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# Occurrence of ventricular late potentials in patients with active acromegaly

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## Summary

**OBJECTIVE Patients with acromegaly have an increased risk of ventricular dysrhythmias and sudden death. Late potentials in a signal-averaged electrocardiogram (SAECG), a predictor of ventricular dysrhythmias, are frequently seen in patients after previous myocardial infarction, but little is known about the prevalence of late potentials in acromegaly. The aim of our study was to investigate the prevalence of late potentials in patients with acromegaly and their relation to the activity of the disease and to myocardial hypertrophy.**

**PATIENTS The study included 48 patients with acromegaly [27 males, 21 females, mean age 52·3 ± 14·2 years, 16 active disease, 32 cured or 'well controlled', under treatment with sandostatin analogues (12/32)] and 38 healthy volunteers as a control group.**

**RESULTS Late potentials were detected in 9/16 (56%) patients with active acromegaly *vs.* 2/32 (6%) with cured/well controlled acromegaly ($P = 0{\cdot}001$), defined as normal age-related IGF-1 levels and GH levels suppressible below 1 μg/l after an oral glucose load (75 g). Late potentials were not related to muscle mass index (127 ± 35 active *vs.* 123 ± 34 g/m$^2$ cured/well controlled). The association of disease activity with the detection of late potentials was independent of age, gender, duration of the disease and body mass index. In comparison to the control group, the prevalence of late potentials was significantly higher in patients with acromegaly (23%) than in the control group (0%; $P < 0{\cdot}001$).**

**CONCLUSIONS Late potentials in the SAECG are frequently seen in active acromegaly and may represent an early and sensitive parameter to detect myocardial injury in acromegaly.**

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Acromegaly reduces life expectancy (Bengtsson *et al.*, 1988; Rajasoorya *et al.*, 1994) by increasing mortality from cardiovascular and cerebrovascular disease (Morvan *et al.*, 1991). Little is known about the incidence and the severity of cardiac dysrhythmias in acromegaly and their relation to endocrine parameters. Compared to controls, acromegalic patients show more frequent and complex ventricular dysrhythmias (Kahaly *et al.*, 1992). In patients with coronary heart disease, presence of low-amplitude, high-frequency waves in the terminal tract of QRS-complexes are detected and called 'late-potentials' (Breithardt *et al.*, 1991; Vazquez *et al.* 2000) and may be thought of as an 'arrhythmogenic substrate' (Breithardt *et al.*, 1989). Sufficient data are available to recommend the use of late potentials in a signal-averaged electrocardiogram (SAECG) in patients recovering from myocardial infarction without bundle branch block to help to determine their risk for developing sustained ventricular tachydysrhythmias (Breithardt *et al.*, 1991; Brembilla-Perrot *et al.*, 1999). Approximately 25% of patients with previous myocardial infarction (within 2 weeks after injury) have late potentials (Seale *et al.*, 1990) and these have been established as a strong predictor of arrhythmic events (Breithardt & Borggrefe, 1987; Kozer *et al.* 2000).

We performed the following study to evaluate whether late potentials in SAECG can be detected in patients with acromegaly in the absence of previous myocardial infarction, and whether their occurrence is related to the activity of acromegaly.

## Patients and methods

### *Patients*

Forty-eight patients (27 males, 21 females; mean age 52·3 ± 14·2 years, range: 30–80) suffering from acromegaly were included in the study. Thirty-eight of 48 patients had undergone transsphenoidal or transfrontal surgery and 17/48 patients had undergone radiation of the pituitary. The diagnosis

of acromegaly was made on the basis of physical examination, IGF-1 and GH levels after an oral glucose load (75 g). Considering the consensus statement of criteria for cure of acromegaly, 16 patients had active disease and 32 patients were cured or 'well controlled'. Cure was defined as IGF-1 levels within the age-adjusted normal range and nadir GH after an oral glucose load of less than 1 μg/l (Giustina *et al.* 2000). Patients treated with somatostatin analogues were defined as 'well controlled' with an age-adjusted normal range of IGF-1 levels (25–39 years: 114–492 μg/l; 40–54 years: 90–360 μg/l; ≥ 55 years: 71–290 μg/l).

Twelve patients in the cured/well controlled group were treated with somatostatin analogues [three lanreotide (30 mg every 2 weeks i.m.), seven octreotide (300 μg/day), two octreotide acetate (30 mg sandostatin LAR® (Novartis Pharma GmbH, Nuernberg, Germany) every 4 weeks i.m.)] *vs.* five patients in the active group [one lanreotide (30 mg every 2 weeks i.m.), three octreotide (300 μg/day), one octreotide acetate (30 mg sandostatin LAR® every 4 weeks i.m.)]. All of the patients underwent standard electrocardiogram, exercise electrocardiogram and echocardiography before the study of late potentials. None of them had intraventricular conduction defects, ventricular aneurysms and obstructive hypertrophic cardiomyopathy or history of myocardial infarction, and none had received antiarrhythmic drugs. Two patients had a history of coronary heart disease and had undergone coronary angioplasty 1 and 4 years before study entry. At the time of study entry, no patient had clinical signs of coronary heart disease.

For every patient, the following parameters were measured in the morning after an overnight fast: weight, height, body mass index (BMI), waist to hip circumference, systolic and diastolic blood pressure and lipid profile. Pituitary function was assessed by measuring free thyroxine, trijodthyronine, TSH, cortisol, testosterone, FSH, LH, oestradiol, prolactin, GH and IGF-1. All patients with anterior pituitary insufficiency were receiving adequate substitution therapy at the time of the study. The duration of the disease (years) was determined from the year of diagnosis of acromegaly.

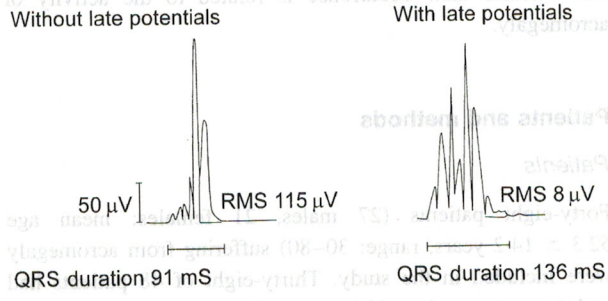


**Fig. 1** Example of two acromegalic patients with and without late potentials in signal-averaged electrocardiogram (SAECG).

### *Control group*

A group of 38 healthy volunteers (20 males, 18 females; mean age 51·6 ± 12·7, range: 30–76), without symptoms or signs of cardiac disease served as nonacromegalic controls for electrocardiogram (SAECG) measurements.

### *Analytical determinations*

Serum GH levels were determined by a chemiluminescence immunometric assay (Nichols Institute Diagnostics GmbH, Bad Nauheim, Germany). The assay was calibrated against the WHO First International Standard (80/505) for human GH. The 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 an immunoradiometric assay (Nichols Institute Diagnostics GmbH). The assay was calibrated against the WHO First International Reference Reagent 87/518. Intra- and interassay CVs for low IGF-I concentrations were 2·4% and 5·2%, respectively. In our laboratory, the normal IGF-I ranges were 114–492 μg/l for adults aged 25–39 years, 90–360 μg/l for adults aged 40–54 years and 71–290 μg/l for adults aged ≥ 55 years. All other parameters were determined by routine methods.

### *SAECG*

Time domain analysis for detection of ventricular late potentials was performed (Marquette Hellige, Medical Systems, Freiburg i. Br., Germany) by applying three supplementary bipolar leads (X, Y, Z) orientated along the three cartesian axes, in addition to the standard ones. At least 250 beats were averaged with a noise level which was lower than 0·7 μV and a filter setting of 80–250 Hz. Examination was made between 1000 h and 1200 h. (Nakagawa *et al.*, 1998).

For valid detection of late potentials, two of the three following pathological criteria had to be present (Fig. 1): (i) filtered QRS complex duration (ms) of ventricular depolarization (QRS duration): > 120 ms; (ii) root-mean-square voltage of the terminal 40 ms (μV) of the filtered QRS (RMS 40): < 20 μV; (iii) time (ms) during which the terminal portion of the filtered QRS complex remaining below 40 μV (LAS 40): > 38 ms.

### *Echocardiographic examination*

Images were recorded with patients in the left lateral decubitus position with a 3·75-MHz sector probe using a Toshiba SSA 380A Power Vision (Toshiba, Neusss, Germany) or a Hewlett Packard Sonos 1500 machine (Hewlett Packard, Ratingen,

**Table 1** Clinical characteristics in patients with acromegaly (mean ± SD)

| | Active | Cured/well controlled | |
|---|---|---|---|
| Number of patients | 16 | 32 | |
| M/F | 9/7 | 18/14 | NS* |
| Age (years) | 54·5 ± 13·7 | 51·3 ± 14·6 | NS |
| Body mass index (kg/m$^2$) | 27·4 ± 3·4 | 29·5 ± 3·8 | NS |
| Duration of the disease (years) | 8·8 ± 8·9 | 5·7 ± 6·0 | NS |
| Hypertension | 6 (38%) | 10 (31%) | NS* |
| Gonadotropin deficiency | 8 (50%) | 19 (59%) | NS* |
| ACTH deficiency | 6 (38%) | 13 (41%) | NS* |
| Surgery | 11 (69%) | 27 (84%) | NS* |
| Radiation | 5 (31%) | 12 (38%) | NS* |

*P*-value determined by Wilcoxon test; mean ± SD; NS, not significant; *Fisher's exact test (two-tailed).

Germany) (both commercially available). For each patient, an electrocardiogram was simultaneously recorded. The echocardiographic examination was performed by an investigator who had no knowledge of the clinical or angiographic data of the patients. Standard views were recorded according to the guidelines of the American Society of Echocardiography (Rakowski *et al.*, 1996). For recordings of the mitral inflow velocity pattern, the sample volume (size 2 mm) of the pulsed Doppler was placed between the tips of the mitral leaflets in the apical four-chamber view. Left ventricular outflow velocity was recorded from the apical long-axis view with the sample volume of the pulsed Doppler positioned just below the aortic annulus. Two-dimensional and Doppler tracings were recorded over five cardiac cycles at a sweep speed of 50 or 100 mm/s and stored on videotape for later playback and analysis.

### *Statistical analyses*

The data represent the mean ± SD, unless otherwise indicated. In case of skewed distribution, the median was also determined. Comparisons of dichotomous variables were carried out by Fisher's exact test. Continuous data were tested statistically by the *U*-test according to Wilcoxon, Mann and Whitney on differences between the groups. All tests were two-tailed, and $P < 0{\cdot}05$ was considered statistically significant. To explore possible interdependencies of the active *vs.* cured/well controlled form of acromegaly (or acromegalic patients *vs.* the control group) to the late potentials with other explanatory variables, the variables age, gender and BMI were entered one at a time into a logistic model. A change in estimate of the effect of late potentials towards zero was taken to indicate a spurious association mediated by a third variable.

**Table 2** Hormone parameters, blood pressure, lipid profile and echocardiographic parameters in patients with acromegaly (mean ± SD)

| | Active | Cured/well controlled | |
|---|---|---|---|
| IGF-1 (μg/l) | 485 ± 182 | 225 ± 109 | $P = 0{\cdot}0001$ |
| Growth hormone (μg/l) | 19·0 ± 47·2 | 1·2 ± 1·0 | $P = 0{\cdot}0001$ |
| Systolic blood pressure (mmHg) | 139 ± 21 | 132 ± 18 | NS |
| Diastolic blood pressure (mmHg) | 84 ± 11 | 86 ± 11 | NS |
| Total cholesterol (mmol/l) | 5·55 ± 1·86 | 5·77 ± 1·08 | NS |
| Triglycerides (mmol/l) | 1·41 ± 0·59 | 1·75 ± 0·75 | NS |
| Blood glucose (mmol/l) | 5·34 ± 0·73 | 5·69 ± 0·92 | NS |
| Intraventricular septum diameter (cm) | 1·2 ± 0·3 | 1·2 ± 0·2 | NS |
| Posterior wall thickness (cm) | 1·0 ± 0·2 | 1·0 ± 0·2 | NS |
| Muscle mass index (g/m$^2$) | 127 ± 35 | 123 ± 33 | NS |
| Ejection fraction (%) | 63 ± 8 | 58 ± 6 | $P = 0{\cdot}015$ |
| Shortening fraction (%) | 34 ± 7 | 35 ± 6 | NS |
| Tei index | 0·51 ± 0·15 | 0·54 ± 0·20 | NS |

*P*-value determined by Wilcoxon test; mean ± SD; NS, not significant.

**Table 3** Number of SAECG abnormalities in patients with acromegaly *vs.* control group

| | No ABN CRI | One ABN CRI | Two ABN CRI | Three ABN CRI |
|---|---|---|---|---|
| Active ($n = 16$) | 5 | 2 | 4 | 5 |
| Cured/well controlled ($n = 32$) | 22 | 8 | 1 | 1 |
| Control group ($n = 38$) | 31 | 7 | 0 | 0 |

ABN, abnormal; CRI, criteria; *n*, number of patients.

## Results

### *Endocrinological investigations*

Forty-eight patients with acromegaly were examined. Sixteen patients had active acromegaly and 32 were cured/well controlled (IGF-1: 484 ± 182 μg/l (range: 225–803) active group *vs.* 226 ± 109 μg/l (range: 54–471) cured/well controlled group, Wilcoxon test, $P = 0{\cdot}0001$; basal GH: 19·0 ± 47·2 μg/l (median: 3·9, range: 1·1–189) *vs.* GH: 1·2 ± 1·0 μg/l (median: 0·8, range: 0·5–5·3), Wilcoxon test, $P = 0{\cdot}0001$). Clinical, biochemical and echocardiography data can be seen in Tables 1 and 2. The association of the disease activity with the detection of late potentials was independent of age, gender, duration of disease and BMI.

### *SAECG and late potentials*

In patients with active acromegaly, late potentials were detected in 9/16 (56%) *vs.* 2/32 (6%) in the cured/well controlled group (Fisher's exact test, $P = 0{\cdot}001$; Tables 3 and 4). The mean QRS duration and the LAS 40 in the active group was significantly higher than in the cured/well controlled group, whereas the RMS 40 in the active group was lower but not significant ($P = 0{\cdot}051$, Table 5). Within the active group ($n = 16$), absolute IGF-1 or GH levels were not correlated with the detection of late potentials. In comparison to the control group, the prevalence of late potentials was significantly higher in patients with acromegaly (23% *vs.* 0%). All three parameters of the SAECG [QRS ($P = 0{\cdot}0027$), RMS 40 ($P = 0{\cdot}0002$) and LAS 40 ($P = 0{\cdot}0004$)] differed significantly in patients with acromegaly compared to the control group (Table 6). In 12 patients of the acromegalic group, and in 10 of the control group, SAECG was repeated some days later at the same time of day. In all these patients, the results were reproducible. The association of the disease activity with the detection of late potentials was independent of age, gender and BMI (multivariance logistic model, $P < 0{\cdot}05$), 17 patients were aged more than 60 years. Three of them had detectable late potentials, two had active acromegaly and one patient was cured. Two patients in the cured/well controlled group were treated with somatostatin analogues and had no late potentials. Three of five patients with new diagnosis of acromegaly had detectable late potentials. The two patients who had undergone percutaneous transluminal coronary angioplasty did not have late potentials.

**Table 4** Detection of late potentials in SAECG in patients with acromegaly

| | Late potentials |
|---|---|
| Active ($n = 16$) | $n = 9$ (56%) |
| Cured/well controlled ($n = 32$) | $n = 2$ (6%) |

Fisher's exact test, $P = 0{\cdot}001$ (two-tailed).

### *Echocardiography*

Ejection fraction was elevated in the active group (63 ± 8 active *vs.* 58 ± 6% cured/well controlled; range: 41–75%), although fractional shortening (34 ± 7 *vs.* 35 ± 6%; range: 14–44%), and the tei index (0·51 ± 0·15 *vs.* 0·54 ± 0·17; range: 0·23–1·17) did not differ between the active and the cured/well controlled group and did not correlate with the detection of late potentials. Some 25% (12/48) of acromegalic patients and 41% (7/17) of the patients treated with somatostatin analogues (2/7 with detectable late potentials) had an increased muscle mass index, defined as $> 132$ g/m$^2$, but no association was found to the detection of late potentials. In addition, there was no association between the intraventricular septum diameter and the posterior wall thickness (Table 2). One of the 48 acromegalic patients had a mitral valve prolapse without detection of late potentials.

### *ECG and stress ECG*

Resting ECG and stress ECG (maximum heart rate 131 ± 22/

**Table 5** Criteria of late potentials in SAECG (active *vs.* cured/well controlled)

| | Criteria (normal range) | | |
|---|---|---|---|
| | QRS duration (≤ 120 ms) | RMS 40 (≥ 20 μV) | LAS 40 (≤ 38 ms) |
| Active ($n = 16$) | 123 ± 15 | 26 ± 17 | 42 ± 11 |
| Cured/well controlled ($n = 32$) | 111 ± 6 | 31 ± 13 | 35 ± 5 |
| *P*-value | $P = 0{\cdot}0017$ | NS ($P = 0{\cdot}051$) | $P = 0{\cdot}04$ |

*P*-value determined by Wilcoxon test; mean ± SD.

minute, maximum blood pressure 193 ± 24/101 ± 15 mmHg) were perfomed in all patients. Sinus rhythm was observed in all ECGs. In none of the patients was stress ECG terminated because of angina pectoris or dyspnoea. Due to increase in ventricular ectopic beats (bigeminy or doublets), two patients did not accomplish a full stress test. During stress ECG, 3/16 (19%) patients in the active group had complex ventricular dysrhythmias (Lown III–IV) *vs.* 4/32 (13%) in the cured/well controlled group (not significant). The severity of ventricular dysrhythmias in both groups did not correlate with abnormalities in SAECG or to hormone levels. None of the 48 patients had significant ST segment changes, including the two patients with coronary heart disease who had been treated with percutaneous transluminal coronary angioplasty before stress ECG. In one patient, SAECG was performed before angioplasty and, in the other patient, 4 years after angioplasty.

## Discussion

Acromegalic patients show more frequent and complex ventricular arrythmias (Kahaly *et al.*, 1992), which seem to be related to left ventricular hypertrophy. Concerning dysrhythmias, the role of the activity of the disease is still unclear. In the present study, we have shown that late potentials in SAECG occur in patients with acromegaly and are associated with disease activity.

Although most data of late potentials and their predictive value are available in patients with previous myocardial infarction, late potentials can also be detected in patients with aneurysms caused by coronary heart disease (Kozer *et al.* 2000) and in patients with nonischaemic congestive cardiomyopathy (Mancini *et al.*, 1993). In patients with normal left ventricular function, late potentials have rarely been seen (Breithardt & Borggrefe, 1987; Danford *et al.*, 1989).

In the present study, 23% (11/48) of acromegalic patients had late potentials similar to the prevalence (25%) in patients with previous myocardial infarction within 2 weeks after injury (Seale *et al.*, 1990). None of the 48 patients with acromegaly had significant ST segment changes during stress ECG, including the two patients with coronary heart disease who had been treated with percutaneous transluminal coronary angioplasty 1 and 4 years before stress ECG. Although the other patients had not been examined by coronary angiography, none of them had clinical evidence of coronary heart disease at the time of the study.

In patients with coronary heart disease and previous myocardial infarction, late potentials originate from asynchronous electrical activity in bundles of surviving muscle, mostly

**Table 6** Patients with acromegaly (mean ± SD) *vs.* control group

| | Acromegalic patient | Control group | |
|---|---|---|---|
| Number of patients | 48 | 38 | |
| M/F | 27/21 | 20/18 | NS* |
| Age (years) | 52·3 ± 14·2 | 51·6 ± 12·7 | NS |
| Body mass index (kg/m$^2$) | 28·8 ± 3·8 | 27·8 ± 4·2 | NS |
| QRS duration (ms) | 115 ± 11 | 109 ± 7 | $P = 0{\cdot}0027$ |
| RMS 40 (μV) | 29 ± 15 | 42 ± 19 | $P = 0{\cdot}0002$ |
| LAS 40 (ms) | 37 ± 8 | 30 ± 4 | $P = 0{\cdot}0004$ |

*P*-value determined by Wilcoxon test; mean ± SD; NS, not significant; *Fisher's exact test (two-tailed).

at the border of a myocardial infarction. These surviving muscle cells are separated by fibrous tissue that can form isolating boundaries between them (Sage & Gavin, 1985; Jennings *et al.*, 1995). In patients with acromegaly, myocardial biopsies show a similar boundary between hypertrophied myocytes and fibrosis with a cellular infiltrate (Lie, 1980), which has also been described in obesity (Duflou *et al.*, 1995). It was recently shown that myocyte cell death, apoptotic and necrotic in nature, may be critical for the development of ventricular dysfunction and its progression to cardiac failure with acromegaly (Frustaci *et al.*, 1999). The direct effect of continous GH excess seems to be a predominant factor responsible for histomorphological changes in acromegaly. Histopathological correlates of late potentials are not available in the present study, and any explanations remain speculative. Because late potentials were detected in acromegalic patients with normal as well as with elevated muscle mass index, late potentials seemed to be not only a consequence of myocardial hypertrophy, but also to be an 'early arrhythmic substrate'.

In the present study, the prevalence of late potentials in SAECG of patients with acromegaly was independently related to myocardial hypertrophy and no associations were found to glucose levels and to hypertension, similar to the investigations of Colao *et al.* (2000a) and Lopez-Velasco *et al.* (1997). These authors have shown that hypertension and abnormalities of glucose tolerance were also independently related to myocardial hypertrophy. Although only one patient had a mitral valve prolapse without detectable late potentials, it has been reported that the occurrence of late potentials is associated with mitral valve prolapse (Babuty *et al.*, 1994; Nomura *et al.*, 1997; La Vecchia *et al.*, 1998).

Although late potentials seem to be related to different physiological variables (Danford *et al.*, 1989; Raineri *et al.*, 1990), the detection of late potentials in the present study of acromegalic patients was not related to gender (Maffei *et al.*, 1995) or obesity (Lalani *et al.* 2000). The lower BMI in the active group may be due to alterations of leptin and insulin levels, which influence body composition and BMI in patients with active acromegaly, or due to the lipolytic effect of growth hormone itself (Damjanovic *et al.* 2000).

Although we found a high prevalence of late potentials in patients with active acromegaly, we cannot determine the prognostic value of our findings, because holter monitoring was only performed in a few patients. It would be interesting to determine in the future whether late potentials disappear after optimizing therapy with sandostatin analogues or a GH receptor antagonist (Trainer *et al.* 2000) with or without improvement of cardiac function (Colao *et al.*, 1999; Colao *et al.* 2000b).

In summary, late potentials in the signal-averaged ECG are frequently seen in active acromegaly (56%) and may represent an early and sensitive parameter to detect myocardial injury in acromegaly.

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