TREATMENT WITH GROWTH HORMONE RECEPTOR ANTAGONIST IN ACROMEGALY: EFFECT ON CARDIAC ARRHYTHMIAS

Renata S. Auriemma¹, Rosario Pivonello¹, Maria Cristina De Martino¹, Giuseppe Cudemo², Ludovica F.S. Grasso¹, Mariano Galdiero¹, Ylenia Perone¹, Annamaria Colao¹.

1. Department of Molecular and Clinical Endocrinology and Oncology; 2. Department of Clinical and Experimental Medicine, University “Federico II”, Naples 80131, Italy.

Short Title: Pegvisomant and arrhythmias in acromegaly

Key words: Acromegaly, IGF-I, pegvisomant, arrhythmias, heart rate, left ventricular mass,

Disclosure: The authors have nothing to disclose

Word count: abstract 237, text 2967, tables 2, figures 3, references 34

Correspondence to:

Annamaria Colao, MD, PhD, Prof
Department of Molecular and Clinical Endocrinology and Oncology
"Federico II" University of Naples
via S. Pansini 5, 80131 Naples
Tel. +39-081-7464983
Fax +39-081-5465443
email: colao@unina.it
Objective: to evaluate the effects of short and long-term treatment with pegvisomant (PEG) on arrhythmias in acromegalic patients resistant to long-term high-dose therapy with somatostatin analogues (SA).

Patients and Methods: thirteen patients entered the study. All patients started PEG at initial dose of 10 mg daily, then titrated of 5 mg every 6 weeks on the basis of IGF-I. A standard 24-h ECG registration was performed in all patients at baseline and after 6 and 18 months of PEG to evaluate: mean (HR), maximum (MHR) and minimum (mHR) heart rate, pauses number (P) and duration (PD), supraventricular episodes number (SE) and duration (SED), ventricular ectopic beats number (EB) and duration (EBD). Left ventricular mass (LVM) was also evaluated by standard echocardiography.

Results: A slight but not significant decrease in HR, MHR and mHR was observed after 6-month PEG, whereas a significant decrease in HR (p=0.03), MHR (p=0.05) and mHR (p=0.05) was found after 18-month PEG compared to baseline. LVM significantly (p=0.05) correlated with MRH (r= -0.50) after short-term treatment, and with HR (r= -0.54) and mHR (r= -0.55) after long-term treatment. Long-term PEG induced the complete recover of arrhythmias recorded at baseline in one patient and the improvement of rhythm disorders developed after 6-month therapy in another patient. The prevalence of conduction disturbances passed from 15% to 7.7% after long-term PEG.

Conclusions: Long-term treatment with PEG reduces HR, MHR and mHR and improves rhythm abnormalities in acromegaly.
INTRODUCTION

Acromegaly is associated with an increased morbidity and mortality for cardiovascular disease, including an increased prevalence of arrhythmias (1, 2). The exposure to GH and IGF-I excess induces a typical cardiomyopathy (2), which has been claimed as the most important complication as well as cause of death in acromegaly (2-8). Acromegalic cardiomyopathy develops precociously and progressively induces an initial cardiac hypertrophy associated with an increased heart rate and cardiac output, altogether configuring the hyperkinetic syndrome (8). In the middle phase, hypertrophy becomes more evident, signs of diastolic dysfunction appear, and insufficient systolic function on effort can be documented. In the end-stage of untreated disease, cardiac abnormalities may include systolic dysfunction at rest and heart failure (2).

Cardiac arrhythmias, such as supraventricular and ventricular ectopic beats, paroxysmal supraventricular tachycardia, paroxysmal atrial fibrillation, sick sinus syndrome and bundle branch blocks, have been recorded in 41-48% of acromegalic patients, particularly during physical exercise when compared to healthy control subjects (2, 9-12), and, disappointingly, recovery from acromegaly does not seem to significantly improve this rate (10). Recently, it has been demonstrated that the relative risk to develop cardiac arrhythmias is about 5 times higher in acromegalic patients than in healthy control subjects (11). In particular, the prevalence and the severity of ventricular arrhythmias have been reported to be significantly increased in acromegalic patients (9). Complex ventricular arrhythmias have been observed in 48% of acromegalic patients as compared to 12% of controls (9), and the rate of ventricular premature complexes has been reported to be strongly related to disease duration and, interestingly, to left ventricular mass, but not to circulating hormone concentrations (9). However, supraventricular premature complexes do not occur more frequently in acromegalic patients than in general population (12). Furthermore, acromegalic patients frequently show an abnormally prolonged QT interval, configuring the long-QT syndrome (13), known as a risk factor predisposing to potentially fatal arrhythmias and sudden cardiac death (14).
Both standard electrocardiography (ECG) and 24-hour Holter ECG have clearly documented conduction disorders in acromegaly. However, the standard ECG was able to demonstrate only a minority of rhythm disturbances whereas the Holter ECG was able to show also subclinical conduction disturbances in patients with acromegaly (10).

Control of GH and IGF-I excess, either secondary to surgery or to medical therapy with somatostatin analogues (SA), has been reported to improve or at least to arrest the progression of acromegalic cardiomyopathy. Particularly, 12-month therapy with SA has been reported to successfully improve cardiovascular parameters and cardiomyopathy, leading to a rapid reduction of cardiac hypertrophy and to the improvement of systolic and diastolic performance (15-17). First-line SA treatment has also been found to reduce heart rate more significantly than surgery, although the prevalence of arrhythmias was slightly but not significantly changed by both treatments (18). In acromegalic patients resistant to treatment with SA, the GH-receptor antagonist PEG has been reported to significantly reduce cardiac mass and to increase ejection fraction so that to improve cardiac structure and performance (19). To the best of our knowledge, no data are today available on the effects of PEG on rhythm abnormalities in acromegaly.

The present open-label, prospective study is aimed at investigating the effects of short-term (6 months) and long-term (18 months) term treatment with PEG on rhythm disturbances in a cohort of acromegalic patients proven to be resistant to long-term high-dose treatment with SA.

**PATIENTS AND METHODS**

The inclusion and exclusion criteria, patients characteristics, hormonal assays and treatment protocol have been described in two previous papers (19, 20) where clinical, biochemical and radiological parameters as well as cardiac structure and performance were considered but cardiac rhythm abnormalities were not evaluated.

Patients
Nineteen patients (8 males, 11 females, aged 47±11 years, pts) were enrolled in this study. All patients but three had previously undergone neurosurgery and three had also received radiotherapy after unsuccessful surgery. All patients but three had been previously treated with SA (octreotide LAR 40 mg monthly or lanreotide 120 mg monthly) for at least 6 months before study entry, without achieving clinical and biochemical control of acromegaly. In facts, in our patients SA induced a reduction ranging from 8 to 36% in IGF-I levels, so patients were considered clearly resistant to SA, although they could be defined totally resistant in some cases and partially resistant in many cases. Among patients who did not receive treatment with SA before study entry, one entered the study immediately after diagnosis, whereas two received pre-surgical SA and had disease recurrence after an apparently successful surgery performed more than ten years before. During the study, 6 pts prematurely dropped out due to: poor compliance with the study drug in 4 patients after six months, acute and severe increase in liver enzymes in 1 patient after six months, and progressive increase in tumor size in 1 patient after one year. Among patients who prematurely discontinued PEG, the man treated with beta-blockers was included. Thus, thirteen patients (4 males, 9 females, aged 44±9 years) completed the study. Among patients, none showed abnormalities in serum calcium and/or potassium levels, and none had subclinical or overt hyperthyroidism. Patients profile at study entry is shown in Table 1.

Study design

The present study is an open-label, prospective study. After the baseline evaluation, all patients started the 18-month therapy with PEG. Clinical parameters, including height, weight, body mass index (BMI), as well as hemodynamic parameters, including heart rate (HR), systolic (SBP) and diastolic (DBP) blood pressure, were recorded at study entry and every six weeks thereafter. Similarly, biochemical parameters (fasting glucose and insulin, serum triglycerides, cholesterol) and safety parameters (liver enzymes) were measured at baseline and every six weeks thereafter. Left ventricular mass (LVM) was also evaluated by standard echocardiographic method. This study
considered three points: the baseline evaluation, the short-term (6 months) evaluation and the long-term (18 months) evaluation.

24-hours Holter ECG study

A standard 24-hour Holter ECG recording was performed in all patients to investigate mean (HR), minimum (mHR) and maximum heart rate (MHR) and to detect number (N) and duration (D) of arrhythmias, such as sinus pauses (P), supraventricular episodes (SE) and ventricular ectopic beats (EB), at baseline and after 6 and 18 months of treatment with PEG. The 24-h ECG was recorded on digital flash memories and then analyzed by a specific software in order to measure all QRS complexes as well as mean, minimum and maximum heart rate, and also to identify occasional arrhythmias that could not be revealed by a standard ECG strip. Patients were asked to record a personal diary of all the activities played during the whole monitoring. Pathological supraventricular and/or ventricular arrhythmias were diagnosed when the number of supraventricular episodes and/or ventricular premature beats exceeded 50/24 hour.

STATISTICAL ANALYSIS

Data were analyzed using SPSS Software for Windows, version 15.0 (SPSS, Inc., Cary, NC package). Data are reported as Mean±SD unless otherwise specified. The effects of PEG treatment was analyzed by non parametric test using Wilcoxon test. The comparison between the prevalence of rhythm abnormalities before and after treatment was performed by $\chi^2$ test corrected by Fisher exact test if necessary. The correlation study was performed by linear regression analysis calculating the Pearson’s coefficient. Significance was set at 5%.

RESULTS
Baseline
After a 4-month washout of long-acting SA, as per protocol, all patients had IGF-I levels at least 1.3 times above the upper limit of normality. LVM, calculated by the Devereux’s equation (21), was above the normal range in both men (241±24 g, cut-off point >177 g) and women (192±52 g, cut-off point >118 g). The 24-hour ECG monitoring revealed no conduction abnormalities in 85% of patients. Rhythm disorders, including overt sinus tachycardia and supraventricular episodes, were found in 15% of patients. Particularly, a 55 yr-old woman showed 36 asymptomatic, nocturnal Ps with PD <2.5 sec, 6 SEs with SED of 400 msec and 1 EB with EBD of 200 msec. A 47 yr-old woman had sinus tachycardia, with HR being 102 bpm at rest.

Short-term (6 months) treatment with PEG
At a mean dose of 20.8±5.3 mg and a median dose of 25 mg daily of PEG, IGF-I significantly decreased (p=0.001) compared to baseline, and resulted fully normalized in 65% of patients. GH levels were only slightly but not significantly reduced. The change in GH and IGF-I levels and the concomitant changes in the metabolic profile after short-term treatment with PEG are shown in Table 2. No significant change was found in HR, mHR and MHR (Fig.1), as well in number and duration of P, SE and EB. However, in the youngest patient, who showed no rhythm abnormality at baseline, after 6-month PEG 21 SEs with SED of 920 msec were recorded (Fig.2).

Long-term (18 months) treatment with PEG
At mean dose of 25.4±10.5 mg and a median dose of 25 mg daily of PEG, IGF-I was significantly decreased (p=0.001) compared to baseline, whereas no further reduction was found as compared to 6-month evaluation. IGF-I levels were fully normalized in 85% of patients. GH levels were similar to those recorded at baseline evaluation and only slightly, although not significantly, increased compared to short-term study. The change in GH and IGF-I levels and the concomitant change in the metabolic profile after long-term treatment are shown in Table 2. LVM was significantly lower (p=0.006) than baseline and further reduced (p=0.02) compared to short-term study. HR (p=0.03),
mHR (p=0.05) and MHR (p=0.05) were significantly decreased when compared to baseline evaluation, and mHR was further reduced (p=0.02) compared to short-term study (Fig. 1). After 18 months of treatment, in the youngest patient SEs spontaneously decreased in terms of number (2) and duration (600 msec), although 4 asymptomatic, nocturnal Ps with PD <2.5 sec were recorded, compared to 6-month therapy (Fig. 2). Conversely, in the 55 yr-old woman with overt conduction abnormalities at baseline the 24-hour ECG monitoring showed the complete disappearance of abnormal P, SE and EB after long-term PEG treatment (Fig. 2). Similarly, in the 47 yr-old woman with sinus tachycardia at baseline the reduction of HR was recorded after long-term therapy with PEG (HR=82 bpm at rest). After long-term therapy with PEG, prevalence of rhythm abnormalities passed from 15% to 7.7%.

**Correlation study**

The results of correlation study are shown in Fig. 3. At short-term evaluation, LVM significantly correlated with MHR (r=-0.55, p=0.05), but not with IGF-I, HR and mHR. Percent decrease in LVM (∆LVM) did not correlate with percent decrease in IGF-I (∆IGF-I) and cardiac rhythm parameters. At long-term evaluation, LVM significantly correlated with HR (r=-0.54, p=0.05) and mHR (r=-0.55, p=0.05) but not with MHR, as well as ∆LVM significantly correlated with ∆IGF-I (r=0.54, p=0.05) and with ∆MHR (r=0.53, p=0.05).

**DISCUSSION**

This prospective study firstly demonstrated that treatment with PEG is not arrhythmogenic and induces a significant decrease in heart rate as recorded by the 24-hour Holter ECG monitoring in acromegalic patients.

Conduction disorders have been recorded in 41-48% of patients with active acromegaly (9-12), even in the earlier phase of acromegalic cardiomyopathy (8), and in around 17% of patients with
disease remission after 6-month lanreotide (22). In the majority of cases rhythm abnormalities at Holter ECG have been described as complex ventricular arrhythmias (9, 10, 12). In the series of active patients of the current study, a lower prevalence of rhythm abnormalities (15%), mainly including supraventricular episodes, was found compared to previous literature. It is noteworthy that the great majority of patients of the current study had a long history of the disease and most patients were proven to be resistant to high-dose treatment with SA, which was performed for a long period of time, although with suboptimal response. The reason of a different prevalence and type of cardiac rhythm disorders in the series of patients of the current study is not known. However, the possibility that this evidence is directly related to beneficial effects of previous treatment with SA on cardiac arrhythmias, as well as to the SA-induced relatively scant IGF-I levels decrease cannot be excluded, although it seems to be unlikely considering that even the normalization of IGF-I induced by SA treatment has been described to exert only a slight but not significant change in the prevalence of arrhythmias in patients with acromegaly (10, 18).

SA have been reported to normalize IGF-I levels in up to 60% of patients and to significantly improve hyperkinetic syndrome in acromegaly (13, 15, 22). Particularly, clinical and biochemical control of acromegaly induced by medical therapy with SA have been demonstrated to decrease heart rate more significantly than surgery in patients first-line treated with SA (18), suggesting that SA could directly act on cardiomyocytes and pacemaker cells via somatostatin receptors, that are known to be abundantly expressed in the human heart (23). However, SA are listed among the drugs able to prolong the QT-interval (24), since native somatostatin has been shown to prolong the effective refractory period of the right ventricle in humans (25).

PEG has been demonstrated to normalize IGF-I levels in up to 90% of acromegalic patients (26) and in nearly 80% of those displaying resistance to SA (20). Control of acromegaly induced by PEG has been associated with an improvement of glycometabolic profile and cardiomyopathy in terms of decrease in cardiac mass and increase in ejection fraction (19), so that to enhance cardiac performance and to prevent cardiac failure. The present study confirmed that PEG induces a significant improvement in hypertrophic cardiomyopathy, and demonstrated that after treatment
with PEG, LVM significantly correlated with maximum heart rate after short-term treatment, and to mean and minimum heart rate after long-term treatment, so suggesting that PEG might exert a beneficial effect on rhythm disorders and hyperkinetic syndrome, known to be the *primum movens* of cardiomyopathy in acromegaly.

The role of hypertrophic cardiomyopathy and myocardial fibrosis as key factors in the pathogenesis of rhythm disorders, including malignant ventricular arrhythmias and sudden death, has been extensively investigated and elucidated (27-33). Heart rate is reportedly inversely associated with LVM (27). Myocardial fibrosis has been demonstrated to be present in 96% of non-acromegalic patients with arrhythmias and hypertrophic cardiomyopathy (28-33), so that to be implicated as an important substrate in the genesis of life-threatening arrhythmias. In active acromegaly, the underlying structural changes of the heart, most likely due to GH and IGF-I excess on cardiac walls, are myocardial hypertrophy, most invariably present and, and myocardial fibrosis found in 85% of cases in the largest autopic series (29). Therefore, it is likely that hypertrophic cardiomyopathy and myocardial fibrosis are responsible of the rhythm abnormalities in acromegals as well, and, consequently, the improvement of these cardiac abnormalities, where possible, could induce improvement of arrhythmias. In searching early markers of disturbed cardiac function in active acromegaly, Herrmann *et al.* (34) have focused on the occurrence of ventricular late potentials, and have showed that as many as 56% of patients with active acromegaly had late potentials on ECG compared to 6% of patients with well-controlled acromegaly after SA treatment and none of controls. In our patient population, taking into account the long average disease duration (>10 years), the mean age >40 years, the high levels of IGF-I at study entry, the presence of hypertrophic cardiomyopathy in 100% of patients and the failure of previous long-term high-dose treatment with SA in normalizing IGF-I excess and controlling systemic complications, the presence of rhythm abnormalities does not surprise. Noteworthy, despite previous literature reported that recovery from acromegaly does not seem to significantly improve the rate of conduction disorders (10, 18), the results of the current study demonstrated that IGF-I normalization was associated to the reduction by 50% in the prevalence of arrhythmias, and in one patient the complete disappearance of rhythm
disorders after 18-month PEG was observed. Moreover, the present study first documented a significant decrease in mean, minimum and maximum heart rate after 18-month PEG. The mechanism underlying this positive effect of PEG treatment on cardiac rhythm in acromegalic patients has been not completely clarified. LVM reduction is likely mediated by normalization of IGF-I levels, and in turn the significant decrease in LVM after 18-month PEG could significantly impact the prevalence of arrhythmias. However, PEG might exert a beneficial effect on rhythm abnormalities most likely via a direct action on pacemaker cells and on membrane calcium channels, by binding and blocking GH receptors expressed in the cardiac conduction system. It is noteworthy that in a patient of the current study a dramatic increase in supraventricular episodes was recorded after short-term therapy with PEG and spontaneously decreased after long-term PEG treatment. The reasons of this unexpected worsening are still unclear, although in this patient IGF-I and LVM were only slightly reduced after 6-month PEG and normalized only after 18-month PEG. Interestingly, in the patient population of the current study, despite a significant reduction of LVM after short-term treatment a significant decrease in mean, minimum and maximum heart rate was observed only after 18-month PEG. Therefore, it can be hypothesized that the decrease in IGF-I levels obtained with PEG treatment is able to rapidly reduce LVM but require more time to improve the heart rate because of a possible relapse in hyperkinetic syndrome occurring after SA discontinuation. This hypothesis seem to be confirmed by the evidence that rhythm parameters are significantly correlated with the change in LVM and the change in IGF-I levels only after long-term therapy with PEG. Alternatively, a long time is necessary before the block of GH action on cardiac conduction system induce a definite change in heart rate in patients with acromegaly.

In conclusion, the results of the present study demonstrates that in acromegalic patients resistant to long-term high-dose treatment with SA PEG treatment induces a significant decrease in mean, maximum and minimum heart rate, suggesting that this treatment may play an important role in the improvement of cardiac arrhythmias associated with acromegaly. Further studies are mandatory to
clarify the exact mechanism by which PEG treatment induces this beneficial effect on cardiac rhythm in patients with acromegaly.

DECLARATION OF INTEREST

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

FUNDING

This study did not receive any specific grant from any funding agency in the public, commercial, or not-for-profit sector.
REFERENCES


24. The University of Arizona Health Science Center. Center for Education and Research on Therapeutics. Drugs to be avoided by congenital long QT patients. 2002 [www.QTdrugs.org](http://www.QTdrugs.org).


LEGEND TO FIGURES

**Fig. 1**: effects of short (6 months) and long (18 months) term treatment with pegvisomant on mean heart rate (up, left), maximum heart rate (bottom, left) and minimum heart rate (right).

**Fig. 2**: Left, case n.1. The youngest patient, who did not show rhythm disturbances at baseline, after short-term treatment had 21 supraventricular episodes that spontaneously decreased to 2 after 18-month PEG (up, left). Supraventricular episodes duration also spontaneously reduced after long-term therapy (up, right). On the other hand, after long-term PEG treatment 4 sinus pauses (bottom, left) with duration of 200 msec (bottom, right) were recorded. Right, case n.2. At baseline, one patient showed 36 sinus pauses (up), 6 supraventricular episodes (middle) and 1 ectopic beat (bottom). After long-term treatment with PEG no pause, no supraventricular episode and no ectopic beat were recorded.

**Fig. 3**: correlation between left ventricular mass and heart rate. After short-term treatment with PEG, LVM was significantly related to MHR (up), whereas after long-term treatment LVM was significantly related to HR (bottom, left) and mHR (bottom, right).
Mean Heart Rate (bpm)

- **Baseline**
- **6 Months**
- **18 Months**

- **p = 0.03**

Maximum Heart Rate (bpm)

- **Baseline**
- **6 Months**
- **18 Months**

- **p = 0.05**

Minimum Heart Rate (bpm)

- **Baseline**
- **6 Months**
- **18 Months**

- **p = 0.02**

Fig. 1
6-month PEG

$r = -0.55, p=0.05$

18-month PEG

$r = -0.54, p=0.05$

$r = -0.55, p=0.05$
Table 1: patients profile at study entry.

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>13</td>
</tr>
<tr>
<td>Age (years)</td>
<td>44±9</td>
</tr>
<tr>
<td><strong>BMI</strong> (kg/m(^2))</td>
<td>28.9±4.3</td>
</tr>
<tr>
<td>Disease duration (years)</td>
<td>11.5±5.4</td>
</tr>
<tr>
<td>GH (µg/L)</td>
<td>29.9±40.1</td>
</tr>
<tr>
<td>IGF-I (µg/L)</td>
<td>719±156</td>
</tr>
<tr>
<td>ULN</td>
<td>2.9±0.7</td>
</tr>
<tr>
<td>Glucose (mg/dl)</td>
<td>100±23.5</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>130±15</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>86.5±13</td>
</tr>
<tr>
<td>LVM (g)</td>
<td>221±61.5</td>
</tr>
<tr>
<td>HR (bpm)</td>
<td>73±6.7</td>
</tr>
</tbody>
</table>

BMI: body mass index; LVM: left ventricular mass; HR: heart rate
**Table 2**: effects of short (6 months) and long (18 months) term treatment with pegvisomant on clinical, biochemical and hemodynamic parameters and on heart rate.

<table>
<thead>
<tr>
<th></th>
<th>BASELINE (A)</th>
<th>6 MONTHS (B)</th>
<th>18 MONTHS (C)</th>
<th>A vs B</th>
<th>A vs C</th>
<th>B vs C</th>
</tr>
</thead>
<tbody>
<tr>
<td>IGF-I (µg/L)</td>
<td>719±156</td>
<td>280±186</td>
<td>279±230</td>
<td>0.001</td>
<td>0.001</td>
<td>NS</td>
</tr>
<tr>
<td>GH (µg/L)</td>
<td>29.8±40</td>
<td>25.2±31.6</td>
<td>30.3±41.8</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>28.9±4.2</td>
<td>29.2±4.5</td>
<td>28.6±3.0</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>130±15.3</td>
<td>128.1±12.3</td>
<td>126.1±22.2</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>86.5±13.1</td>
<td>84.6±9.5</td>
<td>80±12.1</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>LVM (g)</td>
<td>220.9±61.5</td>
<td>213.3±59.2</td>
<td>200.3±51.9</td>
<td>0.03</td>
<td>0.006</td>
<td>0.02</td>
</tr>
<tr>
<td>Glucose (mg/dl)</td>
<td>100±23.5</td>
<td>90.1±13.5</td>
<td>87.5±12.7</td>
<td>0.01</td>
<td>0.006</td>
<td>0.05</td>
</tr>
<tr>
<td>HbA₁c (%)</td>
<td>5.4±0.6</td>
<td>5.1±0.4</td>
<td>4.9±0.3</td>
<td>NS</td>
<td>0.05</td>
<td>0.05</td>
</tr>
<tr>
<td>Insulin (µU/ml)</td>
<td>12.6±6.9</td>
<td>12.5±6.1</td>
<td>9.4±5.3</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>118.5±43.9</td>
<td>115.5±66.7</td>
<td>120.9±45.8</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Cholesterol (mg/dl)</td>
<td>219.8±45.7</td>
<td>218.5±31.5</td>
<td>221.7±35.9</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>HR (bpm)</td>
<td>82±5.7</td>
<td>78.8±7.02</td>
<td>76.1±8.5</td>
<td>NS</td>
<td>0.03</td>
<td>NS</td>
</tr>
<tr>
<td>mHR (bpm)</td>
<td>57.7±8.7</td>
<td>55.4±7.3</td>
<td>50.6±10.8</td>
<td>NS</td>
<td>0.05</td>
<td>0.02</td>
</tr>
<tr>
<td>MHR (bpm)</td>
<td>128.1±12.1</td>
<td>126.6±11.2</td>
<td>124.3±14.1</td>
<td>NS</td>
<td>0.05</td>
<td>NS</td>
</tr>
</tbody>
</table>

**HR=** mean heart rate; **mHR=** minimum heart rate; **MHR=** maximum heart rate