Short Term Effects of Atenolol in Patients with Dilated Cardiomyopathy

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Abstract

Dilated cardiomyopathy is a common cause of heart failure with systolic dysfunction. Medications used to treat this condition are usually for symptomatic relief. We studied the effect of atenolol in heart failure caused by dilated cardiomyopathy in a double blinded randomized fashion. There were 17 males and 5 females. All patients underwent right and left heart catheterization, coronary angiography, endomyocardial biopsy, exercise testing and doppler echocardiography. By 3 months, atenolol significantly reduced resting and exercise heart rate and pulmonary capillary wedge pressure. There was no difference in exercise capacity. We conclude from this study that atenolol improve hemodynamic condition in patients with dilated cardiomyopathy without improving exercise capacity during this short observertion period.

The use of beta-receptor antagonists in the treatment of heart failure due to systolic dysfunction is controversial. In dilated cardiomyopathy, several studies have suggested that long term treatment with beta-receptor antagonists in individual patients reduces symptoms and increases exercise capacity[1-4]. Because of its negative inotropic property, newer agents, some with ancillary properties, such as intrinsic activity and vasodilation, may have advantages[5-7]. The mechanisms by which some patients improve are still obscure. Protection against receptor down regulation, restoration of receptor density, protection against cardiotoxicity of catecholamines, and improvement in ischemic systolic and diastolic left ventricular function are all possible benefits[8-10]. The fear that beta-receptor antagonists are dangerous in heart failure is in most instances not warranted, but an initial deterioration may have to be accepted in order to gain long-term beneficial effects. Titrating

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regimen beginning with extremely low but increasing dosage of it has been shown to be reasonably well tolerated. Many beta-blockers, for example, metoprolol, bucindolol, carvedilol, were previously studied and shown to have benefit over placebo. Atenolol which is a commonly used beta-blocker, however, has never been studied.

This is a double-blind control study in patients with proven non-ischemic dilated cardiomyopathy comparing atenolol with placebo. The objectives of this study were to determine the short term benefit of atenolol in patients with documented dilated cardiomyopathy in terms of hemodynamics and exercise capacity.

METHOD

Study Population

This study was approved by the local Ethic Committee. All participants were informed and gave their consent. Twenty to sixty-five year old patients who were diagnosed as having heart failure due to systolic dysfunction with NYHA functional class II - III underwent echocardiographic examination. Those with cardiac chamber dilatation and diffuse hypokinesis from echocardiographic finding and estimated left ventricular ejection fraction less than 40 per cent underwent right and left heart catheterization, coronary angiography and endomyocardial biopsy. Those with histopathologic findings compatible with dilated cardiomyopathy were (i.e varying degrees of interstitial fibrosis and myocyte hypertrophy without evidence of myocarditis) then enrolled into study. Exclusion criteria included 1) active myocarditis 2) coronary artery disease 3) renal impairment 4) liver impairment 5) diabetes mellitus 6) alcoholic cardiomyopathy 7) asthma 8) heart block 9) history of beta-blocker hypersensitivity 10) other active diseases which are known to cause cardiomyopathy.

Study Protocol

Patients were symptomatic and were hemodynamically stable during conventional treatment before the initiation of beta-blockers. All conventional medications including diuretics, digoxin and vasodilators were continued and were kept unchanged during the period of one week before follow up exercise testing and cardiac catheterization.

Patients were then randomized to either atenolol or placebo. Placebo tablets were made. The initial dose of atenolol was 12.5 mg daily and increased to 25 mg OD and then 50 mg OD and 100 mg twice daily on a weekly basis. The goal was a heart rate of 50 - 70 bpm regardless of the knowledge of investigator on the randomization status. Temporary increase in the dose of diuretics were permitted during the introduction.

All patients underwent right and left heart catheterization, coronary angiography, endomyocardial biopsy, exercise stress test and Doppler echocardiography before randomization and 3 months after randomization. Hemodynamic parameters were derived during cardiac catheterization.

Exercise Stress Test

Exercise treadmill testing was performed in the fasting state using Naughton protocol starting at 2 mph. This protocol resulted in a gradual increase in workload which enabled a more accurate evaluation of exercise capacity. A 12 lead ECG was recorded immediately before exercise and every 2 minutes during exercise. Lead II, V_1, V_5 were continuously monitored. Exercise was continued until fatigue, abnormal blood pressure response or significant ventricular arrhythmia 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. Measurement variables included baseline and peak heart rate, baseline and peak blood pressure, exercise duration and METs achieved.

Statistical analysis

Results are expressed as mean $\pm$ standard error of mean. Comparison of per cent changes in measurement variables between 0 and 3 months of atenolol and placebo group were performed by Student's *t*-test for unpaired or paired variables wherever appropriate. Chi-square test was used for the comparison of categorical variables. Differences were considered significant at $p < 0.05$.

Sample size calculation

Calculation of sample size is based on 25 per cent difference in mean exercise duration between the 2 groups at the end of the study. Considering significant level at 0.05, power of test = 80 per cent and standard deviation of exercise duration = 90 seconds and 20 per cent drop out rate, 12 patients were needed for each group.

RESULTS

The study group comprised of 17 males and 5 females. Ages ranged from 22 to 68 years with an average age of 44 years. All patients had documented dilated cardiomyopathy from echocardiography and endomyocardial biopsy as described earlier. All patients were in NYHA functional class II and III with the median duration of symptoms of 6 months (ranged 0.5 month to10 years). Ninety per cent of patients were on angiotensin converting enzyme inhibitors, 86 per cent were on digoxin, 82 per cent were on diuretic and 68 per cent were on triple medications. There were no significant differences in baseline characteristics between the two groups (Table 1) except for older patients in the placebo group.

Table 2 shows the comparison of result from exercise testing at baseline and changes at 3 months after intervention between atenolol group and placebo. Atenolol significantly reduced resting and exercise heart rate. There was no significant difference in the change of exercise duration heart rate and blood pressure between the two groups. Hemodynamic data derived during cardiac catheterization at baseline and at 3 months' of study are shown in Table 3. Atenolol significantly reduced pulmonary capillary wedge pressure at 3 months compared to placebo. There were no differences in other hemodynamic parameters between the two groups. There were also no significant differences in echocardiographic findings between the two groups. (Table 4)

DISCUSSION

The primary result of our study is that 3 month atenolol administration in patients with documented dilated cardiomyopathy reduced pulmonary capillary wedge pressure. However, there was no significant difference in exercise capacity between the atenolol group and placebo group.

Table 1. Baseline characteristics.

	Atenolol (n=12)	Placebo (n=10)	p-value
Male : Female	7 : 5	10 : 0	
Mean age	38.5 ± 9.9	51.1 ± 11	0.01
NYHA functional class			
- Class II	7	4	0.45
- Class III	5	6	
Medication			
- digitalis	10	9	0.99
- ACE - inhibitor	12	8	0.37
- diuretic	9	9	0.72
- all 3 medications	9	6	0.77

NYHA = New York Heart Association , ACE = angiotensin converting enzyme

Table 2. Comparison of exercise parameters.

		Baseline			% Changes at 3 months		
		Atenolol	Placebo	p-value	Atenolol	Placebo	p-value
Resting	HR (bpm)	85.3 ± 6.2	83.1 ± 6.1	0.81	-9.7 ± 4.8	-0.2 ± 10.2	0.37
	SBP (mmHg)	122.8 ± 4.6	136.2 ± 8.9	0.17	1.6 ± 5.2	-5.3 ± 6.8	0.42
	DP	10398.1 ± 2620.2	11484.3 ± 390.13	0.45	-9.2 ± 5.1	-2.5 ± 14.2	0.67
Peak	HR (bpm)	158.9 ± 9.6	144.5 ± 10.2	0.32	-9.2 ± 5.3	-1.8 ± 6.5	0.39
	SBP (mmHg	185.3 ± 12.0	161.5 ± 13.3	0.20	11.1 ± 10.5	21.0 ± 17.0	0.61
	DP	29274.6 ± 7693.1	23201.3 ± 7496.3	0.08	-0.1 ± 11.6	14.4 ± 12.0	0.40
Exercise duration (sec)		929.5 ± 98.5	776.3± 127.0	0.34	19.5 ± 11.4	22.5 ± 12.3	0.86
METS		8.8 ± 1.0	6.7 ± 1.1	0.19	25.5 ± 17.6	13.4 ± 10.0	0.59

HR = heart rate, SBP = systolic blood pressure, DP = double product

Table 3. Comparison of hemodynamic data from cardiac catheterization.

	Baseline			% Changes at 3 months		
	Atenolol	Placebo	p-value	Atenolol	Placebo	p-value
CO (T)	4.2 ± 0.4	3.5 ± 0.4	0.20	10.8 ± 13.7	8.6 ± 10.6	0.90
CI (T)	2.6 ± 0.2	2.1 ± 0.2	0.21	10.8 ± 13.7	9.1 ± 10.8	0.93
SV	44.8 ± 3.3	43.2 ± 4.1	0.77	37.7 ± 20.8	19.0 ± 15.4	0.50
SI	27.2 ± 2.1	26.6 ± 2.6	0.86	37.5 ± 20.4	19.9 ± 15.8	0.53
SVR	1980.2 ± 145.0	2224.4 ± 251.3	0.40	6.6 ± 14.4	9.2 ± 16.9	0.91
PVR	201.7 ± 25.6	243.7 ± 37.4	0.35	22.2 ± 19.9	17.5 ± 26.3	0.89
RAP	5.3 ± 0.9	6.7 ± 1.2	0.34	-32.6 ± 36.8	60.2 ± 59.8	0.68
MPAP	27.2 ± 2.9	27.0 ± 3.8	0.97	-6.0 ± 10.9	26.0 ± 23.4	0.19
PCWP	17.4 ± 2.7	16.6 ± 2.6	0.83	-23.3 ± 12.0	32.4 ± 25.8	0.047

CO = cardiac output, T = thermodilution technique, CI = cardiac index, SV = stroke volume, SI = stroke index,
SVR = systemic vascular resistance, PVR = pulmonary vascular resistance, RAP = right atrial pressure,
MPAP = mean pulmonary arterial pressure, PCWP = pulmonary capillary wedge pressure

Table 4. Comparison of echocardiographic data.

	Baseline			% Changes at 3 months		
	Atenolol	Placebo	p-value	Atenolol	Placebo	p-value
LVID-D	66.0 ± 4.5	67.7 ± 4.3	0.37	-10.6 ± 3.7	-4.1 ± 2.7	0.24
LVID-S	57.5 ± 5.4	60.2 ± 5.4	0.27	-18.4 ± 5.7	-13.1 ± 3.6	0.45
LA-size	42.5 ± 7.1	46.9 ± 9.9	0.25	-5.6 ± 3.9	-4.7 ± 8.8	0.92
EDV	233.9 ± 38.4	237.6 ± 37.1	0.84	-22.1 ± 8.8	-10.8 ± 4.1	0.32
ESV	172.4 ± 36.0	177.9 ± 26.9	0.71	-32.4 ± 9.8	-22.6 ± 6.0	0.45
FS	12.7 ± 3.8	12.3 ± 4.5	0.83	78.0 ± 24.0	72.4 ± 28.8	0.88
LVEF	26.7 ± 6.9	23.3 ± 9.7	0.35	85.8 ± 24.5	68.1 ± 23.3	0.63

LVID-D = left ventricular internal diameter during diastole, LVID-S = left ventricular internal diameter during systole,
LA = left atrium, EDV = end diastolic volume, ESV = end systolic volume, FS = fractional shortening,
LVEF = left ventricular ejection fraction

Based on pathophysiology of congestive heart failure[11,12], increased sympathetic activity is part of the neurohomornal compensatory mechanism in addition to salt and water retention as a result of activation of renin-angiotension-aldosterone system and increasing anti-diuretic hormone level. The initial effect only increased cardiac output mainly by positive inotropy and maintaining blood pressure by increasing peripheral vascular resistance.

However, long-term activation of neurohormonal system leads to a diminution of their favorable physiological effects. Sustained sympathetic activation causes down regulation of beta-receptors, uncoupling of beta-receptors from their effective enzyme and change in the cardiac beta-adrenergic pathway. Finally systolic function cannot be sustained and cardiac output falls.

Example of drugs that counteract with neurohormonal activity are ACE-inhibitor and beta-adrenergic antagonists[12]. There have been studies of the use of beta-blockers in patients with heart failure from systolic dysfunction mainly due to dilated cardiomyopathy and ischemic cardiomyopathy. A metoprolol trial showed benefit in the improvement of hemodynamic and exercise tolerance in 383 patients with heart failure from dilated cardiomyopathy[13]. Most benefit occurred after 2 months of medication and continued to improve up to 12 months. Some studies also

showed reduction of plasma norepinephrine level (14). Later studies have shown the benefit of beta-blocker which has with vasodilating properties in heart failure patients(5-7) with more than 60 per cent improvement in survival in one study(6). However, the result of these studies are not consistent. By studying diastolic and systolic function, Anderson et al demonstrated that maximal effects on diastolic function can be reached within the first 3 months but prominent effect on systolic function is seen later(10).

Atenolol is one of the commonly used beta-blockers in Thailand. Little is known about the use of atenolol in dilated cardiomyopathy patients. Atenolol has no vasodilating property. Although atenolol and metoprolol are selective beta1-receptor antagonists, they differ in their lipid solubility. As a result, they may differ in their central nervous system effects which may influence sympathetic modulation *via* neural control.

In this study, all patients had biopsy proven dilated cardiomyopathy with left ventricular ejection fraction less than 40 per cent and in NYHA functional class II and III. We demonstrated that atenolol significantly reduced resting and exercise heart rate and significantly improved hemodynamic status compared to placebo by reducing pulmonary capillary wedge pressure at 3 months of treatment. However, we could not demonstrate the benefit in terms of exercise capacity. This finding is much like the result of the carvedilol trial reported by Olsen et al(7) on 60 patients with heart failure from systolic dysfunction. They showed that at 4 months after randomization, there was an improvement in hemodynamic status in the carvedilol group but no difference in exercise duration.

There are several possible explanations for this finding. First, the follow-up time may not be long enough to see the full benefit of beta-blocker. From the metoprolol dilated cardiomyopathy trial (13), the improvement started 2 months after treatment. Second, there may be a lag time between hemodynamic and exercise tolerance. As reported by Anderson et al(10) diastolic function improved within 3 months whereas improvement in systolic function takes longer. Exercise tolerance may depend more on systolic function. Third, indices of left ventricular performance at rest may not correlate with exercise capacity as demonstrated by Francisco et al(15). Fourth, beta-blocker may have maximal benefit only in those with the worst heart failure and presumably the highest norepinephrine levels. All patients in this study were in functional class II and III which is not the most severe group. Lastly, the sample size may be inadequate. We found that the standard deviation of exercise duration in this study was more than what we assumed for sample size calculation. The finding should not be due to inappropriate dosage of atenolol since there was a significant reduction in resting and exercise heart rate in the atenolol group.

We conclude from this study that atenolol significantly reduced pulmonary capillary wedge pressure at 3 months in patients with symptomatic dilated cardiomyopathy but did not improve exercise capacity.

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การใช้ยา atenolol ในการรักษาผู้ป่วย dilated cardiomyopathy

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Dilated cardiomyopathy เป็นสาเหตุที่พบได้บ่อยอย่างหนึ่งของภาวะหัวใจล้มเหลวชนิดที่มีความผิดปรกติของการบีบตัวของกล้ามเนื้อหัวใจ ยาที่ใช้รักษาภาวะนี้ส่วนใหญ่เป็นการรักษาตามอาการ ยากลุ่ม beta-receptor antagonist เป็นยาชนิดหนึ่งที่สามารถรักษาความผิดปรกติทาง neurohormonal ที่พบในผู้ป่วยกลุ่มนี้ จุดมุ่งหมายของการศึกษานี้เพื่อศึกษาผลของยา atenolol ในผู้ป่วยหัวใจล้มเหลวที่เป็นจาก dilated cardiomyopathy เราทำการศึกษาผู้ป่วยชาย 17 คน และหญิง 5 คน ผู้ป่วยทุกคนได้รับการตรวจสวนหัวใจซีกขวาและซ้าย, การฉีดสีตรวจหาหลอดเลือดหัวใจ, การตรวจชิ้นเนื้อหัวใจ, การตรวจโดยการออกกำลังบนสายพาน และการตรวจคลื่นเสียงสะท้อนของหัวใจ ผลการศึกษาพบว่า หลังให้ยา 3 เดือน atenolol สามารถลดอัตราการเต้นของหัวใจขณะปรกติและขณะออกกำลัง และสามารถลด pulmonary capillary wedge pressure เราไม่พบความแตกต่างของสมรรถภาพการออกกำลังระหว่างกลุ่ม atenolol และกลุ่มที่ได้ยาหลอก จากการศึกษานี้สรุปได้ว่า atenolol สามารถทำให้ hemodynamic ของผู้ป่วยดีขึ้น แต่ไม่มีผลต่อสมรรถภาพการออกกำลังในผู้ป่วยกลุ่มนี้

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