Effect of Atenolol on Symptomatic Ventricular Arrhythmia Without Structural Heart Disease

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Abstract

Ventricular arrhythmia (VA) from right ventricular outflow tract (RVOT) is a common problem. Symptomatic patients are usually treated with beta-blockers. There is little data on the systematic evaluation of the drug efficacy. The objectives of this study were 1) To determine proportion of exercise induced ventricular arrhythmia among patients with symptomatic ventricular arrhythmia and 2) to determine the response to beta blockers and the correlation between the response to betablockers and exercise induced VA.

We prospectively studied 46 consecutive patients with symptomatic ventricular arrhythmia. Patients recorded their symptom scores underwent exercise testing and 24-hour ambulatory monitoring before treatment and 1 month after atenolol. Exercise induced ventricular arrhythmia was demonstrated in 28 per cent of patients with symptomatic ventricular arrhythmia. Atenolol improves symptoms, decreases PVC count from ambulatory monitoring, increases exercise duration and suppresses malignant form of VA during exercise. These effects are at a similar extent in both groups of patients: those with and without exercise induced VA. However, the effect on ventricular arrhythmia suppression during exercise of atenolol was seen only in patients with increased PVC during exercise.

In conclusion, atenolol is a good option in treating patients with symptomatic VA from RVOT regardless of the pattern of PVC response to exercise. Atenolol can suppress PVC during exercise testing better in patients with exercise induced VA compared to those without.

Key word : Atenolol, Ventricular arrhythmia

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Ventricular arrhythmia (VA) is a common problem in clinical practice[1]. It could be asymptomatic or symptomatic. The prevalence has been reported to be 0.7-1.6 per cent from routine ECG in the Thai population[2]. The most common symptom is palpitation but some patients may have presyncope or syncope[3]. Ventricular arrhythmia from right ventricular outflow tract (RVOT) is a common form of VA. Most patients have no structural heart disease and excellent prognosis[1,3,4]. Mechanisms of arrhythmia may be automaticity or triggered activity. Some patients had a worsening of symptoms during physical exertion. It is believed that increased sympathetic tone might play a major role in the aggravation of this form of VA. Therefore a beta blocker is frequently used to treat symptomatic cases. Because of its benign nature, physicians prefer it and choose not to use other antiarrhythmic agents.

There have been only a few reports on the efficacy of beta blockers in treating this group of patients[5,6].

The objectives of this study were to determine 1) the prevalence of exercise induced VA 2) the response to beta-blockers and 3) whether exercise induced VA predicts response to beta blockers in patients with symptomatic VA from RVOT.

MATERIAL AND METHOD

Study population

This study was approved by the ethical committee for Human rights research. We studied patients with VA that had LBBB and inferior axis morphology. All patients are highly symptomatic and VA disturbs their normal daily activities. Structural heart disease was excluded by history, physical exam and Doppler echocardiography. Exclusion criteria were 1) asthma 2) congestive heart failure 3) heart block 4) lactating or pregnant woman 5) active hyperthyroidism 6) taking cardiac stimulant medication 7) allergic to beta-blocker 8) in need of antiarrhythmic medication 9) refusal to participate in this study.

All patients underwent exercise testing, 24-hour ambulatory ECG monitoring (AECG). Symptoms were recorded in both frequency of symptom and duration of each episode. To be qualified, patients needed to have PVC of LBBB and inferior axis more than 100 beats per hour from AECG and the correlation between symptom and VA needed to be documented.

After data collection all patients were given atenolol. Atenolol 50 mg per day was administered if the average heart rate from AECG was less than 70 bpm, and 100 mg per day was used if the heart rate is above 70 bpm. Symptom recording, AECG and exercise testing were performed again 1 month after medication. A pill count was used to assess compliance to medication.

Ambulatory ECG monitoring

A three-channel ECG recording was performed in each patient for a 24-hour period during normal daily outpatient activities at a screening visit, 1 month after medication, and 1 month after RFCA. A Zymed digital recorder was used to obtain the ECG data. Electrodes were attached at 5 different positions for the standard EASI lead system. This will enable us to acquire 12-lead ECG data comparable to standard ECG[7,8]. Patients were encouraged to continue their normal daily activities during the period of monitoring. All patients kept a detailed diary recording the time of each episode of symptoms. Patients were instructed to activate the event button when palpitation, presyncope were experienced so that the ECG playback would automatically display the ECG at that time. Tapes were analyzed with Zymed system. All ventricular arrhythmia were manually edited to make sure that the ventricular arrhythmia were correctly identified and the morphology was confirmed. A count of ventricular arrhythmia was automatically done for the whole 24-hour.

Exercise testing

Exercise testing was performed on the treadmill using modified Bruce protocol in the fasting state. This protocol resulted in a very gradual increase in workload which enabled a more accurate evaluation of changes in the frequency of VA than a more abruptly increasing workload protocol. A 12-lead ECG was recorded in supine, sitting and standing position, at the end of each stage until at least 6 minute into recovery phase. Leads 2, V1, V5 were continuously monitored. Exercise was continued until limiting symptom such as fatigue, chest pain, near syncope, abnormal blood pressure response, ST depression 3 mm or more, or nonsustained VT occurred. Blood pressure was measured by cuff manometric technique prior to exercise, every 2 minutes during exercise, and after exercise until baseline blood pressure was reestablished.

Patients were instructed to inform the investigator immediately of the onset and resolution of symptoms. Number and type of VA was recorded for 3-minute intervals at resting state before exercise, during each 3-minute stage of exercise until 6 minutes into recovery. Malignant VA is defined as the presence of ventricular couplets, triplets or ventricular tachycardia.

Statistical analysis

Continuous variables were described as mean ± SE and categorical variables were described as frequencies and percentages. Patients were classified into 2 groups depending on whether they had VA increased (group 1) or not increased (group 2) by exercise. A comparison of continuous variables were made by the unpaired *t*-test and comparison of categorical variables were made by chi-square test. Data before and at 1 month of atenolol were compared by the use of repeated measure ANOVA with the exercise grouping effect. In all tests, the criterion for statistical significance was two-sided $p \leq 0.05$. For analysis purposes for evaluating severity of symptoms we used total duration of symptom in one month calculating from the product of frequency of attack and average duration of each episode. Data from exercise testing at rest and during the last complete stage of exercise were used for analysis.

RESULTS

There were a total of 46 patients. Six patients (13%) were male. Mean age was 43.4±1.6 years. All patients had no evidence of structural heart disease from echocardiography. Presenting symptoms were palpitation (100%), presyncope (8.7%), and syncope (6.5%). Symptoms were aggravated by exertion in 35 per cent of patients and emotional stress in 17 per cent of patients. Patients had symptom for an average of 28.8±6.1 months before referring to us. Total duration of symptoms was 1819±630 minutes per month.

Exercise testing showed exercise induced ventricular arrhythmia in 13 patients (28%). Exercise induced ventricular arrhythmia was defined as an increase in PVC count or appearance of more malignant forms of ventricular arrhythmia during exercise. There were no significant differences between exercise parameters between group 1 and 2 except for the PVC count and the presence of malignant VA during exercise (Table 1). Malignant VA was present at rest in 13 per cent of patients

Table 1. Comparison of baseline characteristics between patients in group 1 and group 2.

	Group 1 (VA increased by exercise)	Group 2 (VA not increased by exercise)	P value
Number of patients	13	33	
% male*	30.8	6.1	0.02
Age (y)	46.0±3.6	42.4±1.7	0.31
Symptom			
Palpitation (%)	100	100	1
Presyncope or syncope (%)	15.4	15.2	0.98
Onset of symptom (month)	33.4±11.4	27.0±7.3	0.64
Symptom duration in 1 month (min)	763±349	2235±861	0.30
Exercise testing			
Resting HR (bpm)	80.5±4.0	77.8±1.8	0.54
Resting SBP (mmHg)	122.9±4.6	125.2±3.7	0.72
Resting PVC count (in 3 min)	48.1±11.0	49.5 ±9.1	0.93
Presence of MVA at rest (%)	15.4	12.1	0.77
Peak HR (bpm)	135.2±6.6	141.0±4.4	0.48
Peak SBP (mmHg)	171.2±10.1	180.8±7.5	0.48
Peak PVC count (in 3 min)*	59.2±13.8	11.2±5.1	<0.01
Presence of MVA at exercise (%)*	53.8	6.1	<0.01
Exercise duration (sec)	669.7±70.7	686.2±43.2	0.84
Holter monitoring			
Average HR (bpm)	77.1±1.3	76.5±1.7	0.80
PVC count (24 hours)	20512±2758	19067±2142	0.71
Presence of MVA (%)	76.9	72.7	0.77

* significant p-value

Table 2. Effects of atenolol on symptom, exercise testing and ambulatory monitoring data.

	Before Atenolol	After Atenolol	P value
Symptom duration in 1 month (min)*	1819±630	390±199	0.03
Exercise testing			
Resting HR (bpm)*	78.8±2.3	67.1±2.3	<0.01
Resting SBP (mmHg)	124.3±2.9	118.2±3.8	0.08
Resting PVC count (in 3 min)	40.2±8.5	26.3±6.0	0.09
Presence of MVA at rest (%)	13	4.3	0.22
Peak HR (bpm)*	145.0±4.3	119.8±4.6	<0.01
Peak SBP (mmHg)	172.3±7.1	162.8±7.6	0.30
Peak PVC count (in 3 min)	10.0±3.7	6.0±2.6	0.24
Presence of MVA at exercise (%)*	19.6	2.2	<0.01
Exercise duration (sec)*	703.9±49.0	829.3±37.2	0.03
Holter monitoring			
Average HR (bpm)*	76.9±1.1	65.5±1.1	<0.01
PVC count (24 hours)*	19475±1710	12919±1716	<0.01
Presence of MVA (%)	73.9	63	0.18

* significant p-value

and during exercise in 20 per cent of patients. Group 1 had a higher male proportion than group 2.

AECG showed an average PVC count of 19475±1710 per 24 hour: 74 per cent had ventricular couplet, 41 per cent had ventricular triplet and 20 per cent had ventricular tachycardia. Average heart rate from AECG was 76.9±1.0 bpm. There were no significant differences between group 1 and 2 in all ambulatory monitoring parameters.

Effect of atenolol (Table 2)

Atenolol significantly decreased total duration of symptoms. Atenolol significantly decreased the occurrence of the malignant form of VA during exercise and increased exercise duration. On ambulatory monitoring, atenolol significantly decreased the average heart rate, average PVC count but had no influence on the occurrence of malignant VA.

Differences in response to atenolol between group 1 and 2

There were no significant differences between group 1 and 2 in the response to atenolol in term of improvement in symptom, ambulatory monitoring and changes in heart rate or blood pressure during exercise testing. However, there was a significant interaction ($p = 0.007$) between group factor and changes in PVC count during exercise. After atenolol, PVC decreased markedly during exercise in patients in group 1 (25.3±11.0 to 4.2± 2.1) but PVC count didn't change in group 2 (5.1± 2.9 to 6.6±3.4).

DISCUSSION

In our study among patients with symptomatic ventricular arrhythmia from right ventricular outflow tract without structural heart disease, exercise induced VA is demonstrated in 28 per cent of patients. Atenolol improves symptoms, decreases PVC count from ambulatory monitoring, increases exercise duration and suppresses malignant form of VA during exercise.

The prevalence of exercise induced VA is approximately 2 per cent in healthy men[9]. Some reported that this phenomenon is more common in patients with structural heart disease[9]. A beta-blocker is frequently used to treat VA both in patients with organic heart disease and in those without. Exercise induced VA has been shown to be a prognostic indicator in patients with VA[10].

Mechanisms of VA from RVOT are mainly abnormal automaticity or triggered activity. The VA usually occurred in the absence of structural heart disease as in our study. In about one-fourth of patients in our study, VA increased during exercise. This has been thought to be sympathetic dependent. A beta blocker is usually recommended in symptomatic patients because of its safety profile compared to other antiarrhythmic agents. However a significant response to beta blocker has been reported to be approximately 50 per cent[5,6]. Sometime other drugs are needed. RFCA may be used as a final option in selected patients who are extremely symptomatic and do not respond to medication[11-13].

Patients with exercise induced VA had the same level of severity in terms of symptoms and PVC count from ambulatory monitoring. The only difference is gender distribution which is more in the male proportion in patients with exercise induced VA.

The authors demonstrated that atenolol improves symptoms, decreases PVC count from ambulatory monitoring. The benefit was shown not only in patients with exercise induced VA but also in those without. Atenolol almost completely suppresses malignant VA during exercise and improve exercise duration. PVC count during exercise markedly decreases after atenolol only in patients with exercise induced VA but not in those without.

The authors concluded from our study that atenolol is a good option in treating patients with symptomatic VA from RVOT regardless of the pattern of PVC response to exercise. Atenolol can suppress PVC during exercise testing more efficiently in patients with exercise induced VA.

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ผลของ atenolol ในการรักษา ventricular arrhythmia ในผู้ป่วยที่ไม่มี structural heart disease

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การวิจัยนี้เป็นการประเมินผลการรักษาด้วยยา atenolol ในผู้ป่วยที่มีหัวใจเต้นผิดปกติ ventricular arrhythmia (VA) ที่เกิดจากตำแหน่ง right ventricular outflow tract (RVOT) ซึ่งเป็นชนิดที่พบบ่อย ในผู้ป่วยที่ไม่มีที่ structural heart disease เป็นการศึกษา prospective ศึกษาความแตกต่างระหว่างกลุ่มที่หัวใจเต้นผิดจังหวะเพิ่มขึ้น และไม่เพิ่มขึ้น ระหว่างการออกกำลังกายบนสะพาน มีผู้ป่วยทั้งหมด 46 คน inclusion criteria คือผู้ป่วยต้องมีอาการจากหัวใจเต้นผิดจังหวะและต้องมี PVC เฉลี่ยอย่างน้อย 100 ตัวต่อชั่วโมงจาก ambulatory ECG monitoring (AECG) ผู้ป่วยทุกคนจะได้รับการตรวจ exercise test, AECG และได้รับการบันทึกความรุนแรงของอาการเป็นความบ่อยและระยะเวลาของอาการ ก่อนการให้ยาและ 1เดือนหลังได้รับยา atenolol 50–100 มก. ต่อวัน (ขึ้นกับอัตราการเต้นหัวใจของผู้ป่วย) ผลการศึกษาพบว่า 28% ของผู้ป่วยกลุ่มนี้มี VA เพิ่มขึ้นขณะออกกำลังกาย atenolol ช่วยทำให้อาการดีขึ้นช่วยลดจำนวน PVC จาก AECG ช่วยเพิ่ม exercise duration ได้ทั้งในผู้ป่วยทั้ง 2 กลุ่ม (กลุ่มที่ VA เพิ่ม และไม่เพิ่มขึ้นขณะออกกำลัง) ผลในการลดจำนวน PVC ระหว่าง exercise เห็นชัดเจนในกลุ่มที่ PVC เพิ่มขึ้นขณะ exercise

โดยสรุป atenolol ให้ผลดีในการรักษาผู้ป่วย VA จาก RVOT ทั้งในผู้ป่วยที่มี PVC เพิ่มขึ้น และไม่เพิ่มขึ้นขณะ exercise

คำสำคัญ : ยากั้นเบต้า, หัวใจห้องล่างเต้นผิดจังหวะ

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