Effects of Atorvastatin on Ventricular Late Potentials and Repolarization Dispersion in Patients with Hypercholesterolemia

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Emerging evidence suggests that statins have a favorable impact on the reduction of arrhythmia events and sudden cardiac death in patients with structural heart disease. We aimed to investigate the possibly and directly favorable effects of statins on ventricular late potentials, QT dispersion, and transmural dispersion of repolarization attained by analyzing clinical electrocardiography (ECG) risk stratification parameters in patients with hypercholesterolemia without structural heart disease. In total, 82 patients (45 females; mean age, 62±10 years) with hypercholesterolemia were enrolled in this prospective study to examine the effects of statin therapy (atorvastatin 10 mg/day for 3 months) on ECG risk stratification parameters. Surface 12-lead ECG and signal-average ECG (SAECG) were recorded before and after statin treatment. The SAECG parameters, QT dispersion, Bazett-corrected QT (QTc) dispersion, T wave peak-to-end interval (Tpe), and percentage of Tpe/QT interval were calculated and compared before and after statin therapy. Twelve-lead ambulatory 24-hour ECGs were recorded in 12 patients. The results demonstrated that after statin therapy for 3 months, serum levels of total cholesterol and low-density lipoprotein cholesterol were significantly reduced (both p values <0.001). However, neither significant changes of each SAECG parameter nor the frequency of late potentials were demonstrated after atorvastatin therapy. In addition, no significant changes in QT dispersion, QTc dispersion, Tpe, or Tpe/QT were found. However, 24-hour ambulatory ECG revealed a flattening effect of circadian variation of QTc dispersion after atorvastatin therapy. In conclusion, the favorable antiarrhythmia effect of atorvastatin (10 mg/day) therapy cannot be directly reflected by analyzing these noninvasive ECG risk stratification parameters in low-risk patients with hypercholesterolemia.

Key Words: atorvastatin, electrocardiography, late potentials, QT dispersion, transmural dispersion

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Statin (HMG-CoA reductase inhibitors) therapy has favorable impacts in reducing cardiovascular mortality in major clinical trials [1,2]. Beyond lipid lowering and pleiotropic effects, it has been suggested that statins decrease mortality by reducing life-threatening ventricular arrhythmia [3,4]. A previous study indicated that hypercholesterolemia *per se* was associated with electrophysiologic remodeling and increased vulnerability to ventricular fibrillation in an animal model [5]. Recently, hypercholesterolemia was found to be associated with altered ventricular repolarization [6].

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Evidence of antiarrhythmic effects after statin therapy has been explored in different patient populations, including patients with acute myocardial infarction, patients receiving implantable cardioverter-defibrillator therapy, and patients with symptomatic extrasystolic activity [7–10]. This antiarrhythmic effect was postulated as a new pleiotropic effect of statin therapy [11].

Several noninvasive surface electrocardiography (ECG) tools including signal-average ECG (SAECG) and QT dispersion have been used to identify ventricular electrical abnormalities for arrhythmic risk stratification [12,13]. The transmural dispersion of ventricular repolarization was suggested to be reflected in the duration of T wave peak-to-end interval (Tpe) on surface ECG and analysis of Tpe was suggested as a new index of the risk of ventricular arrhythmia [14,15]. Although the antiarrhythmic effects of statin therapy were evaluated with late potentials from SAECG and QT dispersion from surface 12-lead ECG [7,10,11], the results remain controversial [16]. Furthermore, effects of statin therapy on the Tpe interval remain unknown.

The aim of this study is to investigate the direct electrocardiographic evidences of antiarrhythmic effects after statin therapy by ECG risk stratification tools in patients with hypercholesterolemia.

Methods

Patients

A total of 82 patients with hypercholesterolemia (total cholesterol ≥200 mg/dL or low-density lipoprotein [LDL] cholesterol ≥160 mg/dL) at an outpatient clinic were enrolled in this prospective clinical study between December 2003 and July 2005. Patients were excluded if they had evidence of renal or hepatic disease, severe hypertriglyceridemia, anemia, acute illness, leukocytosis (white blood cell count >10,000), thrombocytosis (platelet count >450,000), chronic inflammatory diseases, New York Heart Association class III or IV congestive heart failure, history of myocardial infarction, mitral valve prolapse, right or left bundle branch block, use of psychotropic drugs (which may affect the QT interval) or antiarrhythmic drugs (except β-blockers), blood pressure >180 mmHg (systolic) or >110 mmHg (diastolic), positive history of drug or alcohol abuse, current use of any medication known or suspected to inhibit or induce the cytochrome P450 3A enzyme system. The protocol for this study was approved by the Institutional Review Board at Kaohsiung Medical University and written informed consent was obtained from all patients.

Study design

After a 4-week washout period for any lipid-lowering therapy undertaken prior to the study, patients took atorvastatin 10 mg/day for 3 consecutive months. Concomitant therapies for other illnesses were given and maintained during the entire study. At baseline and again after the end of treatment, lipid profiles after a 12-hour fast, surface ECGs, and SAECG recordings were obtained between 8 and 10 am. Twelve-lead ambulatory 24-hour ECGs were recorded in 12 patients both before and after atorvastatin treatment. Compliance was monitored in weeks 4, 8, and 12.

SAECG

The time-domain SAECG recordings were performed using a high-resolution electrocardiograph (1200 EPX, Arrhythmia Research Technology, Austin, TX, USA) in accordance with the recommended standards for analysis of ventricular late potentials on SAECG [16]. The signal-averaging process was performed by using three standard orthogonal bipolar X, Y, and Z leads in supine position in each patient. About 400 QRS complexes were amplified, averaged, and filtered with a 40-Hz high-pass filter, and combined into a vector magnitude $X^2+Y^2+Z^2$ according to the method described by Gomes et al [17]. Significant efforts were made to limit the noise level to under 0.5 μV during all recordings. The onset and offset of the QRS complex were determined by an algorithm that calculates the filtered QRS duration (QRSd), the root-mean-square voltage of the last 40 ms (RMS 40) of the QRS complex, and the duration of the terminal low (<40 μV) amplitude signals (LAS 40) of the QRS complex. Late potentials were considered to be present, if the SAECG met two of the three of the following Gomes criteria: filtered QRS duration >114 ms; RMS 40 <20 μV; or LAS 40 >38 ms [17,18].

QT dispersion

The duration of QT interval was measured at each lead of the standard 12-lead surface ECG according to Perkiomaki et al [19]. QT interval was measured from the onset of the Q wave to the return of the T wave at the isoelectric line. If a large U wave was present, the

end of the T wave was taken at the intersection of the tangent to the repolarization slope with the isoelectric line. If T wave < 0.1 mV in amplitude, then it was excluded. QT dispersion was calculated by subtracting the shortest QT from the longest QT in absolute value ($QT_{max} - QT_{min}$). Bazett's formula ($QTc = QT/\sqrt{RR}$) was used to obtain QT interval corrected for the heart rate [20]. All measurements were made by two observers blinded to the experimental design.

Transmural dispersion of repolarization

The interval of Tpe and Bazett-corrected Tpe (Tpec) was obtained from a digitized V5 lead in surface 12-lead ECG before and after atorvastatin therapy in each patient [21]. The peak of the T wave was defined as the peak of the parabola with the highest-amplitude change after the QRS complex. The end of the T wave was defined as the point at which the steepest tangent after the T wave apex and the baseline cross. Only upright monophasic T waves were measured and the low-amplitude T waves < 0.1 mV were excluded. The data were expressed as the absolute interval in milliseconds as well as relative to the QT interval (Tpe/QT × 100%).

Ambulatory 24-hour ECG

Twelve-lead ambulatory 24-hour ECGs (Rozinn Electronics, NY, USA) were performed in 12 patients before and after statin therapy to look for circadian changes in QT and QTc dispersion and in Tpe [22]. The data were analyzed on a computer screen and the QT interval as well as the Tpe were measured manually at a screen rate of 50 mm/s using an on-screen caliper amplified at two times the voltage. The intervals of QT dispersion calculated from the 12-lead ambulatory ECG and Tpe calculated from digitized lead V5 were measured every hour. There were at least 21 data points available for each patient in a 24-hour recording. The circadian changes in QT dispersion, QTc dispersion, Tpe, and Tpe/QT were analyzed and compared before and after statin therapy [22].

Statistical analysis

All data are expressed as mean ± SD. Continuous variables were tested for normal distribution with Kolmogorov–Smirnov test and compared by means of paired student's *t* test before and after statin therapy. In cases of non-normal distribution, nonparametric methods were used (Mann-Whitney *U* test or Wilcoxon signed rank test). Correlations were determined using Pearson's correlation test and Spearman's rank order correlation test. Changes in the frequency of ventricular late potential on SAECG before and after atorvastatin therapy were compared using McNemar test. The differences in 24-hour ambulatory recordings were evaluated by a one-way repeated-measurement ANOVA followed by the appropriate *post hoc* test. A p value < 0.05 was considered statistically significant. All reported p values are two tailed and all confidence intervals were computed at the 95% level. Statistical analysis was performed with SPSS version 11.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

Changes in lipid profiles

Baseline characteristics of the 82 patients in this study are summarized in Table 1. Diabetes and hypertension were present in 16 (19%) and 25 (30%) patients, respectively. The changes in lipid profiles after statin therapy are shown in Table 2. At baseline, total cholesterol levels > 300 mg/dL and between 240 and 299 mg/dL were present in five (6.1%) and 46 (56.1%) patients,

Table 1. Baseline characteristics of the study population ($n = 82$)

Characteristics	Value
Age (yr)	62 ± 10
Male/female	37/45
Body mass index (kg/m^2)	24 ± 5
Diabetes mellitus, *n* (%)	16 (19)
Hypertension, *n* (%)	25 (30)
Cigarette smoking, *n* (%)	10 (12)
LVEF (%)	62 ± 5
Lipid profiles (mg/dL)	
Total cholesterol	248 ± 31
LDL cholesterol	157 ± 36
HDL cholesterol	49 ± 12
Triglycerides	164 ± 131
Concomitant medications, *n* (%)	
Sulfonylurea	15 (18)
Metformin	4 (5)
Aspirin	12 (17)
β-blocker	10 (12)
Calcium antagonist	19 (23)
ACE inhibitor/ARB	31 (37)

LVEF = left ventricular ejection fraction; LDL = low-density lipoprotein; HDL = high-density lipoprotein; ACE = angiotensin converting enzyme; ARB = angiotensin receptor blocker.

Table 2. Summary of lipid profiles and all studied ECG parameters before and after atorvastatin 10 mg/d for 3 months ($n = 82$)*

Parameters	Baseline	3 mo	p
Lipid profiles (mg/dL)			
Total cholesterol	248 ± 31	192 ± 39	< 0.001
LDL cholesterol	157 ± 36	112 ± 36	< 0.001
HDL cholesterol	49 ± 12	47 ± 11	0.238
Triglycerides	164 ± 131	141 ± 94	0.092
SAECG parameters			
Total filtered QRSd (ms)	96 ± 17	95 ± 15	0.155
RMS 40 (μV)	43 ± 29	45 ± 28	0.657
LAS 40 (ms)	31 ± 10	29 ± 10	0.099
Surface 12-lead ECG			
Heart rate (bpm)	86 ± 19	83 ± 21	0.956
QT_{max} interval (ms)	405 ± 39	391 ± 28	0.297
QT dispersion (ms)	46 ± 19	43 ± 18	0.215
QTc dispersion (ms)	42 ± 19	39 ± 18	0.192
Tpe interval (ms)	77 ± 11	75 ± 6	0.317
Tpe/QT (%)	18 ± 3	17 ± 4	0.159

*All data are expressed as mean ± SD. ECG = electrocardiography; LDL = low-density lipoprotein; HDL = high-density lipoprotein; SAECG = signal-average ECG; QRSd = QRS duration; RMS 40 = root-mean-square voltage of terminal at 40 ms of QRS complex; LAS 40 = low-amplitude signals; Tpe = T wave peak-to-end interval.

respectively. LDL cholesterol levels > 200 mg/dL and between 160 and 199 mg/dL were present in seven (8.5%) and 29 (35.4%) patients, respectively. After atorvastatin 10 mg/day therapy for 3 months, significant reductions in both total cholesterol (decreased by 22.5%, $p < 0.001$) and LDL cholesterol (decreased by 28.6%, $p < 0.001$) levels were demonstrated. No significant changes were observed in serum levels of HDL cholesterol or triglycerides.

Changes in SAECG parameters

Results of SAECG parameters at baseline and after statin therapy are summarized in Table 2 and Figure 1. No correlations were found between serum levels of total cholesterol or LDL cholesterol versus each SAECG parameter at baseline or after statin therapy. At baseline, there were three (3.6%), 19 (23.2%), and 17 (20.7%) patients with filtered QRSd > 114 ms, RMS 40 < 20 μV, and LAS 40 > 38 ms, respectively. After statin therapy for 3 months, three (3.6%), 14 (17.0%), and 14 (17.0%) patients demonstrated filtered QRSd > 114 ms, RMS 40 < 20 μV and LAS 40 > 38 ms, respectively. The mean values of each SAECG parameter before and after statin therapy did not show significant differences

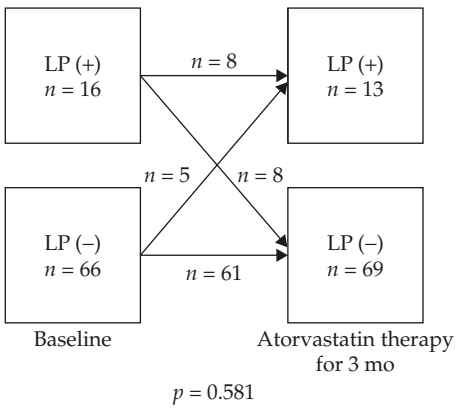

Figure 1. *Effects of atorvastatin therapy on the frequency of ventricular late potentials by signal-averaged ECG analysis in each patient. No significant difference in frequency of late potentials between baseline and after statin therapy was demonstrated ($p = 0.581$ by McNemar test). LP = late potential.*

(all p values > 0.05) (Table 2). Changes in the rates (%) of patients with positive late potentials before and after atorvastatin therapy are illustrated in Figure 1. Sixteen patients had positive late potentials at baseline, of which eight of them became negative and the other eight patients remained positive after statin therapy. Sixty-six patients had negative late potentials at baseline, of which 61 patients remained negative and the other five patients became positive after statin therapy. However, the changes in the rates of positive late potentials before and after statin therapy did not reach significant levels ($p = 0.581$, McNemar test).

Changes in study parameters of 12-lead surface ECG

Changes in QT dispersion and Tpe calculated from 12-lead surface ECG before and after statin therapy are summarized in Table 2. No correlations were found between total cholesterol and LDL cholesterol versus QT dispersion or QTc dispersion at baseline. The mean values of QT_{max} interval, QT dispersion, and QTc dispersion were consistently less after statin therapy. However, the differences in the values of these parameters before and after statin therapy did not achieve statistical significance (all p values > 0.05) in all subjects ($n = 82$) or in subgroup analysis for those patients with baseline QTc > 440 ms ($n = 15$). The mean values of Tpe, Tpec, and ratio of Tpe/QT obtained from the digitized V5 lead at baseline were 77 ± 11 ms, 70 ± 10 ms, and 18 ± 3%, respectively. No correlations were found between total and LDL cholesterol level versus Tpe, Tpec, or Tpe/QT ratio at baseline. After statin therapy, no significant

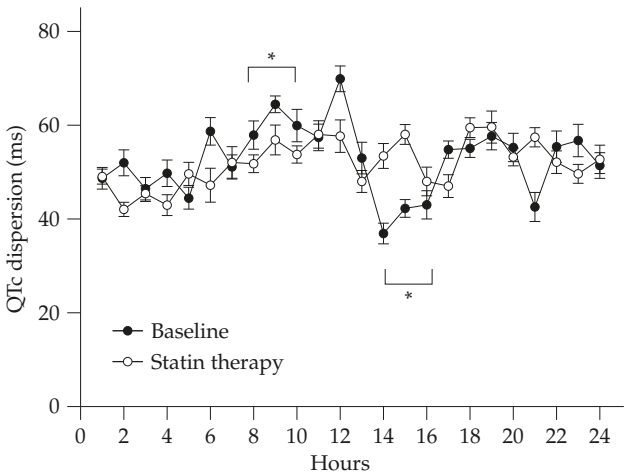

Figure 2. *Curves of QTc dispersion displayed over 24 hours by ambulatory 12-lead ECG recordings in 12 patients with hypercholesterolemia at baseline and after atorvastatin therapy. Significant differences were found between 8 and 10 am and between 2 and 4 pm in the baseline curve. After statin therapy, the QTc dispersion curve became flat and without significant circadian changes. Data are displayed as mean ± standard error. *p < 0.05.*

differences could be demonstrated in the changes of Tpe, Tpec, and Tpe/QT (all p values > 0.05) in all subjects or in subgroup analysis for those patients with baseline QTc > 440 ms.

Changes in study parameters of 24-hour ambulatory ECG

Distribution of QTc dispersion obtained from 24-hour recordings of 12-lead ambulatory ECGs is displayed in Figure 2. From the baseline 24-hour QTc dispersion curve, significant higher and lower QTc dispersion could be demonstrated in the morning between 8 and 10 am and in the afternoon between 2 and 4 pm, respectively. After statin therapy, differences in QTc dispersion for each hour diminished and became nonsignificant. The differences in 24-hour curves of QT dispersion, Tpe, or Tpe/QT (%) on ambulatory ECG before and after statin therapy were not statistically significant.

DISCUSSION

The aim of this study was to evaluate whether the antiarrhythmic effects conferred by statin therapy could be demonstrated by use of noninvasive ECG risk tools including surface 12-lead ECG, SAECG, and 24-hour Holter ECGs. However, almost all the study parameters failed to exhibit significant changes after 3 months of atorvastatin 10 mg/day treatment, except for the flattening effect of QTc dispersion on 24-hour ambulatory ECG during 8–10 am and 2–4 pm, while serum levels of total and LDL cholesterol were significantly reduced.

It remained unclear whether statin therapy had "direct" antiarrhythmic effects. Most of the antiarrhythmic benefits after statin therapy observed in high cardiovascular risk patients might be explained by statins' pleiotropic effects, including anti-ischemia, anti-inflammation, antihypertrophy, and by even prompting angiogenesis and modulation of sympathetic activation and autonomic dysfunction [3,4,11]. Recently, hypercholesterolemia *per se* has been reported to induce proarrhythmic sympathetic neural sprouting and ventricular electrophysiologic remodeling, and an increased vulnerability to ventricular fibrillation in a high-fat-fed animal model [5]. In that study, hypercholesterolemic rabbits with serum cholesterol of 2,097 ± 288 mg/dL had longer QTc intervals and higher QTc dispersion than standard rabbits with serum cholesterol of 59 ± 9 mg/dL. The results obtained from such an extremely high ratio (35.5-fold) of lipid profiles were difficult to apply in human beings. Recently, one clinical study by Szabo et al [6] suggested that hyperlipidemia may have a direct effect on ventricular repolarization by demonstrating a positive correlation between lipid profiles and QT dispersions in type IIb hyperlipidemic patients without ischemic heart disease. The mean serum levels of total cholesterol of their patients were 291 mg/dL, significantly higher than that of our patients.

No significant change in the frequency of positive ventricular late potentials on SAECG was demonstrated after statin treatment in this study. This result differed from that reported by Kayikcioglu et al [7] where patients experienced acute myocardial infarction while receiving thrombolytic therapy, and treatment with pravastatin 40 mg/day for 10 days reduced the incidence of ventricular late potentials. Most of the patients in our study lacked late potentials at baseline because of their relative low risk of cardiovascular diseases. The difference might result from the different composites of the subjects of the two studies.

The idea of antiarrhythmic effect as a "new" pleiotropic effect in statin therapy was postulated by Mark and Katona [11]. In their study, treatment with fluvastatin 40 mg/day for 12 months significantly decreased

QT dispersion, though providing only a favorable trend in QTc dispersion in 23 patients with hypercholesterolemia. Another study by Gualdiero et al [10] demonstrated that simvastatin 40 mg/day for 3 months significantly reduced QTc dispersion in patients with isolated hypercholesterolemia and with symptomatic extrasystolic activity. In this study, the differences in QT_{max} interval and QT or QTc dispersion before and after statin therapy did not achieve statistical significance in all subjects or in subgroup analysis for those patients with baseline QTc > 440 ms. Most of our study patients were free of extrasystolic activity. Furthermore, the correlations between lipid profiles and QT dispersion in our study population were not significant, in contrast to the results reported by Szabo et al [6]. The values of serum total cholesterol (291 ± 74 mg/dL) and LDL cholesterol (187 ± 64 mg/dL) in their study population were higher compared with those of our study subjects at baseline. The effect of statin on QT dispersion might be different, depending on different levels of lipid profiles before therapy and different patient populations enrolled.

Effects of statin therapy on the index of transmural dispersion of repolarization are unknown. The terminal portion of the T wave was suggested to reflect the disparity of action potential duration among midmyocardial M cell, epicardial and endocardial cells [15]. In our study, Tpe, Tpec, and the Tpe/QT ratio showed no significant change after atorvastatin treatment 10 mg/day for 3 months. These parameters have been reported by Yamaguchi et al [21] as predictors of *torsade de pointes* in patients with acquired long QT syndrome. They defined that a Tpe/QT ratio > 28% was a good cut-off point for predicting the occurrence of *torsade de pointes*. Both before and after atorvastatin therapy, the values of Tpe/QT in our study were < 28% and did not show significant changes. Results from this study suggest that in patients with isolated hypercholesterolemia and without significant organic heart disease, the transmural dispersion of ventricular repolarization is not significantly prolonged and is not affected by statin therapy.

In our study, 12-lead ambulatory 24-hour ECGs were analyzed in 12 patients. From these 12-lead Holter ECG recordings, we can calculate the changes in QT dispersion at any hour or minute and can analyze the circadian variation in the QT dispersion more thoroughly. Before statin therapy, a circadian variation in QTc dispersion was seen between 8–10 am in the morning and 2–4 pm in the afternoon, which was comparable with previous reports showing that QT dispersion may possess circadian variation during a day [22–24]. However, after 3 months of atorvastatin treatment, the hourly QTc variation diminished and the 24-hour QTc dispersion curve flattened. Liu et al [5] reported that sympathetic hyperinnervation and nerve sprouting remodeling could be demonstrated in their hypercholesterolemic rabbits with increased vulnerability to ventricular fibrillation. Molnar et al [23] postulated that the phenomenon of QTc variability reaching a peak shortly after awakening might be associated with increased autonomic instability and vulnerability to ventricular tachycardia or sudden cardiac death. Accordingly, reduction in the fluctuation of repolarization dispersion after atorvastatin therapy in the present study might be postulated as one possible antiarrhythmic effect that goes against the morning surge of arrhythmic events reported [24]. Further study with a larger sample size is warranted to investigate statin therapy with its possible antiarrhythmic efficacy in terms of circadian variation and autonomic regulation of these repolarization parameters.

Study limitations

Several limitations of this study should be mentioned. First, in this prospective clinical study, patients with hypercholesterolemia were enrolled for atorvastatin 10 mg/day treatment. Effects of higher doses of atorvastatin were not studied. Nevertheless, atorvastatin 10 mg/day in our study achieved therapeutic reduction in total and LDL cholesterol levels. Second, the number of patients in our study was relatively small and the treatment period was limited to 3 months. The differences in ventricular late potential, QT dispersion, or Tpe might change if the number of patients tested was increased or the study duration prolonged. Third, the subjects enrolled in our study were patients with relatively low cardiovascular risk. It was our aim to purely evaluate the magnitude of possible antiarrhythmia effects of atorvastatin therapy by ECG analysis in these low-risk hypercholesterolemia patients who were eligible for statin therapy but without significant structural heart disease. Results from this study might be different from those obtained from high-risk hypercholesterolemia patients with significant organic heart diseases and history of sudden cardiac death [16].

In conclusion, no significant effects of statin therapy on SAECG parameters, QT dispersion, and Tpe

were demonstrated, except for a flattening of the circadian variation of QTc dispersion on 24-hour ambulatory ECG between 8–10 am and 2–4 pm, while serum levels of total and LDL cholesterol were significantly reduced. The favorable impact on cardiovascular morbidity and mortality by statin therapy is not directly reflected in these ECG risk-stratification parameters in patients with hypercholesterolemia.

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References

1. Pignone M, Philips C, Mulrow C. Use of lipid lowering drugs for primary prevention of coronary heart disease: meta-analysis of randomized trials. *BMJ* 2000;321:983–6.
2. Scandinavian Simvastatin Survival Study Group. Randomized trial of cholesterol lowering in 4444 patients with coronary heart disease. The Scandinavian Simvastatin Survival Study (4S). *Lancet* 1994;344:1383–9.
3. Takemoto M, Liao JK. Pleiotropic effects of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors. *Arterioscler Thromb Vasc Biol* 2001;21:1712–9.
4. De Sutter J, Tavernier R, De Buyzere M, et al. Lipid lowering drugs and recurrences of life-threatening ventricular arrhythmias in high-risk patients. *J Am Coll Cardiol* 2000;36:766–72.
5. Liu YB, Wu CC, Lu LS, et al. Sympathetic nerve sprouting, electrical remodeling, and increased vulnerability to ventricular fibrillation in hypercholesterolemic rabbits. *Circ Res* 2003;92:1145–52.
6. Szabo Z, Harangi M, Lorincz I, et al. Effects of hyperlipidemia on QT dispersion in patients with ischemic heart disease. *Can J Cardiol* 2005;21:847–50.
7. Kayikcioglu M, Can L, Evrengul H, et al. The effect of statin therapy on ventricular late potentials in acute myocardial infarction. *Int J Cardiol* 2003;90:63–72.
8. Chiu JH, Abdelhadi RH, Chung MK, et al. Effect of statin therapy on risk of ventricular arrhythmia among patients with coronary artery disease and an implantable cardioverter-defibrillator. *Am J Cardiol* 2005;95:490–1.
9. Vyas AK, Guo H, Moss AJ, et al. MADIT-II research group reduction in ventricular tachyarrhythmias with statins in the multicenter automatic defibrillator implantation trial (MADIT)-II. *J Am Coll Cardiol* 2006;47:769–73.
10. Gualdiero P, Esposito K, Ciotola M, et al. Simvastatin normalized QTc dispersion and reduced ventricular electrical instability in isolated hypercholesterolemia. *J Endocrinol Invest* 2002;25:RC16–8.
11. Mark L, Katona A. Effect of fluvastatin on QT dispersion: a new pleiotropic effect? *Am J Cardiol* 2000;85:919–20.
12. Savard P, Rouleau JL, Ferguson J, et al. Risk stratification after myocardial infarction using signal-averaged electrocardiographic criteria adjusted for sex, age, and myocardial infarction location. *Circulation* 1997;96: 202–13.
13. Lee KW, Kligfield P, Dower GE, et al. QT dispersion, T-wave projection, and heterogeneity of repolarization in patients with coronary artery disease. *Am J Cardiol* 2001;87:148–51.
14. Savelieva I, Yap YG, Yi G, et al. Comparative reproducibility of QT, QT peak, and T peak-T end intervals and dispersion in normal subjects, patients with myocardial infarction, and patients with hypertrophic cardiomyopathy. *Pacing Clin Electrophysiol* 1998;21:2376–81.
15. Lubinski A, Kornacewicz-Jach Z, Wnuk-Wojnar AM, et al. The terminal portion of the T wave: a new electrocardiographic marker of risk of ventricular arrhythmia. *Pacing Clin Electrophysiol* 2000;23:1957–9.
16. Macfarlane PW, Norrie J. WOSCOPS Executive Committee: looking for prognostic information in the ST-T segment—is it really worth it? *J Electrocardiol* 2004; (Suppl 37):209–13.
17. Gomes JA, Winters SL, Stewart D, et al. A new noninvasive index to predict sustained ventricular tachycardia and sudden death in the first year after myocardial infarction based on signal-average electrocardiogram, radionuclide ejection fraction and Holter monitoring. *J Am Coll Cardiol* 1987;10:349–57.
18. Breithardt G, Cain ME, el-Sherif N, et al. Standards for analysis of ventricular late potentials using high resolution electrocardiography: a statement of a Task Force Committee between European Society of Cardiology, the American Heart Association and the American College of Cardiology. *Circulation* 1991;83:1481–8.
19. Perkiomaki JS, Koistinen MJ, Yli-Mayry SM, et al. Dispersion of QT interval in patients with and without susceptibility to ventricular tachyarrhythmias after previous myocardial infarction. *J Am Coll Cardiol* 1995; 26:174–9.
20. Bazett H. An analysis of time-relations of electrocardiograms. *Heart* 1920;7:353–70.
21. Yamaguchi M, Shimizu M, Ino H, et al. T wave peak-to-end interval and QT dispersion in acquired long QT syndrome: a new index for arrhythmogenicity. *Clin Sci (London)* 2003;105:671–6.
22. Lee KT, Lai WT, Chu CS, et al. Circadian variation of QT dispersion determined by twelve-lead Holter electrocardiography. *Cardiology* 2003;100:101–2.
23. Molnar J, Zhang F, Weiss J, et al. Diurnal pattern of QTc interval: how long is prolonged? Possible relation to circadian triggers of cardiovascular events. *J Am Coll Cardiol* 1996;27:76–83.
24. Muller JE, Ludmer PL, Willich SN, et al. Circadian variation in the frequency of sudden cardiac death. *Circulation* 1987;75:131–8.

服用降血脂藥物 Atorvastatin 對於高血膽固醇患者心室晚期電位與再極化期離散性之影響

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越來越多文獻報導指出降血脂藥物 statins 的使用對於有結構性心臟病患者具有降低心律不整以及減少猝死發生的好處。本研究欲利用臨床上評估心律不整風險之心電圖參數，包括心室晚期電位、QT 離散性與穿臟層離散性等，來探討 statins 對於沒有結構性心臟病之高膽固醇血症患者，是否也能呈現直接抗心律不整之好處。總共有 82 位高膽固醇病患 (45 位女性，平均年齡 62 ± 10 歲) 納入本研究並接受為期三個月的降血脂治療 (atorvastatin 10 毫克 / 天)。接受藥物前後分別記錄並分析比較其訊息平均心電圖 (SAECG) 參數、心電圖上 QT 離散性以及再極化期穿臟層離散性參數 (Tpe 值與百分比)。其中有 12 位病患於 atorvastatin 投藥前後更分別記錄其 24 小時行動式心電圖資料。研究結果顯示在 atorvastatin 治療三個月後，雖然病患血中總膽固醇與低密度脂蛋白膽固醇濃度皆有顯著降低 (p 值 < 0.001)，然而 SAECG 的參數以及心室晚期電位的改變並沒有顯著影響。此外，心電圖上再極化離散性參數如 QT 離散性與穿臟層離散性 (Tpe 值與百分比) 也沒有顯著性差異。然而，24 小時心電圖分析可以顯示出 atorvastatin 治療對於 24 小時 QT 離散性的日夜差異有減緩的效應。本研究結論為，在相對低心血管風險的高膽固醇患者，利用非侵襲性心電圖心律不整風險參數分析病患服用 atorvastatin (10 毫克 / 天) 治療三個月前後，並無法反映出 statins 有直接抗心律不整之效果。

關鍵詞：降血脂藥物 atorvastatin，心電圖，晚期電位，QT 離散性，穿臟層離散性
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