Heart in acromegaly – proposal to modify the definition of acromegalic cardiomyopathy

Serce w akromegalii – propozycja modyfikacji definicji kardiomiopatii akromegalicznej

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Abstract

Acromegaly is a systemic disease that significantly affects the cardiovascular system. As a result of increased GH and IGF-1 values, changes occur in the heart, which are commonly called acromegalic cardiomyopathy.

The progress in the treatment of acromegaly and comorbidities has changed the characteristics of this cardiomyopathy, and its last 3rd stage is very rare, with reported rates ranging from 1 to 4%. The advancements in diagnostics and the possibility of using new echocardiographic techniques, such as speckle tracking echocardiography (STE), allow for the recognition of changes at the subclinical level.

Due to the reversibility of certain symptoms, early detection of changes and implementation of treatment are very important. This reduces the risk of cardiac complications, and consequently improves the quality of life and prolongs life.

Introduction

Acromegaly is a systemic disease that affects most organs and systems, including significant effects on the cardiovascular system (1, 2, 3).

As a result of increased GH and IGF-1 values, changes occur in the heart, which are commonly called acromegaly cardiomyopathy. It is mainly characterized by left ventricular hypertrophy (LVH) associated with mildly impaired diastolic function, which can progress to systolic dysfunction (4).

The studies conducted in recent years using echocardiography and cardiac magnetic resonance (CMR), have shown that systolic function in acromegaly, as measured by ejection fraction (EF) is preserved, and overt heart failure is uncommon (1-4%) (5, 6, 7, 8).

Since overt impairment of systolic function with reduced EF is known to be rare in acromegaly, a more sensitive tool has been used for assessment of myocardial contractility: speckle tracking echocardiography (STE). The assessment of myocardial deformation using STE is a sensitive and...
reproducible method, therefore it works very well in detecting early changes at the subclinical level, when ejection fraction is normal. Due to its reproducibility, this is very good technique to monitor the effect of treatment (9).

Physiological effects of GH and IGF-1 on cardiovascular system – in healthy subjects

In normal physiological conditions, GH/IGF-I axis exerts relevant cardiovascular actions aimed at regulating cardiac growth and myocardial contractility, contributing to maintenance of cardiac mass and function (10). The receptors for GH and IGF-I are also expressed in blood vessels (11), and regulate vascular tone and the peripheral resistance, which indirectly affects cardiac performance.

GH and IGF-I have direct effects on myocardial contractility and cardiac output. These effects are mediated by the increased mRNA expression for muscle proteins like troponin and myosin (10, 12, 13).

Moreover, GH and IGF-I increase intracellular calcium content and calcium sensitivity of myofilaments in cardiomyocytes (10). The endothelial cells have high affinity binding sites for IGF-I. The local production of IGF-I causes endothelial-dependent vasodilatation via the stimulation of the nitric oxide production (10). Additionally, IGF-I may cause vasodilatation through nonendothelium-dependent actions, by stimulation Na/KATPase in vascular smooth muscle cells (14).

The effect of GH and IGF-1 on the kidney is stimulation of sodium (Na) and water (H2O) retention in the distal nephron via up-regulation of the epithelial sodium channel (ENaC) (15).

Another important role in the kidney is the increase in GFR – it is a consequence of dilation of the afferent and efferent arterioles via increased synthesis of the endogenous vasodilator nitric oxide (NO) (15).

Hypertension

It is one of the most frequent cardiovascular comorbidities in patients with acromegaly. The prevalence of hypertension among patients with acromegaly ranges from 18 to 60%, with an average of 40% (16).

Acromegaly-associated hypertension is characterized by specific manifestations, including low systolic blood pressure, high diastolic blood pressure and a higher prevalence of non-dipper hypertension (16, 17).

There are some potential mechanisms involved in the development of acromegaly-related hypertension. One is the sodium and water retention caused by GH and IGF-1, leading to the expansion of plasma volume (5, 17).

The other one is stimulation of smooth muscle cell growth by excessive GH and IGF-1, resulting in increased vascular resistance.

The nitric oxide (NO)-mediated vascular endothelium-dependent diastolic function is also impaired in patients with acromegaly (17). Nitric oxide is a powerful vasodilator that can also reduce platelet aggregation and activation, inhibit the proliferation and migration of vascular smooth muscle cells, and reduce the adhesion of white blood cells and endothelial cells (17). A potential contribution of an increased sympathetic tone has also been suggested. Furthermore, coexisting comorbidities, such as cardiac hypertrophy, obstructive sleep apnea and insulin resistance may exacerbate established and long-standing hypertension (18).

The appropriate choice of antihypertensive treatment in patients with acromegaly is crucial. ACE-I/ARB – should be the first line of choice because they act causally on the above-mentioned mechanisms of hypertension: inhibit Na and water retention, reduce systemic vascular resistance and, what is very important, reverse hypertrophy and have antiarrhythmic effects.
Cardiac morphology and function
– acromegalic cardiomyopathy

Heart changes in acromegaly were first defined as acromegaly cardiomyopathy at the end of the 19th century (19).

Actually, findings describing acromegalic cardiomyopathy are based on echocardiographic parameters, but for many years, autopsy examination was the only confirmation of changes in the heart in patients with acromegaly (20).

Echocardiography begins to develop in the 1950s (21). At first it was simple M-mode, then 2D imaging. In the following years, the cardiological software was expanded to include the Doppler function: pulsed, continuous and color.

The 1990s saw the successive development of tissue doppler imaging (TDI), which significantly improved the assessment of left ventricular diastolic function. Since 2005, a new technique of Speckle Tracking Echocardiography (STE) has been slowly entering the practice, which gives the opportunity to detect contractility impairment at the sub-clinical level, while ejection fraction is still normal.

The definition of acromegalic cardiomyopathy that includes 3 phases of the disease has been in effect for over 20 years (22) (Fig. 2).

**Figure 2. Current definition of acromegalic cardiomyopathy.**
Source: own elaboration.

![Figure 2. Current definition of acromegalic cardiomyopathy.](image)

**Comorbidities**
- Metabolic abnormalities
- Hypertension
- Obstructive sleep apnea syndrome (OSAS)

**Figure 3. Impairment of GLS (-16.2%) assessed by 2D STE in a patient with acromegaly before treatment.**

![Figure 3. Impairment of GLS (-16.2%) assessed by 2D STE in a patient with acromegaly before treatment.](image)
In the first stage, it is mainly myocardial concentric hypertrophy, increasing heart rate and increased cardiac output, which are manifestations of hyperkinetic syndrome. In the middle stage, myocardial hypertrophy becomes more overt, and diastolic dysfunction is revealed.

Finally, if acromegaly is untreated or not effectively controlled, and additional complications such as valvular defects or arrhythmia occur, it can progress to more clinically evident heart failure with reduced ejection fraction. Opposite to the first, the last stage is irreversible (23).

The rare occurrence of stage 3 acromegalic cardiomyopathy with symptoms of overt heart failure and reduced EF has been confirmed in a few recent studies (7, 24, 25, 26, 27).

Popielarz et al. in a prospective study of 35 patients with newly diagnosed acromegaly confirmed reduced EF in only 1 patient, which is 2.8% of the initial group (27).

In Volschan's retrospective study, patients excluded due to reduced EF accounted for 5% of the total group (2 out of 40) (26).

Gadhela et al. and Uziębło-Życzkowska et al. did not confirm the occurrence of systolic dysfunction with reduced EF in their studies (24, 25).

In patients with preserved EF, STE is a useful method to assess contractility. This technique allows to evaluate longitudinal, radial, and circumferential deformation (7). The global longitudinal strain (GLS) is a well validated, reproducible tool for the measurement of global left ventricular (LV) systolic function and provides relevant evidence on the diagnostic and prognostic implications (28). Reduction in GLS predicts worse cardiovascular outcomes. GLS describes the activity of longitudinal fibers, which shorten during contraction, therefore the value is given in %, with a minus sign. The more negative GLS value, the better contractility. So far, the cut-off point is -20%.

In the retrospective studies of Uziębło-Życzkowska et al. and Popielarz et al., subclinical systolic dysfunction assessed by GLS was confirmed in patients with active acromegaly and preserved normal EF. The GLS value was -18,1% in acromegaly group vs -19,4% in control group and -16,6% in acromegaly group vs -20,7% in control group; respectively (24, 29) (Fig.3).

Opposite to these studies, Gadhela et al. and Volschan et al. did not find statistically significant differences in GLS values in patients with active acromegaly compared to the control group (25, 27).

The fact that the patients were at different stages of the disease and at different stages of treatment helps to better understand these discrepancies in GLS values and it may be explained by positive effect of treatment. In the first prospective study to date using the GLS parameter to assess the effect of treatment on systolic function, Popielarz et al. confirmed a beneficial effect of treatment and an improvement in the GLS (27) (Fig.4).

The echocardiographic parameter arousing curiosity of researchers, is left atrial volume index (LAVi). It is abnormal in nearly 80% of acromegaly patients. Popielarz et al. showed that 78% of patients had enlarged LA with

Figure 4. Normalization of GLS (-20,1%) in the same patient after debulking surgery and during somatostatin analogues treatment
only mild diastolic dysfunction (in about 50% of patients) and with LVH occurring in less than 50% of patients, however the mean left vetricular mass index (LVMi) was normal (27). It’s unlikely that the changes are the result of the increase of afterload only. It’s interesting that so-called acromegalic heart has several similarities to the athlete’s heart in which atrial remodeling is a physiological adaptation to volume overload allowing for greater volume delivery and increased cardiac output (30).

In patients with acromegaly, volume overload results from the effect of GH and IGF-1 on water and sodium retention in the kidney (5, 17). When we look for similarities between the "acromegalic heart" and the athlete’s heart, it is important to remember that hypertrophy of the LV in athletes occurs just through the activation of the IGF-1 pathway, opposite to pathological hypertrophy with activation of the angiotensin 1 pathway (31).

Regardless of the mechanisms by which LA enlargement occurs, it results in increased risk of arrhythmias, including atrial fibrillation, stroke, mitral regurgitation and heart failure.

Due to the results from recent studies, the description of the so-called acromegaly cardiomyopathy should be modified and supplemented with these two important parameters: GLS and LAVi (Fig. 5).

**Arrhythmia**

Holter ECG should be performed periodically to detect ventricular and supraventricular arrhythmias, which are recorded in 40%-50% of acromegalic patients.

Ventricular arrhythmia, including ventricular tachycardias (VT), may be related to left ventricular hypertrophy and fibrosis. Additionally, IGF-1 has positive ionotropic effect with an increase in the intracellular calcium that contributes to early or delayed depolarizations (32). The left atrium enlargement increases the risk of atrial arrhythmia, including paroxysmal atrial fibrillation (PAF), and – in consequence of stroke.

The risk of arrhythmias, including malignant ventricular tachyarrhythmia, is naturally highest in the third irreversible stage of the disease. It can be the cause of repeated syncop and sudden cardiac death (33).

Subramnaian et al. described a case of a 56-year-old patient who was referred for catheter ablation due to persistent monomorphic ventricular tachycardia, refractory to antiarrhythmic treatment.

The patient had clinical and biochemical features of acromegaly. Other potential causes of arrhythmia, including coronary artery disease, were excluded. After transsphenoidal pituitary surgery (TSS), he remained under observation – without arrhythmia recurrence (34).

Additionally patients during treatment with somatostatin analogues (SSA) may develop symptomatic sinus bradycardia that could be indication for pacemaker implantation (35).

**Summary**

Cardiovascular complications, including mainly hypertension and remodeling of the left ventricle and left atrium, with progressive diastolic dysfunction, and subsequent consequences in the form of ventricular and supraventricular arrhythmias, are the most common complications in patients with acromegaly. From the moment of diagnosis it is very important to strive for radical surgery, which is the first-line choice for patients with acromegaly and gives the greatest chance for normalization of GH and IGF-1 and improvement of echocardiographic parameters.

Pharmacotherapy (SSA, GHR antagonists like Pegvisomant) used in the case of incomplete surgery, while waiting for surgery, and in the case of contraindications to surgery, also has a beneficial effect on cardiovascular changes, proven in studies (27, 36, 37).

It is important that patients are diagnosed early and treated for acromegaly per se as well as comorbidities as soon as possible. This reduces the risk of cardiac complications, and consequently improves the quality and prolongs life.
References


