ANALYSIS OF SHORT-TERM TEMPORAL VARIABILITY OF CARDIAC VENTRICULAR REPOLARIZATION IN SUBJECTS WITH DIFFERENT CLINICAL CONDITIONS

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Summary of PhD Thesis

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Publications related to the subject of the thesis

1. **Orosz A**, Csajbók É, Czékus Cs, Gavallér H, Magony S, Valkusz Zs, Várkonyi TT, Nemes A, Baczkó I, Forster T, Wittmann T, Papp JGy, Varró A, Lengyel Cs: Increased Short-Term Beat-To-Beat Variability of QT Interval in Patients with Acromegaly. *PLoS One.* 2015;10: (4) p. e0125639.
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2. Lengyel Cs, **Orosz A**, Hegyi P, Komka Zs, Udvardy A, Bosnyák E, Trájer E, Pavlik G, Tóth M, Wittmann T, Papp JGy, Varró A, Baczkó I: Increased short-term variability of the QT interval in professional soccer players: possible implications for arrhythmia prediction. *PLoS One.* 2011;6: (4) Paper e18751. 10 p.
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3. **Orosz A**, Baczkó I, Nagy V, Gavallér H, Csanády M, Forster T, Papp JGy, Varró A, Lengyel Cs, Sepp R: Short-term beat-to-beat variability of the QT interval is increased and correlates with parameters of left ventricular hypertrophy in patients with hypertrophic cardiomyopathy. *Can J Physiol Pharmacol.* 2014; Accepted for publication; doi: 10.1139/cjpp-2014-0526.
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List of other publications

1. Nemes A, Piros GÁ, Domsik P, Kalapos A, Lengyel Cs, **Orosz A**, Forster T: Correlations between three-dimensional speckle-tracking echocardiography-derived left atrial functional parameters and aortic stiffness in healthy subjects - Results from the MAGYAR-Healthy Study. *Acta Physiol Hung.* 2015;102: (2) pp. 197-205.
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2. Piros GÁ, Domsik P, Kalapos A, Lengyel Cs, **Orosz A**, Forster T, Nemes A: A jobb pitvar és bal kamra méretének és funkciójának összefüggései egészségesekben. Eredmények a háromdimenziós speckle-tracking echokardiográfiás MAGYAR-Healthy Tanulmányból. *Orv Hetil.* 2015;156(24): 972-8.

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5. Nemes A, Domsik P, Kalapos A, Lengyel Cs, **Orosz A**, Forster T: Comparison of Three-Dimensional Speckle Tracking Echocardiography and Two-Dimensional Echocardiography for Evaluation of Left Atrial Size and Function in Healthy Volunteers (Results from the MAGYAR-Healthy Study). *Echocardiography.* 2014;31(7): 865-71.
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1. Introduction

Myocardial hypertrophy in pathological settings in humans and in animal models, especially in the chronic atrioventricular (AV) block dog model and heart failure models, has been shown to cause electrophysiological remodeling where the expression of different ion channels, including potassium channels critical for repolarization (i.e. I_{Ks}, I_{Kr} and I_{K1}), is downregulated. These changes have been associated with increased incidence of serious ventricular arrhythmias probably due to decreased repolarization reserve. It is conceivable that prolonged repolarization and a possibly impaired repolarization reserve might represent increased risk for the development of ventricular arrhythmias, including Torsades de Pointes ventricular tachycardia (TdP) that can degenerate into ventricular fibrillation and lead to sudden cardiac death (SCD).

The identification of patients at risk for serious ventricular arrhythmia and SCD is critically important. Current techniques for the reliable prediction of TdP and other, potentially fatal ventricular arrhythmias remain unsatisfactory. Electrocardiographic (ECG) parameters have been studied for their utility as prognostic non-invasive markers in SCD risk assessment. The prolongation of the frequency corrected QT interval (QTc) and increased QTc dispersion (characterizing spatial repolarization heterogeneity) were observed in patients with hypertrophic cardiomyopathy (HCM). However, QTc prolongation and QTc dispersion have been found not to be predictive for SCD in HCM patients. Moreover, QT interval prolongation alone cannot reliably predict the development of ventricular arrhythmias including TdP, since cardiac repolarization reserve may be reduced even without significant changes in the duration of cardiac repolarization.

The Tpeak-Tend interval (the duration of the T wave from the peak to the end), another ECG parameter representing spatial (including transmural) dispersion of repolarization, has been shown to more reliably predict the development of TdP in congenital and acquired long QT syndromes than QTc prolongation or increased QT dispersion.

Based on recent evidence, in addition to the prolonged QTc or Tpeak-Tend intervals, the short-term variability of the duration of repolarization (STV_{QT}) might be a better parameter to predict serious ventricular arrhythmias and SCD, and could be superior to QT interval prolongation in identifying patient populations at risk for ventricular arrhythmias and might be able to accurately predict individual risk.

Physical conditioning in *competitive athletes* induces cardiovascular adaptation including lower resting heart rate (increased vagal tone) and increased cardiac mass

(hypertrophy), called „athlete's heart". Sudden death among young athletes is rare, however, it is still 2–4 times more frequent than in age-matched controls. Numerous congenital and acquired cardiac diseases have been identified as causes of SCD in athletes; however, in 5-10 % of SCD cases no structural abnormalities are detected in the heart during autopsy. The exact mechanism of SCD in these cases is not established and is mostly attributed to ventricular fibrillation.

Hypertrophic cardiomyopathy (HCM) is a common inherited cardiac characterized by marked but variable left ventricular hypertrophy and myocardial fibrosis. HCM is associated with lethal ventricular arrhythmias, and it is the most common cause of SCD in young individuals and in competitive athletes younger than 35 years. The reliable assessment of SCD risk in individual HCM patients is critically important. The current SCD risk assessment algorithm in HCM is still considered incomplete, exhibit a low positive predictive value and hampered by lack of sufficient evidence for all elements. This notion is supported by SCD events in HCM patients who were not considered to be at high risk for SCD.

Acromegaly, caused by pituitary tumors, is well-known to be associated with cardiovascular complications, such as hypertension, left ventricular hypertrophy, asymmetric septal hypertrophy, cardiomyopathy, and congestive heart failure. Excessive secretion of growth hormone (hGH) and insulin-like growth factor 1 (IGF-1) can result in major structural and functional changes in cardiac system, and a specific cardiomyopathy develops in acromegaly associated with life-threatening dysrhythmias. Moreover, acromegaly can also be associated with cardiovascular diseases contributing to increased mortality among patients.

2. Aims

The aims of this study were:

1. to compare conventional ECG parameters as well as the short-term beat-to-beat temporal variability of the RR and QT intervals of professional soccer players to age-matched controls who do not participate in competitive sports;

2. to compare conventional ECG parameters of repolarization and STV_{QT} in HCM patients and age-matched healthy volunteers;

3. to determine beat-to-beat QT variability in patients with acromegaly.

3. Methods

3.1. Patient population

The study population consisted of 76 male professional soccer players from the Hungarian Premier League, 37 patients with HCM and 30 patients with acromegaly. Age- and sex-matched healthy volunteers were eligible for this study as control subjects. Study subjects were excluded if they had excessive ectopic beats, were in a rhythm other than normal sinus, had repolarization abnormalities, had a permanent pacemaker or any other disorders influencing the study, were on any medication likely to affect the investigated ECG parameters or consumed significant amount of food or drank alcohol, coffee or smoked.

3.2. Electrocardiography

Five-minute 12-lead electrocardiograms were recorded at rest. In athletes, baseline ECG recordings were taken before a competitive soccer game and also approximately 20 minutes after the end of the game. ECG signals were digitized, stored on a personal computer for later off-line analysis.

The RR, QT and Tpeak-Tend intervals were measured as the average of consecutive 30 beats. Out of the repolarization parameters we analyzed the QT dispersion (QTd), frequency corrected QT intervals (QTc) performed by the Bazett's, Fridericia, Framingham and the Hodges formulas. The PQ and QRS intervals were measured as the average of 15 consecutive beats using lead II.

Using 30 consecutive beats, the instability of beat-to-beat heart rate and repolarization were characterized by the short-term variability (STV) of the RR and QT intervals, and were calculated using the following formula: $STV = \sum|D_{n+1}-D_n| / (30 * \sqrt{2})$, where D is the duration of the RR or QT intervals.

3.3. Echocardiography and cardiac MRI

All HCM and acromegalic patients, all controls and 23 professional soccer players underwent transthoracic echocardiographic examination to determine standard morphological and functional parameters [left ventricular end-systolic diameter (LVESD), left ventricular end-diastolic diameter (LVEDD), ejection fraction (EF), left atrial diameter (LA), resting left ventricular outflow tract (LVOT) peak gradient]. Maximal left ventricular wall thickness (LVmax) was defined as the largest wall thickness of the left ventricle at any left ventricular segment. LVmax was also normalized for body surface area (LVmax BSA).

In all HCM patients, cardiac magnetic resonance imaging (MRI) was carried out to determine the left ventricular mass (LVM). LVM was also normalized for body surface area (LVM BSA).

3.4. Autonomic function and laboratory assessment in patients with acromegaly

Autonomic function was assessed by means of five standard cardiovascular reflex tests and a score was created to express the severity of autonomic neuropathy (AN). Fasting venous blood samples were obtained from each patient and controls for the determination of serum glucose, hGH and IGF-1 levels.

3.5. Statistics

All data are expressed as means ± standard error of the mean (SEM) for professional soccer players and as mean ± standard deviation (SD) for HCM and acromegaly patients. Comparisons between controls and patients were made using the unpaired Student's *t*-test. Degree of association between two variables was expressed by the Pearson correlation coefficient (r). A p value of < 0.05 was considered significantly different.

4. Results

4.1. Short-term variability of the QT interval in professional soccer players

4.1.1. Echocardiographic measurements in study subjects

Professional soccer players exhibited significantly higher values in interventricular septum, left ventricular posterior wall thickness and in left ventricular end-diastolic diameter compared to age-matched controls. These results were not unexpected and were supportive of the presence of athlete's heart in these professional soccer players.

4.1.2. Heart rate and QTc intervals in soccer players

In professional soccer players the RR intervals were significantly longer and consequently, the heart rate was lower before the game compared to the control group. However, after the soccer game the heart rates of athletes were significantly higher than in controls. The frequency corrected QT interval (QTc) calculated with Fridericia and Hodges correction formulas were significantly longer in players before the game. In addition, QTc was significantly prolonged in soccer players following the game compared to control values calculated with all correction formulas.

4.1.3. Short-term beat-to-beat variability of the RR (STV_{RR}) and QT intervals (STV_{QT})

Soccer players before the competitive game exhibited a significantly larger STV_{RR} compared to controls (44.9 ± 3.3 *vs* 28.2 ± 2.2 ms, $p < 0.001$); however, this difference disappeared after the game, when their heart rates were close to controls (23.4 ± 4.1 ms). The STV_{QT} was significantly higher in soccer players before game compared to controls (4.8 ± 0.1 ms *vs* 3.5 ± 0.1 ms, $p < 0.001$). Importantly, and unlike the STV_{RR}, the STV_{QT} was still significantly higher in soccer players compared to controls (4.3 ± 0.1 ms *vs* 3.5 ± 0.1 ms, $p < 0.001$), but was also reduced after the game compared to pre-game values.

4.2. Short-term variability of the QT interval and correlation with parameters of left ventricular hypertrophy in patients with hypertrophic cardiomyopathy

4.2.1. Study population and electrocardiographic parameters in HCM patients and controls

Among the 37 HCM patients, who were enrolled into the study, 24 patients were taking beta blockers and 8 patients were taking verapamil as first line therapy. Three patients were taking cardiac medications known to prolong QT interval (two were taking amiodarone and one was taking propafenone). None of the patients were on any other drug therapy with known QT interval prolonging effect.

Patients with HCM exhibited significantly increased RR, PQ and QRS intervals. QTc was significantly prolonged in HCM patients, regardless of the four methods used for QTc correction. The Tpeak-Tend interval, QT dispersion and STV_{QT} were also markedly increased in patients with HCM compared to controls. The largest relative increase was seen with regard to STV_{QT} with a relative increase of 41% (4.5 ± 2 *vs* 3.2 ± 1 ms, $p < 0.001$).

4.2.2. Correlation of repolarization parameters in HCM patients

The QTc prolongation correlated significantly with the prolongation of the Tpeak-Tend interval, but not the QRS width, indicating that the QTc prolongation was, at least in part, due to the prolongation of the terminal phase of the T wave. STV_{QT} showed a relatively strong correlation with the QTc prolongation and with the Tpeak-Tend interval. The QT dispersion did not correlate with any of the repolarization parameters.

4.2.3. Correlation between repolarization parameters and indices of left ventricular hypertrophy determined by cardiac MRI technique in HCM patients

Degree of correlation between repolarization parameters and indices of left ventricular hypertrophy (maximal left ventricular wall thickness and left ventricular mass, measured by cardiac magnetic resonance imaging) with normalization for body surface area increased in almost all comparisons. STV_{QT} showed significant, albeit modest correlation, with both un-normalized and normalized indices of left ventricular hypertrophy (LVmax; LVmax BSA and LVM BSA). Tpeak-Tend interval also correlated significantly with some of the hypertrophy parameters, but showed no significant correlation to the most reliable hypertrophy parameter, i. e. LVM indexed for BSA.

4.3. Short-term variability of QT interval in patients with acromegaly

4.3.1. Clinical data and echocardiography measurements in study subjects

As expected, significant differences were seen in serum hGH and IGF-1 levels between acromegalic and control groups. Furthermore, significantly higher average hGH and IGF-1 concentrations were measured in active acromegalic subgroup (n = 17) compared to inactive one (n = 13).

Patients with acromegaly exhibited significantly higher values in LVEDD, LVESD, IVS and PW compared to age-matched controls. These results were not unexpected and were supportive of the presence of myocardial hypertrophy in the acromegalic patients. However, no significant difference was detected in the echocardiographic parameters measured between active and inactive acromegaly subgroups.

4.3.2. Electrocardiographic parameters in study subjects

Comparison of acromegalic patients and controls revealed no significant differences in heart rate, the PQ, QRS, QT, QTc intervals and the QT dispersion. However, the Tpeak-Tend interval was significantly increased in acromegalic patients compared to controls.

STV_{QT} was significantly increased by 36% in acromegalic patients compared to controls (4.23 ± 0.1 ms *vs* 3.02 ± 0.8 ms, $p < 0.001$); however STV_{QT} values did not differ significantly between active and inactive acromegalic patient subgroups (4.16 ± 0.9 *vs* 4.33 ± 1.2 ms). We could not find any significant correlation between the STV_{QT} values and the left ventricular hypertrophy parameters in acromegaly patients or in the subgroups of active and inactive patients.

4.3.3. Autonomic function

Standard cardiovascular reflex tests indicated significant deteriorations in Valsalva ratio, 30/15 ratio, and AN score in patients with acromegaly. AN score was significantly lower in active acromegaly subgroup, than in inactive group (2.1 ± 1.7 *vs* 3.9 ± 2.2; p = 0.0260), whereas other autonomic functions did not differ significantly in our two acromegalic subgroups.

4.3.4. Correlation of serum hGH and IGF-1 x ULN levels with cardiovascular data and autonomic neuropathy parameters

Pearson coefficient values indicated that neither hGH nor IGF-1 x ULN hormone level correlated with STV_{QT} or any other ECG parameters measured. However, serum hGH concentration negatively correlated with diastolic blood pressure, PW and AN score; whereas IGF-1 x ULN levels positively correlated with Valsalva ratio.

5. Discussion

5.1. Electrophysiological background

In series of animal experiments, in dogs with chronic AV block, myocardial hypertrophy and downregulation of potassium channels, most notably of the slow component of the delayed rectifier potassium current (I_{Ks}), develop. These animals are more susceptible to lethal ventricular arrhythmias subjected to various challenges. I_{Ks} has been identified as a key component in the somewhat redundant repolarizing capacity of the myocardium, termed repolarization reserve. Repolarization reserve refers to the heart's compensating ability for loss or impaired function of one or more potassium currents critical for normal repolarization. Impaired repolarization reserve does not necessarily lead to clinically manifest repolarization abnormalities on the ECG but makes the heart more susceptible to arrhythmia development. The downregulation of repolarizing potassium currents, including the I_{K1},I_{to},I_{Kr} and I_{Ks} has also been shown both in animal models and patients with heart failure, leading to prolonged repolarization manifested as QT prolongation on the surface ECG and increased dispersion of repolarization with concomitant increase in the incidence of serious ventricular arrhythmias. Prolongation of repolarization can facilitate delayed afterdepolarization and can also precipitate serious ventricular re-entry type arrhythmias via promoting early afterdepolarization generation. It might be plausible that myocardial hypertrophy, whatever the underlying cause, may lead to potassium channel downregulation and may result in decreased repolarization reserve and increased propensity for arrhythmias including Torsades

de Pointes, a characteristic arrhythmia that can degenerate into ventricular fibrillation and culminate in sudden cardiac death.

It is well established that there are marked transmural and regional differences in the expression of cardiac transmembrane ion channels, including potassium channels, that create some spatial heterogeneity or variability of repolarization already in normal circumstances. Clinically, on surface ECG, QT dispersion is considered to be an indirect measurement of spatial heterogeneity of ventricular repolarization. The variability of cardiac repolarization can also be determined as temporal or beat-to-beat variability, which means beat-to-beat alternation of the action potential duration measured *in vitro* in a certain myocardial region. Clinically, the short-term beat-to-beat variability (STV) can be defined as the alternation (variability) of several consecutive QT intervals measured in a certain lead of surface ECG.

The heterogeneity of repolarization can be significantly enhanced by impaired repolarization reserve, thus creating an *arrhythmia substrate*. It should be emphasized that the creation of an arrhythmia substrate, i.e. the increased repolarization heterogeneity following repolarization prolongation, is not enough in itself to precipitate arrhythmias. A *trigger* extrasystole critically timed to the vulnerable period that can travel re-entry paths is also required for arrhythmia induction. Enhanced repolarization heterogeneity results in longer vulnerable periods and with more frequent extrasystoles the chance for serious arrhythmia generation is greater.

The reliable identification of patients at risk for serious ventricular arrhythmia and sudden cardiac death remains elusive. Accumulating evidence suggests that QT interval prolongation alone cannot reliably predict the development of TdP since cardiac repolarization reserve may be reduced without significant changes in the duration of cardiac repolarization. A number of clinical studies and data from *in vivo* animal experiments, as well as *in vitro* studies strongly suggest that the short-term variability of the duration of repolarization (STV) may be a better novel parameter to predict serious ventricular arrhythmias. These studies found that increased STV_{QT} correlated with elevated incidence of lethal ventricular arrhythmias and sudden cardiac death. Therefore, based on these studies and the present results, the elevated temporal beat-to-beat variability may indicate a larger repolarization instability and an increased propensity for ventricular arrhythmias.

5.2. Short-term variability of the QT interval in professional soccer players

In competitive athletes, the cardiovascular system adapts to chronic physical exercise by the development of ‘‘athlete’s heart’’, characterized by lower resting heart rate (increased vagal

tone), increased ventricular mass (hypertrophy) and volume to meet the increased demand. It should be noted that few animal experimental data are available on the effect of endurance exercise training on cardiac hypertrophy and electrophysiology in species that are highly relevant to human. Some of these studies observed slowed heart rate, prolonged QT interval and ECG signs of cardiac hypertrophy in such animals.

Based on autopsy findings, hypertrophic cardiomyopathy (HCM) is the most common cause of SCD in young athletes, however, it is quite difficult to distinguish normal compensatory cardiac hypertrophy from HCM. There are a number of other cardiac diseases and pathologies that have been associated with SCD in athletes, including arrhythmogenic right ventricular cardiomyopathy, congenital coronary artery anomalies, myocarditis, commotio cordis, aortic stenosis, Wolff-Parkinson-White and Brugada syndromes, however, these are mostly identified upon autopsy.

Increased vagal tone in athletes lowers heart rate that favors prolonged repolarization and increased inhomogeneity. The possible potassium channel downregulation due to myocardial hypertrophy also prolongs repolarization and reduces repolarization reserve. Theoretically, in this scenario a number of conditions, compounds and dietary constituents can create and enhance the *arrhythmia substrate* and they can precipitate such events of sudden cardiac death in athletes.

In conclusion, the short-term temporal variability of the QT interval is elevated in professional soccer players, which, according to our present knowledge, might indicate increased repolarization instability even without any underlying cardiac disease. It may be beneficial to screen athletes for elevated repolarization instability by adding the relatively low cost STV_{QT} determination to routine ECG examinations. It is important to emphasize that no arrhythmias were observed among soccer players in this study and further, more comprehensive investigations are needed to establish whether the higher STV_{QT} relates to higher arrhythmia propensity in this population.

5.3. Short-term variability of the QT interval and correlation with parameters of left ventricular hypertrophy in patients with hypertrophic cardiomyopathy

Hypertrophic cardiomyopathy is characterized by morphological and structural changes, including left ventricular hypertrophy, myocardial fibrosis, myofiber disarray, and small vessel disease among them, that may represent an *arrhythmogenic substrate* of the disease. Remodeling in HCM is a progressive process and a very recent study highlighted a close correlation between the development of adverse remodeling and increased risk for SCD in

HCM patients. The decreased repolarization capacity due to HCM leads to markedly impaired repolarization reserve and increased arrhythmia susceptibility in HCM, where even drugs or dietary constituents with only mild repolarization inhibitory effects can provoke serious ventricular arrhythmias and SCD.

QT variability has been previously shown to be increased in patients with HCM. The normalized QT variability index (QTVI) and normalized QT variability (QTVN) were higher in HCM patients than in controls, and the greatest abnormality was detected in patients with malignant HCM mutations. QTVI or QTVN provide a measure of overall QT variability measured during the whole duration of the ECG recording and does not take into account beat-to-beat variations, which might be equally, or even more important.

In our work, STV_{QT} showed correlation with different indices of LV hypertrophy. Myocardial hypertrophy is an inherent feature of HCM, the magnitude of which is shown to be related to adverse cardiac events, including sudden cardiac death, in patients with HCM. Indeed, pronounced myocardial hypertrophy, defined as left ventricular wall thickness >30 mm is an independent predictor for SCD in HCM, and a prophylactic ICD implantation for primary SCD prevention is suggested in such cases by current clinical guidelines. Left ventricular mass, measured by MRI, might be an even stronger predictor for such adverse events, as markedly increased LV mass index was proved to be more sensitive with regard to HCM-related death, than maximal wall thickness. It is of note that ECG voltage parameters, indicating the magnitude of myocardial hypertrophy, also correlates with adverse events in HCM. However, the study was not designed to assess link between QT variability and increased risk of sudden cardiac death. With this regard, it would be necessary to prove in a large patient cohort that increased STV_{QT} is directly linked to SCD risk in HCM.

5.4. Short-term variability of QT interval in patients with acromegaly

Cardiac rhythm abnormalities during exercise and resting electrocardiological changes have been demonstrated by ECG and Holter studies in acromegaly. The severity of ventricular arrhythmias correlated with increases in left ventricular mass and the frequency of ventricular premature complexes increased with the duration of acromegaly. Acromegalic cardiomyopathy is frequently present at diagnosis and the majority of patients with acromegaly meet echocardiographic criteria for left ventricular hypertrophy. No significant difference in left ventricle hypertrophy was observed between active and inactive acromegalic patients in our study, which may indicate that adequate treatment of acromegaly could not turn back the process.

Patients with acromegaly may also develop congestive heart failure (indicating the downregulation of potassium channels), coronary heart disease or systemic complications affecting the Framingham risk score. hGH receptor antagonist therapy improved the score and reduced the risk for coronary heart diseases. It should be noted that myocardial fibrosis occurring in acromegaly can also contribute to the underlying *arrhythmia substrate* in the heart due to disturbances in conduction.

Our observations indicate deterioration in autonomic function assessed by standard cardiovascular reflex tests in acromegalic patients. The reflex tests primarily reflecting parasympathetic functions decreased in acromegaly in our study and those demonstrating sympathetic activity did not change significantly in acromegalic patients. These results indicate a moderate parasympathetic dysfunction in our study, which could represent a predisposition to proarrhythmic activity in acromegalic patients.

In conclusion, STV_{QT} is increased in patients with acromegaly while more conventional parameters of ventricular repolarization were unchanged. STV_{QT} values did not differ between active and inactive acromegalic patients and did not correlate with actual serum concentrations of hGH and IGF-1. The elevated STV_{QT} suggests instability of ventricular repolarization and may be an early indicator of increased liability to arrhythmia in patients with acromegaly. Further prospective clinical studies are needed to identify individual risk for ventricular arrhythmias in acromegalic patients.

6. New observations and conclusions

1. The main and novel finding of this study is that short-term beat-to-beat temporal variability of the QT interval (STV_{QT}) is significantly increased in professional soccer players compared to age-matched healthy volunteers. The increased STV_{QT} was accompanied by a prolonged QT, and a lengthened frequency corrected QT interval calculated by Fridericia and Hodges formulas in these athletes.

2. In this study we also found that all ECG repolarization parameters, including frequency corrected QT interval, QT dispersion, short-term beat-to-beat temporal variability of QT interval and the duration of the T wave from the peak to the end (Tpeak-Tend) were significantly increased in patients with hypertrophic cardiomyopathy. STV_{QT} exhibited the largest relative increase among the different parameters and also showed the best correlation with indices of left ventricular hypertrophy, i.e. maximal left ventricular wall thickness or

magnetic resonance imaging derived left ventricular mass, indexed or unindexed for body surface area.

3. Although a connection between acromegaly and increased cardiovascular morbidity and mortality was established previously, this study is the first to demonstrate increased short-term beat-to-beat temporal variability of the QT interval in acromegalic patients. There was no significant difference between STV_{QT} values measured in clinically and biochemically active acromegalic patients and those in inactive patients, which may suggest that elevated STV_{QT} is related to the presence of acromegaly and not to the efficacy of the treatments applied.

4. In this study, we showed that a novel parameter of repolarization instability, the short-term beat-to-beat variability of the QT interval, is increased in cardiac hypertrophy initiated by different clinical conditions: competitive sport training, hypertrophic cardiomyopathy or acromegaly.

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