ORIGINAL ARTICLE

# Markers of Ventricular Tachyarrythmias in Patients with Acromegaly

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## Summary

**Introduction:** Sudden cardiac death is a known complication of acromegaly. Little is known of the exact mechanism leading to sudden cardiac death in these patients. Ventricular tachyarryhthmias may be an important cause. If this is so, clinical markers of ventricular tachyarrhythmias may be more common in this group of patients. The presence of these markers allow better risk stratification among acromegalic patients.

**Methods:** We performed signal averaged electrocardiography and analysed 12 lead electrocardiography for QT dispersion on 17 acromegaly patients who attended the UKM endocrine clinic within a period of 5 months and compared them with similar age matched controls. Signal averaged electrocardiogram was performed using Marquette Mac 12/15 ECG analyser and QT intervals were measured manually from 12 lead ECG tracings. Late potential positivity was defined by the standard Breithardt criteria. QT dispersion was defined as the longest minus the shortest QT interval from all 12 lead tracings. Echocariography was done to assess left ventricular hypertrophy in patients and controls.

**Results:** Late potential positivity was found to be more common in acromegaly patients compared with controls (chi-square, $p<0.05$, $n=34$) and QT dispersion was also found to be significantly higher in the acromegaly group compared with control s (mean ± SE QT dispersion respectively $121.0\pm8.6$ms vs $86.2\pm7.0$ms, t-test, $p<0.05$, $n=34$). Left ventricular hypertrophy was present in five acromegaly patients and two in the control group.

**Conclusion:** Acromegaly patients have a higher incidence of late potential positivity and higher QT dispersion compared with age matched controls. These findings might explain the increase susceptibility of these patients to sudden cardiac deaths from ventricular tachyarryhmias.

*Key Words:* Acromegaly, QT dispersion, Signal averaged ECG, Ventricular arrhythmias

## Introduction

Cardiovascular events are important factors limiting the prognosis of patients with acromegaly[1]. An association between acromegaly with heart disease has been known for over 100 years. Huchard[2] described cardiac enlargement and congestive cardiac failure in patients with acromegaly. In a prospective study, Mcguffin[3] reported a 23% incidence of hypertension among acromegalic patients. Nine of the 57 patients had symptomatic heart disease including four with arrhythmias (supraventricular tachycardia), two with coronary heart disease, two with cardiomyopathy and one with congestive cardiac failure. These heart disease were not related to hypertension.

A review of cardiac pathology in 27 autopsy cases of acromegaly[4] found cardiomegaly in 25 out of 27 cases (93%), the largest being 1,300gm (3.7 times the normal). Cardiomegaly was related to the duration of the disease but was unrelated to the presence of hypertension or coronary heart disease. Significant coronary heart disease was present in three of 27 cases. Gross evidence of old myocardial infarction was found in four of 27 cases. Cardiac histology showed varying degrees of myocardial hypertrophy and intertersial fibrosis. In another study[5], cardiac arrhythmias at rest or during exercise test (using bicycle ergometer), were found to be present in six out of eight patients. The arrhythmias consisted of ventricular premature contractions and premature supraventricular contractions.

Hayward[6], in reporting a larger series of 256 acromegalics, found only 10 patients with heart disease not attributed to any causes, except acromegaly. The heart disease was manifested by effort dyspnoea, cardiac failure, palpitations and ECG changes of cardiomegaly. Electrocardiograms were abnormal in 9 patients with repolarisation disorders or interventricular conduction defects. Rhythm disturbances (ventricular ectopics, paroxysmal supraventricular ectopics and sick sinus syndrome) were found in six patients.

While the heart in acromegaly has been well studied in terms of its gross anatomy and internal diameters, little attention has been given to studying arrhythmias in acromegaly. Increase in ventricular mass, neurohumoural changes and disturbances of autonomic function may be the mechanism underlying the cardiac changes seen in acromegaly patients. These changes can predispose them to life threatening arrhythmias and sudden cardiac death.

With the advent of new prognostic markers of life threatening ventricular tachyarrhythmias such as assessment of ventricular premature beats in Holter monitoring, QT dispersion analysis and high resolution ECG, it is possible to identify patients who are at risk of sudden cardiac death. The aim of this study is to assess the presence of these markers in acromegaly patients and compare them with normal subjects. It will help in understanding the pathophysiology of cardiac disorders in acromegaly as well as help in identifying the patients who are at risk of sudden cardiac death.

## Materials and Methods

### Subjects

Acromegaly patients who attended the Endocrine Clinic, University Kebangsaan Malaysia, over a period of five months were enrolled into the study. There were seventeen acromegalic patients, 8 females and 9 males, with a mean age of 40.5 years (range 23 - 68 years). The mean duration of illness (assessed from the time the first symptom was noticed) was 106.6 months (range 12 - 324 months). Table I shows the detailed description of these patients. The diagnosis of acromegaly and activity of the disease after surgical or medical therapy were determined by measuring serial growth hormone during an oral glucose tolerance test. Growth hormone levels which failed to suppress or showed a paradoxical rise during the test, confirmed the diagnosis of acromegaly or indicated disease activity. In 15 patients, (except patients number 9 and 10), the disease was still active post therapy. Twelve patients had been treated with a combination of transfrontal/trans-sphenoidal surgery, radiotherapy and medical (bromocriptine) therapy. Two patients were only on medical therapy, awaiting surgery and radiotherapy (patients number 3 and 7). One patient had trans-sphenoidal surgery and was currently on bromocriptine (patient number 16), and another patient (patient number 11), had been treated with radiotherapy only. Three patients were new cases (number 3, 7 and 14) of acromegaly awaiting surgery, two of whom were on bromocriptine. Only one acromegaly patient was hypertensive.

All acromegaly patients were matched with normal age and sex matched controls (within 5 years). The controls were randomly taken, from patients awaiting elective minor surgery. Control patients were without hypertension, diabetes, coronary heart disease, thyrotoxicosis. Alcoholics and smokers were also excluded.

**Table I**

| Pt. No. | Age (yrs.)/Sex | Race | Treatment | Assoc. Illness | Duration (months) |
|---|---|---|---|---|---|
| 1 | 46/M | Mal | S, DXT, MED | | 84 |
| 2 | 68/F | Mal | S, DXT, MED | Hypertension | 48 |
| 3 | 48/F | Mal | MED | Asthma | 36 |
| 4 | 39/F | Mal | S, DXT, MED | | 192 |
| 5 | 27/F | Mal | S, DXT, MED | Thyrotoxicosis | 108 |
| 6 | 37/F | Mal | S, DXT, MED | | 48 |
| 7 | 36/M | Mal | MED | | 144 |
| 8 | 41/M | Mal | S, DXT, MED | | 156 |
| 9 | 43/M | Mal | S, DXT, MED | | 324 |
| 10 | 36/F | Mal | S, DXT, MED | | 96 |
| 11 | 68/M | Mal | DXT | | 192 |
| 12 | 33/M | Mal | S, DXT, MED | | 60 |
| 13 | 25/F | Mal | S, DXT, MED | Turners | 12 |
| 14 | 35/M | Ind | MED | | 36 |
| 15 | 46/F | Chi | S, DXT, MED | | 60 |
| 16 | 36/M | Chi | MED | | 12 |
| 17 | 35/M | Mal | S, DXT, MED | | 204 |

*Mal* : *Malay*
*Ind* : *Indian*
*Chi* : *Chinese*
*S* : *Surgery*
*DXT* : *Deep X-ray therapy*
*MED* : *Medical therapy*

### Blood investigations for disease activity

#### *Oral glucose tolerance test and growth hormone measurement*

The oral glucose test for the diagnosis of acromegaly were carried out between 8am and 9am, after an overnight fast. Blood samples for glucose and growth hormone measurements were obtained before and every 30 minutes for 150 minutes of drinking 75gm glucose in water.

#### *Growth hormone assay*

Growth hormone was measured by the radio immunoassay method, by the Institute Of Medical Research[7]. The intra-assay coefficients of variation at concentrations 2.7, 13.6 and 28.2miU/L were 6.5%, 4.3% and 3.7% respectively and the corresponding inter-assay coefficients of variation were 8.9%, 5.6% and 4.9% respectively.

#### *Assessment of cardiac function*

All the patients and the control subjects had 12 lead ECG for QT analysis and high resolution ECG for signal averaging. Details of the methods of analysis is described below.

*a. High Resolution ECG (Signal Averaged ECG)*

Signal averaging is a technique that uses high resolution ECG to average the signals of a few hundred QRS complexes to minimise noise in an attempt to maximise the signal to noise ratio. Obscuring random noise, it allows the detection of low amplitude wave forms in the terminal portion of the QRS complex, also known as late potentials.

The Mac 12/15 ECG high resolution (Hi-Res) analyser was used to measure the ventricular late potentials in this study. This analyser is equipped with a low noise 14 lead wire. For recording late potentials from the surface of the body, an XYZ lead system, formed by 3 orthogonal bipolar electrode was used[8]. This lead system is known as the Frank lead system. The surface electrodes are amplified between $10^3$ to $10^5$ time with a wide frequency band pass. A computer in this system, converts the original continuous analogue ECG signal into a digital signal of voltages sampled at frequent, fixed time intervals. The signal from each lead of the XYZ system, is filtered using the Fast Fourier Transform (FFT) filtering technique to accentuate late potentials present in the ECG. The final report contains, signal averaged ECGs from the X, Y and Z channels in three forms: unfiltered at 20mm/mv and 50mm/mv; and filtered (40 - 250Hz) at 1000mm/mV (Fig. 1). All the 3 leads were combined into a vector magnitude (VM) plot. Vector magnitude was calculated as square root of ($X^2$ + $Y^2$ + $Z^2$), from which the late potentials parameters were extracted. The QRS vector indices were measured by an automated algorithm, and the presence of late potentials was determined from the presence of all of the following standard criteria[9,10]:

1. A filtered QRS duration >114 milliseconds (QRSd)
2. Root mean square voltage of the terminal 40 milliseconds <20$\mu$V (RMS voltage)
3. Low amplitude (<40$\mu$V) high frequency signal duration >38 milliseconds (HFLA)

*b. 12-Lead ECG QT Dispersion analysis*

12 Lead ECG was done using Marquette MAC 12/15 ECG analyser at a paper speed of 25mm/sec and 1mm/volt amplification. The QT interval was measured manually using calipers and measuring the length using a caliper and ruler with a minimum of 0.5mm unit by a single

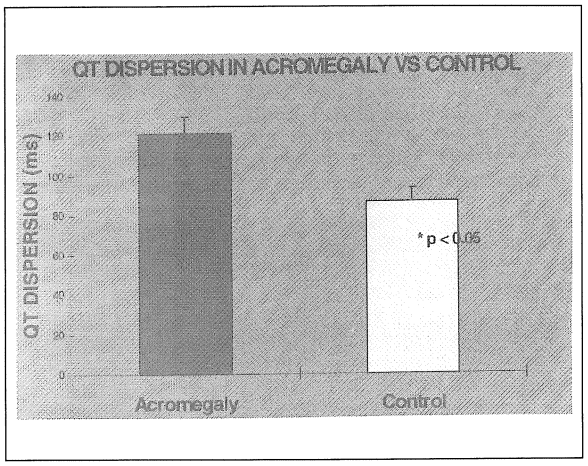


**Figure 1: QT Dispersion in acromegaly vs. controls. (Error bars represent ±S.E.)**

observer who was blinded of the other results and of the subjects. The Q point was taken at the beginning of the deflection of the Q wave and T point was taken as the point of return to the isoelectric line of the T wave or the nadir of the T wave in ECGs with prominent U waves. The U waves were not included in the QT measurement.

An independant blinded observer analysed 10 ECG's for assessment of inter-observer variabilty. There was 0.5±0.2 (S.D.)mm inter-observer variability present and paired t-test showed no significant differences between the two sets of measurements. QT dispersion was taken as the longest minus the shortest QT interval of all the 12 leads.

*c. Holter monitoring*

The Medilog 4500 Ambulatory ECG Recorder system, consists of a compact recorder (worn on a belt around the waist), two leads recording chest and limb leads, standard disposable electrodes and an analysis unit capable of trending ST segment, classifying and counting ectopics and arrhythmias. Patients were instructed to record symptoms or events suggesting arrhythmias by triggering a button easily accessible on the portable system. The tapes were played back on the software analysis package using a 486 DX33 personal

**Table II**
**Lown's Grading System for Ventricular Ectopy in Holter Analysis**

| Lown's Grade | Description of Ventricular Extrasystoles |
|---|---|
| 0 | None |
| 1 | Less than 30 per hour |
| 2 | 30 or more per hour |
| 3 | Multiform |
| 4A | Two consecutive |
| 4B | 3 or more consecutive |
| 5 | R on T |

computer which allowed manual and automated analyses and printing of a summary data, as well as events recorded by patients. For purposes of classifying ventricular ectopics, the Lown's grading system[11] was used (Table II).

*d. Echocardiography for left ventricular hypertrophy*

Echocardiography was performed using a Hewlett Packard Sonos 1000, capable of performing M-mode, 2-D echocardiogram, pulsed and continuous wave doppler studies. Left ventricular hypertrophy was measured using the in-built programme based on diastolic and systolic septal wall thickness and poterior wall thickness measued in M-mode at the level of the distal mitral valve leaflet (mid-ventricle) in the long parasternal axis view.

### Statistics

All data are presented as value ± standard error of mean (S.E.). Chi squared test with yates correction was used for the analysis and comparison of discrete data and one-tailed paired students t-test was used for for continuous data.

## Results

The clinical data are summarised in Table I. There were 17 acromegalic patients, eight females and nine males. The average age of the patient population was 41 years (Age range: 25 - 68 years), with a mean duration of illness of 106.6 months (range 12 - 324 months). All the patients except one, recieved either medical, surgical or radiotherapy. In 15 patients, the disease was still active post therapy. Only one patient had hypertension.

### *Body mass index*

There was a significant difference in the average body mass index of the acromegaly group (average±SE; 26.69 (7.85kg/m) compared with control group (24.53+2.00kg/m$^2$), (t-test, p=0.02).

### *Cardiac arrhythmias*

Ventricular ectopics were observed in three of the 17 acromegalic patients, and none in the controls. Two patients (No. 2 and 9), had ventricular ectopy with Lown's Grade 1. One patient (No. 11), had Lown's Grade 4A. Acromegaly as evident from hormonal assays, was active in these patients. The number of patients with ventricular ectopics were too small for statistical anlaysis. There were no ST-T changes noted in any of these patients. There were also no Bundle branch block or intra-ventricular conduction abnormalities seen in the holter analysis.

### *Signal averaging*

Twelve acromegalic patients had abnormal QRSd (filtered duration of >114ms), and of these, eight had abnormal HFLA and nine had abnormal RMS voltage. The control group had only four patients with abnormal QRSd, of which two had abnormal HFLA and abnormal RMS voltage. Defining late potential positivity an abnormalituies in all three parameters, there were only eight acromegalic patients with late potentials as compared to two in the control group. Late potential positivity was found to be more common in acromegaly patients compared with controls (chi-square test, $p<0.05$, $n=34$)

### *QT dispersion*

Average QT dispersion in the whole population was 103.6±7.5 (S.E.). In the acromegaly group, QT dispersion was found to be significantly higher compared with controls (mean±SE QT dispersion respectively 121.0±8.6ms vs 86.2±7.0ms, $p<0.05$, n=34).

### Echocardiographic measurement of left ventricular hypertrophy

Left ventricular hypertrophy was found to be present in five acromegaly patients compared with two in the control group (p=n.s.) There were no significant correlation between left ventricular hypertrophy and QT dispersion or late potentials.

## Discussion

Animal studies have confirmed the direct effects of growth hormone or IGF-I which induces the expression of genes for specific contractile protiens and those for myocyte hypertrophy. It also increases the force of contraction and shifts the myosin form to the low ATPase activity V3 isoform[12]. Short term administration of growth hormone increases myocardial contractility and heart rate[13]. Long term effects include increase in left ventricular mass, stroke volume and cardiac output and decrease in total peripheral resistance and systolic blood pressure[14]. Somatostatin has an effect on the heart beyond that induced by its effect on growth hormone. Infusion of somatostatin causes bradycardia and a fall in cardiac output. In some cases of supraventricular arrhythmias, somatostatin administration restores sinus rhythm[15]. Cardiac nerves have been shown to contain somatostatin, suggesting that this hormone may be an important physiological regulator of cardiac conduction[16].

The most common cardiac abnormality observed in acromegaly is cardiomegaly, especially in patients above fifty years of age. It will appear on echocardiography as concentric or assymetrical septal hypertrophy. These changes may be primarily be due to the effects of growth hormone, but other factors including hypertension and atherosclerosis also plays an important role.

The other cardiovascular manifestations that have been reported to be more common in acromegaly include: hypertension, premature coronary artery disease, congestive cardiac failure and cardiac arrhythmias, particularly frequent premature ventricular premature beats and intraventricular conduction defects. Indeed, because of of the frequent occurrence of congestive heart failure and cardiac arrhythmias in patients who have no predisposing factors, (e.g. no hypertension or arteriosclerosis), it has been suggested that a specific acromegalic cardiomyopathy exists.

With the above observations, patients with acromegaly have an increased suceptibility to sudden deaths from myocardial infarction or ventricular arrhythmias. It is therefore also important to stratify their risk of sudden cardiac death in order to plan follow-ups and therapeutic and invasive interventions. Among the recommended strategies include ischaemia detection by means of ECG, stress tests and if nescessary, coronary angiography. Conduction and electrical disturbances can also be detected in this process. This study suggests further investigations to detect prognostic markers of life threatening arrhythmias.

Seventeen acromegalic patients, eight females and nine males, with a mean age of 40.5 years and mean duration of illness of 106.6 months were studied, age and sex matched with control subjects. Only two patients were inactive by hormonal assays. As expected the body mass index of the patients was higher than the controls. Holter monitoring documented increased ventricular ectopy in only three patients, all of whom had late potentials.

Signal averaging is a noninvasive method to identify patients at risk for ventricular arrhythmias and/or sudden cardiac death. The late potentials (LP) consists of low amplitude electrical activity occuring at the end of the QRS complex. Kanousky et al[17] found that in patients with ventricular tachycardia after myocardial infarction, there was a 99% probability of developing ventricular tachycardia over 46 weeks, when all three parameters were abnormal. Those without any abnormal parameters had a 4% probability of developing ventricular tachycardia, while those with any two parameters had 82% to 88% probability of developing ventricular tachycardia. Those with only one abnormal parameter, had a 30% probability. Thus combination of all three parameters, increased specificity (69%) and

sensitivity (89%)[17]. Signal averaging however has not been used in investigating arrhythmia potentials among acromegalic patients. This study found a significant higher number in acromegalic patients, eight out of 17 patients, as compared to two in the control patients. This may suggest an increase in the substrate for ventricular ectopics, thus an increase in their susceptibility to develop ventricular tachyarrhythmias.

This finding is supported by the results of QT dispersion analysis. The average QT dispersion of patients with acromegaly was significantly higher than controls. QT dispersion is a measure of spatial repolarisation differences among different leads representing different area of the ventricles. It has been shown in many studies to indicate presence of arrhythmic subtrate causing differences in ventricular repolarisation across the area studied[18]. Although many methods have been suggested in measuring QT dispersion, the most accepted technique is the method employed in this study[19]. QT dispersion is defined as the longest minus the shortest QT interval measured in all 12 leads.

This study demontsrates that the group of patients with acromegaly have a higher incidence of having positive prognostic markers of ventricular tachyarrhythmias. This findings may be part of a syndrome which is loosely named as acromegalic cardiomyopathy. It is defined as cardiac dysfunction in acromegaly patients with no evidence of hypertension or atherosclerosis. It has been suggested that these are manifestations of cardiomyopathy which is related to the higher collagen content per gram of heart than in normal myocardium[4]. Histological observations show cellular bypertrophy, patchy fibrosis, and myofibrillar degeneration. Sudden death has been associated with inflammatory and degenerative damage to the sinoatrial perinodal nerve plexus and degeneration of the AV node.

Some studies have shown that nearly 50 per cent of acromegalic patients have electro-cardiographic abnormalities[20,21]. The most common findings are ST-segment depression with or without T-wave abnormalities, patterns consistent with left ventricular hypertrophy, intraventricular conduction disturbances-specifically, bundle branch block and, supraventricular or ventricular ectopic rhythms. Indeed, in one controlled study, 48 per cent of acromegalic patients had Lown grade III or IV complex ventricular arrhythmias, compared with 12 per cent of normal subjects. Although no correlation has been found etween the severity of ventricular arrhythmias and growth hormone levels, the frequency of premature ventricular contractions increases with the duration of acromegaly[20,21].

Studies have also shown that, administration of a somatostatin analog, octreotide, which inhibits secretion of growth hormone on cardiac function can reverse cardiac abnormalities found in acromegaly patients. In one study, seven patients with acromegaly were given octreotide subcutaneously three times daily. After 3 months of therapy, right catheterisation showed an 18 per cent increase in stroke volume and a return of the cardiac index to normal. Within 40 days of treatment, the three patients with congestive heart failure had a dramatic clinical improvement, which was sustained for up to 3 years[22]. In an extension of the study, within 1 week of initiating octreotide therapy, left ventricular mass was found to be reduced, as assessed by echocardiography[22]. The study also found, in 11 normotensive patients with active acromegaly, 6 months of octreotide therapy produced a significant reduction in left ventricular mass index, mean wall thickness, and isovolumic relaxation time, as well as a significant increase in the ratio of early to late peak velocity of right ventricular filling[22]. These encouraging results, however, have not been extended to involve studies on electrophysiological changes in the heart although as mentioned previously, somatostatin has been shown to restore sinus rhythm in some supraventricular tachycardias.

It would be interesting, based on the above results, to follow-up our study patients to observe for arrhythmic events and also study the effects of somatostatin analogue treatment on the prognostic markers measured in this study. It is still too early to predict the effects of antiarrythmics on patients with positive markers. However, future large studies can be planned to study the benefits of intervention to decrease complications of cardiac arrhythmias or sudden cardiac deaths in these high risk patients.

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