

Electrophysiological effects of diltiazem in chronic bifascicular block

Ajaz A Lone¹, Khalid Mohiud Din² and Syed Manzoor Ali^{2,*}

¹Department of Cardiology, Sher-I-Kashmir Institute of Medical Sciences (SKIMS), Soura, Bemina, Srinagar, Jammu and Kashmir 190011, India

²Department of Cardiology, Govt Medical College Srinagar (GMC), Karan Nagar, Srinagar, Jammu and Kashmir 190010, India

Abstract

Background: Literature on diltiazem in intraventricular conduction defects is meagre. We studied effects and safety of diltiazem in chronic bifascicular block using His-bundle electrocardiography and pacing.

Methods: 23 patients with chronic bifascicular block were enrolled, all were in normal sinus rhythm. A baseline EP study, including, sinus cycle length (SCL), intra-atrial conduction time (PA), AV nodal conduction time (AH), intraventricular conduction time (HV), corrected sinus node recovery time (cSNRT), sinoatrial conduction time (SACT) and AV node wenchebach time, were assessed at baseline and repeated after diltiazem 0.25mg/kg followed by 0.0012mg/kg/min for 20 minutes.

Results: Patients with normal sinus node function (N=21), showed significant prolongation of SCL (+18%, P=.001), cSNRT (+63% P=.002), SACT (+18%, P=.001), AH (sinus), AH (paced), and wenchebach point. Patient with sinus node disease (N=2) had greater prolongation of SCL (+52%), cSNRT (695 to 4260msec) and SACT (+140%). Both patients developed left atrial rhythm. HV interval, spontaneous (59 + 11msec to 60 + 12msec P=NS) and paced (59msec + 12 to 60 + 12msec P=NS), QRS and QTc intervals did not change significantly.

Conclusion: Diltiazem causes greater depression of SA and AV node in patients with sinus node dysfunction. Diltiazem did not affect the intraventricular conduction even in patients with prolonged baseline HV interval.

Keywords: diltiazem; chronic bifascicular block; sinusnode; Hispurkinje function

***Corresponding author:** Dr. Syed Manzoor Ali, Assistant professor Department of Cardiology, Govt Medical College Srinagar (GMC), Karan Nagar, Srinagar, Jammu and Kashmir 190010, India. Mobile:+91 9419006441; Email: syedmanzooral@gmail.com

Received 07 July 2017; Revised 04 September 2017; Accepted 14 September 2017; Published 22 September 2017

Citation: Lone AA, Din KM, Ali SM. Electrophysiological effects of diltiazem in chronic bifascicular block. J Med Sci Res. 2017; 5(4):121-127. DOI: <http://dx.doi.org/10.17727/JMSR.2017/5-23>

Copyright: © 2017 Lone AA, et al. Published by KIMS Foundation and Research Center. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Introduction

The cardiac action potential is composed of both fast and slow components. A fast initial inward sodium current and a slow second inward current which are carried by sodium and calcium ions. Diltiazem is a benzothiazepine calcium antagonist, that has been in use for several years for various cardiovascular diseases like coronary artery disease, coronary artery spasm, systemic hypertension, supraventricular tachyarrhythmias, primary pulmonary hypertension and hypertrophic cardiomyopathy. Diltiazem acts by inhibiting the influx of calcium (Ca^{++}) ions through the slow channels in cardiac and smooth muscle membranes by non-competitive blockade of voltage sensitive L-type calcium channels. The predominant effects of calcium antagonists result from blocking the entry of calcium ions and slowing the recovery of channels [1].

Diltiazem does not cause measurable changes in conduction or refractoriness of normal fast channel cardiac tissues in humans. However slow channels do contribute to action potential of fast channel cardiac tissue and some investigators postulate that slow channels may be the predominant transmembrane flux in certain diseased states that inactivates the fast channels. Diltiazem is relatively free of side effects and is well-tolerated when given orally or intravenously.

Bundle branch block (BBB) implies a severe degree of bundle branch disease resulting in complete interruption of conduction. Prevalence of BBB in general population is around one percent. Patients with chronic BBB have increased risk of progression to complete heartblock and the reported incidence varies from 2%-6% per year [6-10]. The incidence of heart block in asymptomatic patient population studied is close to 2%, while that in patients with neurological symptoms such as syncope, it is closer to 6% per year. Many of the studies reported high mortality associated with intraventricular conduction defects. However, this primarily reflected the underlying heart disease rather than bradyarrhythmias as a cause for high mortality.

Invasive electrophysiological testing by using ventricular extrastimuli to induce ventricular tachycardia (monomorphic sustained VT) have shown positive results in upto 30% to 50% of patients during evaluating for unexplained syncope [11, 12].

Although diagnostic yield for inducing VT is high in patients with organic heart disease, in patients with structurally normal heart it is very low, 1% to 3% as compared to bradyarrhythmia response of 14% to 19% [20].

Electrophysiological studies have shown that in therapeutic plasma concentrations, diltiazem prolongs sinus cycle length, lengthens AV nodal conduction time, prolongs AV nodal functional and effective refractory periods and lengthens AV nodal Wenckebach cycle length. Diltiazem does not affect his-purkinje system or ventricular automaticity [13, 14].

The present study was conducted to investigate the electrophysiological effects and safety of diltiazem in patients with pre-existing chronic bifascicular block, with the following objectives: 1. To investigate the safety of diltiazem in patients with pre-existing chronic bifascicular block. 2. To study the effects of diltiazem on sinus node functions in such patients. 3. To study the effects of diltiazem on AV nodal functions in such patients. 4. To determine any detrimental electrophysiological effects on intraventricular conduction induced by diltiazem in such patients.

Material and methods

This was a single centre study performed on patients undergoing electrophysiological studies in a tertiary care centre. A total of 23 patients aged more than 20 years were included. Total duration of the study was 2 years.

Inclusion criteria: 1. ECG documented bifascicular block, 2. Echo documented normal LV systolic functions at the time of study, 3. Giving consent for the study.

Exclusion criteria: 1. Age less than 20 years, 2. History of acute coronary syndrome (less than 6 months old), 3. Pregnancy, 4. Congestive cardiac failure, 5. Patients on cardioactive drugs which could not be stopped before the evaluation, 6. Severe comorbid illnesses.

A complete history and physical examination was recorded in all patients. A standard 12 lead ECG, chest roentgenogram, transthoracic echocardiogram and routine blood tests like hemogram, liver function tests, renal function tests, blood sugar and serum

electrolytes were done in all patients. 24hour Holter (ambulatory) monitoring was done in all patients.

His-bundle electrogram was recorded using the technique of Sherlag. Right heart catheterization was performed in the supine position in a post-absorptive, non-sedated state in each patient. Under local anaesthesia (2% xylocaine), a 6F quadripolar ring electrode catheter [interelectrode distance of 2,10,2mms] was percutaneously introduced through right femoral vein by the modified Seldinger technique. This catheter was fluoroscopically positioned across the tricuspid valve. Another bipolar catheter was parked in high right atrium for pacing. Four surface electrocardiographic leads (I, II, III,V1) were used for rhythm monitoring on multichannel oscilloscopic screen.

The His electrode catheter was slowly withdrawn across the tricuspid valve until a biphasic or triphasic deflection appeared between the atrial and ventricular electrogram, within the PR segment of the surface electrocardiogram. A complete set of electrophysiological measurements including sinus cycle length (SCL), intra-atrial conduction time (PA), AV nodal conduction time (AH), intraventricular conduction time (HV), QRS and QT intervals were obtained. Atrioventricular conduction time [PR] was calculated by adding PA, AH and HV intervals. Corrected QT (QTc) were calculated using Bazett's formula.

A second set of interval measurements was obtained 10 minutes after the first. Right atrium was then paced at the cycle lengths of 750,660,600,500,460,430 and 400 msec. Pacing was started at a cycle length of around 20% less than basic cycle length followed by abrupt termination. Each pacing train was continued for 30 seconds. Continuous recording was done during the last 5 seconds of pacing till the return of the sinus activity at each pacing run. Maximum sinus node recovery time [SNRT], irrespective of the cycle length at which it occurred was recorded and corrected sinus node recovery time [cSNRT] calculated. One minute interval was allowed to elapse between each pacing run. Sino atrial conduction time [SACT] was determined by Narulla method.

After completing the pre-diltiazem protocol, a second set of interval measurements and blood pressures

were recorded. Diltiazem was then administered intravenously, through a pre-placed plastic cannula in the antecubital vein, as a bolus dose of 0.25mg/kg./min over 2 minutes. This was followed by continuous diltiazem infusion at 0.0012mg/kg/min dissolved in 50ml of 5% dextrose in water. Electrocardiogram was continuously monitored on the oscilloscopic screen. Interval recordings and BP measurements were obtained at 5, 10, 15 and 20 minutes. A complete electrophysiological measurements were obtained before diltiazem and were repeated at intervals between 20 and 30 minutes post diltiazem, during which diltiazem infusion was continued. Atrial pacing protocol was kept same before and after the diltiazem. The patients were observed and asked to report any symptoms during the procedure. Any complaint reported by patients were recorded.

A total of 23 patients with bifascicular block attending the cardiac clinic were evaluated for assessment of electrophysiological effects of diltiazem. The study group consisted of 16 (72%) males and 7 (28%) females with a mean age of 65+9 (range 46-82 years)

All twenty three (100%) patients were symptomatic and had one or more episodes of syncope and/or pre-syncope. The number of these episodes ranged from 1 to 12 and the duration of symptoms ranged from 7 days to 8 years at the time of electrophysiological evaluation. All symptomatic patients were taken for electrophysiological evaluation after basic cardiac and neurological evaluation failed to explain these symptoms. All patients were in, normal sinus rhythm, at the time of electro physiological study.

Two patients had clinical diagnosis of sick sinus syndrome. One had intermittent sinus bradycardia observed on ECG monitor and the other patient had sinus pauses with junctional escape rhythm recorded on ECG.

X-ray chest revealed cardiomegaly (Cardio Thoracic Ratio >50%) in 10 patients and echocardiography revealed normal LV functions in all patients with (mean ejection fraction 65%), concentric Left Ventricular Hypertrophy in 5 patients. No patient had echo evidence of any valvular heart disease, wall motion abnormality or pulmonary artery hypertension.

At the time of study, all cardioactive drugs had been discontinued for a time interval exceeding fivehalf lives. Prior to study, no patient was on digoxin. Two patients were taking beta blockers , one for hypertension and the other for myocardial infarction. Both patients had stopped the drug in view of syncope. Five patients were on amlodipine.

Two patients had been taking phenytion prior to electrophysiological study for suspected seizures. It was stopped in both patients by a neurologist, one month before EP study, after a negative neurological workup. All antihypertensive agents excluding beta- blockers and calcium channel blockers were continued like ACE inhibitors, angiotensin receptor blockers and diuretics. In two patients,one taking terazosin for benign prostatic hyperplasia and other hydrochlorthiazide for hypertension, drugs were stopped due to postural hypotension. The 24hr holter monitoring done in all 23 patients did not reveal any high grade AV block, however, features of sick sinus syndrome were present in holter recording in two patients.

Results

During 10 minutes control period there was no change in conduction intervals or blood pressure with the exception of slight increase in spontaneous sinus length from 682+137 m sec to 703+ 124 (+3%, P=.194).

In patients with normal sinus node function, diltiazem prolonged sinus cycle length from 705+130 msec to 831+161 m sec (+18%, p=.001) (Table 1). There was a significantly greater prolongation of sinus cycle length in patient with sick sinus syndrome [720 to 1100 msec (+ 52%)] (Table 2), than in patients with normal sinus node function.

Table 1: Demonstrating effect of IV diltiazem on sinus node functions in patients with normal sinus node.

	Pre-diltiazem	Post-diltiazem	Increase %	P value
Sinus node cycle length	705+130 msec	831+161 msec	+18%	0.001
CSNRT	271+/-89	443+/-227msec	+63%	0.002
SACT	83+21	98+24	+18%	0.001

Table 2: Demonstrating effect of IV diltiazem on sinus node and AV node functions in patients with sick sinus syndrome.

	Pre-diltiazem	Post-diltiazem	Increase %
Sinus node cycle length	720 msec	1100msec	+52%
CSNRT	695 msec	4260 msec	
SACT	70 msec	170 msec	+140%
AV nodal Wenckebach cycle length	346+ 51 msec	397+77 msec	

Corrected sinus node recovery time (cSNRT), was normal in all patients without sick sinus syndrome prior to diltiazem (CSNRT< 550 msec). There was significant change in cSNRT after diltiazem (271 ± 89 vs. 443±227, + 63% p=.002) in these patients (Table 1).

Two patients with sick sinus syndrome had prolonged cSNRT prior to diltiazem and cSNRT got strikingly prolonged after diltiazem (695 to 4260 msec). In patients with normal sinus node function sinoatrial conduction time (SACT) was significantly increased after diltiazem (83+ 21 to 98+ 24, 18% p=.001) (Table 1). Two patients with sick sinus syndrome showed greater prolongation of sinoatrial conduction time after diltiazem (70 to 170 msec, +140%). The AV nodal wenckebach cycle length increased from 346+51 to 397+77 (p=.001) after diltiazem (Table 2). In these 2 patients with sick sinus syndrome, during sinus rhythm AH intervals increased from 85 to 100 msec (+ 18%), and during constant atrial pacing from 130 to 155 msec (+19%) (Table 3).

Table 3: Demonstrating effect of IV diltiazem on AH interval.

	Pre-diltiazem	Post-diltiazem	Increase
AH interval (Baseline)	85 msec	100 msec	+18%
AH interval (Postpacing)	130 msec	155 msec	+19%

Effect of diltiazem on intra atrial conduction

During sinus rhythm, PA interval increased from 41+ 10 m sec to 47+ 9 m sec (+15%, p=.003), and during constant atrial pacing, it increased from 59+14 m sec to 68+13 m sec (+15%, p=.004) in patients without sinus node disease.

Effect of diltiazem on His purkinje and ventricular tissue functions

Prior to diltiazem HV interval was normal in 8 patients and prolonged (HV > 55 msec), in 15 patients. Fourteen patients had mild prolongation of HV interval (HV 56 to 75 msec) and 2 patients had moderate prolongation (HV 76 to 100 msec).

The HV interval did not change significantly after diltiazem during spontaneous rhythm (59+ 11to -60 +12msecs, p= 1) in patients with normal sinus node functions or sick sinus syndrome. During constant atrial pacing also there was no significant change in HV interval (59 + 12 to 60 + 12msec, p= 0.554) (Table 4). There was no significant change in QRS duration (p=0.65) or corrected QT interval (QTc) after diltiazem (p= 0.75).

Table 4: Demonstrating effect of IV diltiazem on HV Interval.

	<i>Pre-diltiazem</i>	<i>Post-diltiazem</i>	<i>P value</i>
HV interval pre-pacing	59+11 msec	61+12 msec	P=1
HV interval post-pacing	59+12 msec	60+12 msec	P=0.554

Effect on blood pressure

There was significant reduction in blood pressure after diltiazem, the systolic blood pressure lowered by 14% and the diastolic blood pressure by 11% (p<.001).

Discussion

Electrophysiological effects of diltiazem have been studied in normal subjects, patients with sick sinus syndrome, and first degree AV nodal block [4-10, 15]. Electrophysiological studies reveal that about 50% of patients with right BBB and left anterior hemiblock, and 75% of patients with left BBB have prolonged intraventricular conduction time (HV interval) [16-18]. However, risk of progression to complete heart block is low in such patients even if symptomatic [19-21].

These results are expected of slow channel blockers on slow channel dependant sinus node. Although no change or a slight decrease in heart rate has been reported after diltiazem [6-10]. Bourassa et al. [9] noticed a tendency of heartrate to fall further after the end of their 15 minutes study period. Mitchell et al. [15] also reported a significant

decrease in heart rate after 10 minutes of diltiazem administration, with peak reduction at 17 minutes. We studied effects between 20-30 minutes after diltiazem administration. We have observed greater depressant effect on sinus node to an extent of 18% increase in SCL in comparison to 7% increase reported by Mitchell et al. [15] in response to similar doses of diltiazem after identical intervals. Possible explanation for this greater effect on sinus node may be the higher mean age of our patients than that in their study. Besides, pre-existing bifascicular block in our patients might have represented a part of diffuse conduction disease with subclinical sinus node involvement, precipitated after diltiazem administration. Amongst 10 patients of Oyama et al. [22] administered with diltiazem, one of the twopatients having complete LBBB showed a slight decrease in sinus cycle length while as, there was an 14% increase in the other. However, only 10 mg of diltiazem was used and the results were studied immediately after diltiazem. In the present study, higher doses were administered and the effects were recorded at least after 20 minutes.

The greater depression of sinus node was also reflected during pacing induced suppression of sinus node in our patients. There was marked prolongation of corrected sinus node recovery time. These results sharply contradict with the findings of previous investigators [6, 8, 10, 15] who observed no significant change in cSNRT even after similar doses of diltiazem.

In 2 patients with sick sinus syndrome, we observed a greater increase of 53% in SCL as compared to only 24% increase observed by Sugimoto et al., [12] in 6 such patients. Both of our patients developed prolonged sinus pauses after overdrive suppression which has been observed by Sugimoto et al. [8] in only 2 of the 6 sick sinus syndrome patients.

During sinus rhythm, AV nodal conduction time (AH interval) was significantly prolonged by 20 % in our patients. This is comparable to the 21% reported by Kawai et al. [10] but is higher than that (12 to 16%) was reported by other investigators [6, 8, 15].

During constant atrial pacing, we have observed prolongation of AH interval by 38% in comparison to 13-24% noticed by various investigators [6, 8, 10, 15]. This suggests that diltiazem possibly

causes greater depression of AV nodal conduction in patients with bifascicular block.

In 2 patients with sick sinus syndrome, we observed 18% and 19% increase in AH interval during sinus rhythm and constant atrial pacing, respectively. In contrast, Sugimoto et al. observed 7% and 11% increase in 6 such patients, respectively. There was also an increase of 29% in Wenckebach cycle length in our patients in contrast to only 10% increase reported by Sugimoto et al. [8] in such patients. As we had only two such patients, we cannot infer whether diltiazem causes greater depression of AV node in sick sinus syndrome patients with associated bifascicular block. Moreover, Sugimoto et al. [8] had used smaller doses of diltiazem and assessed results earlier than that of ours.

During constant atrial pacing, we have observed prolongation of AH interval by 38% in comparison to 13-24% noticed by various investigators [6, 8, 10, 15]. This suggests that diltiazem possibly causes greater depression of AV nodal conduction in patients with bifascicular block. Pre-existing AV nodal disease may be considered as a reason for greater depression of AV node. But we did not observe any significant difference in AH interval after diltiazem among patients with normal or prolonged (>200 msec) baseline PR interval. An increase in AV nodal Wenckebach cycle length by 15% in our patients is consistent with the 10-20% increase reported by other investigators [6, 8, 10].

There was also an increase of 29% in Wenckebach cycle length in our patients contradictory to only 10% increase reported by Sugimoto et al. [8] in such patients. As we had only two such patients, we cannot infer whether diltiazem causes greater depression of AV node in sick sinus syndrome patients with associated bifascicular block. Moreover, Sugimoto et al. [8] had used smaller doses of diltiazem and assessed results earlier than that of ours.

Conclusion

From the present study, the following clinical implication can be drawn in patients with pre-existing bifascicular block: 1. Diltiazem causes greater depression of SA node in patients with normal sinus node functions. 2. In patients with sick sinus syndrome, marked prolongation of cSNRT and sinus arrest can develop after diltiazem. Hence,

diltiazem should be used cautiously in such patients. In addition, transient ectopic left atrial rhythm can be observed in such patients after diltiazem. 3. Diltiazem also causes greater degree of suppression of AV node in such patients. 4. Diltiazem significantly prolongs intraatrial conduction particularly in patients with sick sinus syndrome. 5. Diltiazem does not adversely affect the intraventricular conduction even in patients associated with prolonged baseline HV interval. 6. Diltiazem does not affect the measures of ventricular electrophysiological functions in patients with bifascicular block.

Conflicts of interest

Authors declare no conflicts of interest.

References

- [1] Cranefield PF. The conduction of the cardiac impulse. New York: Futura publishing. 1975; 135-39; 243-63.
- [2] Morad M, Tung L, Greenspan AM. Effect of diltiazem on calcium transport and development of tension in heart muscle. *Am J cardiol.* 1982; 49(3):595-601.
- [3] Colin D, Diltiazem hydrochloride: Therapeutic Drugs. Second Edn. Dollerycolin (Ed.) Churchill Livingstone. 2002; 1(A-H):D139-43.
- [4] Zipes DP, Besch HP, Watanabe AM. Role of the slow current in cardiac electrophysiology. *Circulation.* 1975; 51(5):761-766.
- [5] Antman EM, Stone PH, Muller JE, Braunwald E. Calcium channel blocking agents in the treatment of cardiovascular disorders. Part 1: Basic and clinical electrophysiological effects. *Ann Intern Med.* 1980; 93(6):875-885.
- [6] Oyama Y. Hemodynamic and electrophysiologic evaluations of diltiazem hydrochloride: a clinical study. In: Bing RJ, ed. *New Drug Therapy with a Calcium Antagonist: Diltiazem Hakone Symposium 78.* Amsterdam: Excerpta Medica, 1979:169-89.
- [7] Kinoshita M, Motomura M, Kusukawa R, Kawakita S. Comparison of hemodynamic effects between B-blocking agents and a new antianginal agent, diltiazem hydrochloride. *Jpn Circ J.* 1979; 43: 587-98.
- [8] Sugimoto T, Ishikawa T, Kaseno K, Nakase S. Electrophysiologic effects of diltiazem, a calcium antagonist, in patients with impaired sinus or atrio-ventricular node function. *Angiology.* 1980; 31(10):700-709.
- [9] Bourassa MG, Cote P, Theroux P, Tubau JF, Genain C, et al. Hemodynamics and coronary flow following diltiazem administration in anesthetized dogs and in humans. *Chest* 1980; 78(1 Suppl):224-230.
- [10] Kawai C, Konishi T, Matsuyama E, Okazaki H. Comparative effects of three calcium antagonists, diltiazem, verapamil and nifedipine on the sinoatrial and atrioventricular nodes: experimental and clinical studies. *Circulation.* 1981; 63(5):1035-1042.
- [11] Landmark K, Refsum H. Calcium, Calcium-antagonistic drugs and the heart. *Acta Pharmacol Toxicol.* 1978; 43(1 Suppl):15-32.
- [12] Wit AL, Bigger JT Jr. Possible electrophysiologic mechanisms for lethal arrhythmias accompanying myocardial ischemia and infarction. *Circulation.* 1975; 51(Suppl III):96-115.

- [13] Ellrodit G, Chew CYC, Singh BN. Therapeutic implications of slow channel blockade in cardiovascular disorders. *Circulation*. 1980; 62(4):669-679.
- [14] Ono H, Himori N, Taira N. Chronotropic effects of coronary vasodilators as assessed in the isolated, blood-perfused sino-atrial node preparation of the dog. *Tohoku J Exp Med*. 1977; 121(4):383-390.
- [15] Mitchell LB, Jutzy KR, Lewis SJ, Schroeder JS, Mason JW. Intracardiacelectrophysiologic study of intravenous diltiazem and combined diltiazem and digoxin in patients. *Am Heart J*. 1982; 103(1):57-66.
- [16] Batsford WP, Akhtar M, Damato AN, et al. Electrophysiological studies in asymptomatic patients with RBBB and LAH. *Circulation*. 1974; 50(Suppl III):214
- [17] Narula OS. Interventricular conduction defects. In: Narula OS, ed. *His bundle electrocardiography*. Philadelphia: FA Davis, 1975:178
- [18] Puech D. Atrioventricular block: the value of intracardiac recordings. In: Krikler DM, Goodwin JF, Eds. *Cardiac arrhythmias*. Philadelphia:WB Saunders, 1975:103.
- [19] Dhingra RC, Palileo E, Strasberg B, Swiryn S, Bauernfeind RA, et al. Significance of the HV interval in 517 patients with chronic bifascicular block. *Circulation*. 1981; 64(6):1265-1271.
- [20] McNulty JH, Rahimtoola SH, Murphy E, DeMots H, Ritzmann L, et al. Natural history of "high-risk" bundle-branch block. Final report of a prospective study. *N Engl J Med* 1982; 307:137-43.
- [21] Schelnman MM, Peters RW, Sauve MJ, Desai J, Abbott JA, et al. Value of the H-Q interval in patients with bundle branch block and the role of prophylactic permanent pacing. *Am J Cardiol*. 1982; 50(6): 1316-1322.
- [22] Oyama Y, Imai Y, Nakaya H, Kanda K, Satoh T. The effect of diltiazem on cardiac conduction: A clinical study of His bundle electrogram. *Jap circ journal* 1978; 42(11):1257-1264.
- [23] Razanski JJ, Zaman L, Castellanos A. Electrophysiological effects of diltiazem hydrochloride on supraventricular tachycardias. *Am J Cardiol*. 1982; 49(3):621-628.
- [24] Hoffman BF, Singer DH. Appraisal of the effects of Catecholamines on cardiac electrical activity. *Ann NY Acad Sci*. 1967; 193:914-939.