known about myocardial perfusion abnormalities. In the present study, we investigated a rigorously selected group of patients with active acromegaly using myocardial single photon emission computed tomography (SPECT).

The present study, selected for the absence of coronary artery disease and diabetes mellitus, clearly demonstrate that patients with active acromegaly have an impaired myocardial perfusion in single photon emission computed tomography (SPECT). Compared with an age- and sex-matched non-acromegalic control group, which did not differ significantly regarding plasma glucose, lipids, blood pressure, and muscle mass index of the left ventricle (LVMMI), patients with active acromegaly had lower and non-homogenous ^{201}thallium nuclide uptake, indicating perfusion abnormalities directly related to disease activity. Several earlier studies have shown that perfusion abnormalities in myocardial scintigraphy are influenced by hypertrophy [23, 37]. In

the present study, only two acromegalic patients had an elevated LVMMI (>140 g/m^2), but the nuclide uptake did not correlate with the degree of hypertrophy. This indicates that abnormalities of thallium kinetics are not related to the magnitude of left ventricular hypertrophy, but may be a function of the disease process of active acromegaly itself.

The uptake of the segmental areas of the left ventricle reveals the cellular uptake of ^{201}thallium across the sacrolemmal membrane *via* sodium/potassium pump. The exclusive uptake of ^{201}thallium is similar to potassium, but the intracelluar binding is stronger than that of potassium [38,39]. The impaired nuclide uptake and distribution in patients with active acromegaly may be due to alterations in the morphology of small arterioles, which may lead to a reduced perfusion of cortical tissue [40]. Histological examinations of acromegalic patients showed significant wall thickening of small intramural vessels [41], lymphocyte infiltration, interstitial fibrosis, and recently, increased apoptosis rates [42], which could be a reason for perfusion abnormalities in active acromegaly.

Brachial artery circulation has been used to assess large-artery function and regional blood flow and reflects coronary perfusion [43–47] in non-acromegalic patients. Whether brachial haemodynamics of the brachial artery reflect coronary perfusion in acromegalics remains unclear, considering that Chanson et al. [21] have shown a heterogeneous distribution of cardiac and brachial haemodynamics in acromegaly. In contrast to our observations, they have demonstrated high cardiac output and associated high systemic vascular resistance (brachial artery) in acromegaly [20,21]. In the present study, we have shown normal cardiac output in combination with high brachial blood flow and low vascular resistance. Whether endothelial dysfunction of the brachial artery, determined by flow-mediated dilation, reflects coronary haemodynamics remains speculative, and cannot be answered with our examinations. To verify cardiac haemodynamics of this group of patients to explain the impaired myocardial nuclide distribution, direct coronary measurements of blood flow (intracoronary Doppler measurements and provocative tests with intracoronary acetylcholine) should address this issue, albeit invasive procedures are critical to perform in patients without evidence or symptoms of coronary artery disease. Nevertheless, limitations of the present study are the missing exclusion of coronary artery disease by angiography in 8/11 acromegalic patients, although symptoms and signs of coronary artery disease as well as a positive stress ECG could be excluded. Although *in vivo* data are missing at present, an *in vitro* study of porcine epicardial arteries could demonstrate that IGF-I causes non-endothelium-dependent coronary vasorelaxation and these effects of IGF-I participate in the regulation of the coronary vasomotor tone [48].

Since high doses of growth hormone [49,50] can induce insulin resistance associated with coronary endothelial dysfunction [51,52] and 78% of our patients with active acromegaly were insulin resistant, abnormalities in myocardial nuclide uptake and myocardial perfusions disturbances may be influenced by insulin resistance.

In conclusion, myocardial perfusion is impaired in patients with active acromegaly represent an early stage of cardiac involvement in acromegaly and may be directly mediated by growth hormone excess. Further studies are needed to address this issue.

References

[1] Drange MR, Fram NR, Herman-Bonert V, Melmed S. Pituitary tumor registry: a novel clinical resource. J Clin Endocrinol Metab 2000; 85: 168–174

[2] Lombardi G, Colao A, Cuocolo A, Longobardi S, di Somma C, Orio F, Merola B, Nicolai E, Salvatore M. Cardiological aspects of growth hormone and insulin-like growth factor- I. J Pediatr Endocrinol Metab 1997; 10: 553–560

[3] Lombardi G, Colao A, Ferone D, Marzullo P, Orio F, Longobardi S, Merola B. Effect of growth hormone on cardiac function. Horm Res 1997; 48: 38–42

[4] Kahaly G, Olshausen KV, Mohr-Kahaly S, Erbel R, Boor S, Beyer J, Meyer J. Arrhythmia profile in acromegaly. Eur Heart J 1992; 13: 51–56

[5] Kahaly G, Stover C, Beyer J, Mohr-Kahaly S. Relation of endocrine and cardiac findings in acromegalics. J Endocrinol Invest 1992; 15: 13–18

[6] Ozbey N, Oncul A, Bugra Z, Vural A, Erzengin F, Orhan Y, Buyukozturk K, Sencer E, Molvalilar S. Acromegalic cardiomyopathy: evaluation of the left ventricular diastolic function in the subclinical stage. J Endocrinol Invest 1997; 20: 305–311

[7] Herrmann BL, Bruch C, Saller B, Ferdin S, Dagres N, Ose C, Erbel R, Mann K. Occurrence of ventricular late potentials in patients with active acromegaly. Clin Endocrinol (Oxf) 2001; 55: 201–207

[8] Herrmann BL, Bruch C, Saller B, Bartel T, Ferdin S, Erbel R, Mann K. Acromegaly: evidence for a direct relation between disease activity and cardiac dysfunction in patients without ventricular hypertrophy. Clin Endocrinol (Oxf) 2002; 56: 595–602

[9] Galanti G, Cappelli B, Diricatti G, Mininni S, Vono MC, Gensini GF. Systolic and diastolic cardiac function in acromegaly. An echocardiographic study. Ann Ital Med Int 1996; 11: 27–32

[10] Cuocolo A, Nicolai E, Fazio S, Pace L, Maurea S, Cittadini A, Sacca L, Salvatore M. Impaired left ventricular diastolic filling in patients with acromegaly: assessment with radionuclide angiography. J Nucl Med 1995; 36: 196–201

[11] Sacca L, Cittadini A, Fazio S. Growth hormone and the heart. Endocr Rev 1994; 15: 555–573

[12] Lopez-Velasco R, Escobar-Morreale HF, Vega B, Villa E, Sancho JM, Moya-Mur JL, Garcia-Robles R. Cardiac involvement in acromegaly: specific myocardiopathy or consequence of systemic hypertension? J Clin Endocrinol Metab 1997; 82: 1047–1053

[13] Minniti G, Jaffrain-Rea ML, Moroni C, Baldelli R, Ferretti E, Cassone R, Gulino A, Tamburrano G. Echocardiographic evidence for a direct effect of GH/IGF-I hypersecretion on cardiac mass and function in young acromegalics. Clin Endocrinol (Oxf) 1998; 49: 101–106

[14] D'Angio CT, Ambati J, Phelps DL. Do urinary levels of vascular endothelial growth factor predict proliferative retinopathy? Curr Eye Res 2001; 22: 90–94

[15] Kwak N, Okamoto N, Wood JM, Campochiaro PA. VEGF is major stimulator in model of choroidal neovascularization. Invest Ophthalmol Vis Sci 2000; 41: 3158–3164

[16] Lip PL, Belgore F, Blann AD, Hope-Ross MW, Gibson JM, Lip GY. Plasma VEGF and soluble VEGF receptor FLT-1 in proliferative retinopathy: relationship to endothelial dysfunction and laser treatment. Invest Ophthalmol Vis Sci 2000; 41: 2115–2119

[17] Aiello LP, Avery RL, Arrigg PG, Keyt BA, Jampel HD, Shah ST, Pasquale LR, Thieme H, Iwamoto MA, Park JE et al. Vascular endothelial growth factor in ocular fluid of patients with diabetic retinopathy and other retinal disorders. N Engl J Med 1994; 331: 1480–1487

[18] Wells JA, Murthy R, Chibber R, Nunn A, Molinatti PA, Kohner EM, Gregor ZJ. Levels of vascular endothelial growth factor are elevated in the vitreous of patients with subretinal neovascularisation. Br J Ophthalmol 1996; 80: 363–366

[19] Nagai Y, Ando H, Nohara E, Yamashita H, Takamura T, Kobayashi K. Plasma levels of vascular endothelial growth factor in patients with acromegaly. Horm Metab Res 2000; 32: 326–329

[20] Evans LM, Davies JS. Heterogeneous haemodynamics in acromegaly: evidence of endothelial dysfunction? Clin Endocrinol (Oxf) 1998; 49: 711 – 712
[21] Chanson P, Megnien JL, del Pino M, Coirault C, Merli I, Houdouin L, Harris AG, Levenson J, Lecarpentier Y, Simon A, Chemla D. Decreased regional blood flow in patients with acromegaly. Clin Endocrinol (Oxf) 1998; 49: 725 – 731
[22] Wieneke H, Zander C, Eising EG, Haude M, Bockisch A, Erbel R. Non-invasive characterization of cardiac microvascular disease by nuclear medicine using single-photon emission tomography. Herz 1999; 24: 515 – 521
[23] Astarita C, Nicolai E, Liguori E, Gambardella S, Rumolo S, Maresca FS. Dipyridamole-echocardiography and thallium exercise myocardial scintigraphy in the diagnosis of obstructive coronary or microvascular disease in hypertensive patients with left ventricular hypertrophy and angina. G Ital Cardiol 1998; 28: 996 – 1004
[24] Giustina A, Barkan A, Casanueva FF, Cavagnini F, Frohman L, Ho K, Veldhuis J, Wass J, von Werder K, Melmed S. Criteria for cure of acromegaly: a consensus statement. J Clin Endocrinol Metab 2000; 85: 526 – 529
[25] Buell U, Stirner H, von Dahl J, Uebis R, Kleinhans E, Biedermann M, Grosse W, Simon HJ. Quantitative evaluation of myocardial stress/rest 201TL SPECT: results of a ROI-based method in 108 patients with CHD. Nuklearmedizin 1987; 26: 234 – 240
[26] Radziuk J. Insulin sensitivity and its measurement: structural commonalities among the methods. J Clin Endocrinol Metab 2000; 85: 4426 – 4433
[27] Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985; 28: 412 – 419
[28] Haffner SM, Miettinen H, Stern MP. The homeostasis model in the San Antonio Heart Study. Diabetes Care 1997; 20: 1087 – 1092
[29] Colao A, Baldelli R, Marzullo P, Ferretti E, Ferone D, Gargiulo P, Petretta M, Tamburrano G, Lombardi G, Liuzzi A. Systemic hypertension and impaired glucose tolerance are independently correlated to the severity of the acromegalic cardiomyopathy. J Clin Endocrinol Metab 2000; 85: 193 – 199
[30] Moller N, Jorgensen JO, Abildgard N, Orskov L, Schmitz O, Christiansen JS. Effects of growth hormone on glucose metabolism. Horm Res 1991; 36: 32 – 35
[31] Oscarsson J, Wiklund O, Jakobsson KE, Petruson B, Bengtsson BA. Serum lipoproteins in acromegaly before and 6 – 15 months after transsphenoidal adenomectomy. Clin Endocrinol (Oxf) 1994; 41: 603 – 608
[32] Tsuchiya H, Onishi T, Mogami H, Iida M. Lipid metabolism in acromegalic patients before and after selective pituitary adenomectomy. Endocrinol Jpn 1990; 37: 797 – 807
[33] Colao A, Cuocolo A, Marzullo P, Nicolai E, Ferone D, Florimonte L, Salvatore M, Lombardi G. Effects of 1-year treatment with octreotide on cardiac performance in patients with acromegaly. J Clin Endocrinol Metab 1999; 84: 17 – 23
[34] Colao A, Marzullo P, Ferone D, Marino V, Pivonello R, di Somma C, di Sarno A, Giaccio A, Lombardi G. Effectiveness and tolerability of slow release lanreotide treatment in active acromegaly. J Endocrinol Invest 1999; 22: 40 – 47
[35] Fazio S, Cittadini A, Cuocolo A, Merola B, Sabatini D, Colao A, Biondi B, Lombardi G, Sacca L. Impaired cardiac performance is a distinct feature of uncomplicated acromegaly. J Clin Endocrinol Metab 1994; 79: 441 – 446
[36] Fazio S, Cittadini A, Sabatini D, Merola B, Colao AM, Biondi B, Lombardi G, Sacca L. Evidence for biventricular involvement in acromegaly: a Doppler echocardiographic study. Eur Heart J 1993; 14: 26 – 33
[37] Takata J, Counihan PJ, Gane JN, Doi Y, Chikamori T, Ozawa T, McKenna WJ. Regional thallium-201 washout and myocardial hypertrophy in hypertrophic cardiomyopathy and its relation to exertional chest pain. Am J Cardiol 1993; 72: 211 – 217
[38] Wackers FJ. Myocardial perfusion imaging in ischemic heart disease anno 1990. Curr Opin Cardiol 1991; 6: 590 – 601
[39] Wackers FJ. The birth of a new radiopharmaceutical. Clinical investigative perspective. J Nucl Cardiol 1995; 2: 75 – 77
[40] Hutchins PM, Lynch CD, Cooney PT, Curseen KA. The microcirculation in experimental hypertension and aging. Cardiovasc Res 1996; 32: 772 – 780
[41] Lie JT. Pathology of the heart in acromegaly: anatomic findings in 27 autopsied patients. Am Heart J 1980; 100: 41 – 52
[42] Frustaci A, Chimenti C, Setoguchi M, Guerra S, Corsello S, Crea F, Leri A, Kajstura J, Anversa P, Maseri A. Cell death in acromegalic cardiomyopathy. Circulation 1999; 99: 1426 – 1434
[43] Feinstein SB, Voci P, Pizzuto F. Noninvasive surrogate markers of atherosclerosis. Am J Cardiol 2002; 89: 31C – 43C; discussion 43C-44C
[44] Yamashita N, Nakayama Y, Tsumura K, Nishijima T, Ueda H, Yoshimaru K, Hayashi T, Yoshikawa J. Pulsatility of brachial artery pressure is associated with an increased risk of coronary artery disease in men. J Hypertens 2001; 19: 1589 – 1593
[45] Anderson TJ, Uehata A, Gerhard MD, Meredith IT, Knab S, Delagrange D, Lieberman EH, Ganz P, Creager MA, Yeung AC et al. Close relation of endothelial function in the human coronary and peripheral circulations. J Am Coll Cardiol 1995; 26: 1235 – 1241
[46] Enderle MD, Schroeder S, Ossen R, Meisner C, Baumbach A, Haering HU, Karsch KR, Pfohl M. Comparison of peripheral endothelial dysfunction and intimal media thickness in patients with suspected coronary artery disease. Heart 1998; 80: 349 – 354
[47] Heusch G. Hibernating myocardium. Physiol Rev 1998; 78: 1055 – 1085
[48] Hasdai D, Nielsen MF, Rizza RA, Holmes DR Jr, Richardson DM, Cohen P, Lerman A. Attenuated *in vitro* coronary arteriolar vasorelaxation to insulin-like growth factor I in experimental hypercholesterolemia. Hypertension 1999; 34: 89 – 95
[49] Hansen I, Tsalikian E, Beaufrere B, Gerich J, Haymond M, Rizza R. Insulin resistance in acromegaly: defects in both hepatic and extrahepatic insulin action. Am J Physiol 1986; 250: E269 – E273
[50] Rizza RA, Mandarino LJ, Gerich JE. Effects of growth hormone on insulin action in man. Mechanisms of insulin resistance, impaired suppression of glucose production, and impaired stimulation of glucose utilization. Diabetes 1982; 31: 663 – 669
[51] Lepej J, Spisiakova D, Hrnciar J, Okapcova J, Szentivanyi M, Kurray P. Thallium scintigraphy of the myocardium in evaluation of patients with insulin resistance syndrome and microvascular angina pectoris. Vnitr Lek 2000; 46: 205 – 212
[52] Pinkney JH, Stehouwer CD, Coppack SW, Yudkin JS. Endothelial dysfunction: cause of the insulin resistance syndrome. Diabetes 1997; 46: S9 – S13