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Research Article

EFFECT OF STOPPING BETA-BLOCKERS ON LV REMODELING IN NON-ISCHEMIC CARDIOMYOPATHY PATIENTS WITH NORMALISATION OF LV FUNCTION: A 12 MONTH STUDY

Kenneth Ng[1]., Raymond Lee[2] and Lay Kheng Tan[3]

[1,2]Consultant Cardiologist, Novena Heart Centre
[3]Chief Sonographer, National Heart Centre

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ABSTRACT

Aims: Beta-blockers are given indefinitely to patients with non-ischemic cardiomyopathy with normalization of clinical status and left ventricular function. We sought to determine whether stopping beta-blockers would have adverse effects on left ventricular (LV) remodeling and clinical status.

Methods and Results: Eleven consecutive patients in NYHA class I with non-ischemic cardiomyopathy and normalization of left ventricular function were recruited. The mean duration of heart failure was 23.3 ± 5.6 months. Seven patients were taken off beta-blockers (BBOFF) and 3 patients remained on (BBON). The BBOFF group were significantly heavier and younger. At 12 months, the systolic blood pressure had decreased significantly only in the BBOFF group when compared to baseline. The left ventricular end-diastolic volume index (LVEDVI) and left ventricular end-systolic volume index (LVESVI) in the BBON group were significantly smaller than in the BBOFF group at 3 months and 6 months. Whilst the LVEDVI and LVESVI remained the same in the BBOFF group, they continued to decrease in the BBON group. At 12 months, all patients were still in NYHA I and were alive.

Conclusions: Discontinuing beta-blockers in our study patients did not produce any adverse effects on LV remodeling or clinical outcome.

(193 words)

INTRODUCTION

There has been a significant reduction in mortality due to chronic heart failure in the last two decades due to the use of angiotensin-converting enzyme (ACE) inhibitors and beta-blockers [1]. Some of the mortality benefit of these drugs can be attributed to the effect of reverse remodeling of the left ventricle [2]. A study of consecutive heart failure patients admitted to a general community hospital, 18% of the patients had normalization of the clinical status, left ventricular size (LV) and ejection fraction after 6 to 18 months of therapy [3]. However, even with the normalization of left ventricular function, therapy with ACE-inhibitors and beta-blockers are continued indefinitely. There is currently no evidence for or against stopping therapy in this group of patients. Of the current drug armamentarium, beta-blockers have been documented to have the biggest effect on left ventricular remodeling [4]. In the same study by Cioffi *et al*, multiple logistic regression identified beta-blocker therapy as independently associated with normalization in clinical status, LV size and ejection fraction [3].

We hypothesize that stopping beta-blockers in patients with non-ischemic cardiomyopathy who have experienced normalization in clinical status and the left ventricular function, will not result in the loss of the left ventricular reverse remodeling effect.

METHODS

Entry Criteria

To be eligible, patients must have with a history of a documented admission episode for heart failure due to non-ischemic cardiomyopathy and an ejection fraction of less than 20% during that index admission and subsequently experienced a normalization of clinical status and LV function. Normalization in clinical status and LV function required 2 obligatory states to be detected during at least 1 of the 3 monthly evaluations performed during follow-up: (1) New York Heart Association functional class = 1 and (2) LV

Corresponding author: **Kenneth Ng*
Consultant Cardiologist, Novena Heart Centre

ejection fraction > 40%. The diagnosis of non-ischemic cardiomyopathy was based on the presence of no or minor coronary artery disease on invasive coronary angiography. Patients with significant valvular disease and heart failure due to thyrotoxicosis were also excluded. The patients had to have been on therapy with an angiotensin-converting enzyme inhibitor and a beta-blocker therapy for at least 8 months prior to enrollment into the study. The patients were all part of a comprehensive heart failure disease management program and were followed up closely in the heart failure clinic. The study protocol was approved by the institutional review board of Tan Tock Seng Hospital and all patients provided written informed consent.

Clinical Follow-up

There were two comparison groups in this study. One group had their beta-blockers continued chronically (BBON) and the other group were taken off beta-blockers (BBOFF). The prescribed beta-blockers used in this study were carvedilol (n= 1) and bisoprolol (n= 10). The patients were informed of the study protocol and objectives and were told that there is currently no evidence whether beta-blockers should be continued and were given a choice either to continue the beta-blockers or to stop the beta-blockers. The patient's choice was respected and the beta-blocker was either continued or discontinued according to the decision made and they were then recruited into the study. Their clinical parameters and symptoms were recorded at baseline, 3 month follow-up, 6 month follow-up and 1 year follow-up. An echocardiogram was also performed during these visit intervals. They were monitored closely for deterioration in heart failure status and were put on telephonic follow-up by an experienced heart failure nurse.

Echocardiographic Measurements

All the patients underwent M-mode, 2-D and Doppler echocardiography assessment at the prescribed time intervals using a GE Vivid-7 4D machine (USA) and performed by one sonographer. Standard parasternal and apical views were obtained with the patient in a left lateral position and all information was stored in a digital format on digital video discs. All discs were read in a blinded fashion by one echocardiologist.

The echocardiograms were analyzed with the use of a dedicated offline echocardiography analysis system (GE EchoPac). Left ventricular end-diastolic (LVEDD) and left ventricular end-systolic (LVESD) diameters were assessed from M-mode images in the parasternal long axis views. Left ventricular end-diastolic (LVEDV) and left ventricular end-systolic (LVESV) volumes and the ejection fractions were determined using Simpson's bi-plane method in the apical 4-chamber view as well as the apical 2 chamber view. Left atrial volume (LAV) was determined using Simpson's bi-plane method in the apical 4 and 2 chamber views. All the indices measured were indexed to the patient's body surface area [5].

Pulse-wave Doppler was used to determine the mitral inflow profile and E- and A- wave velocities, E-wave deceleration times. Tissue Doppler was also performed to determine the E' and A' wave velocities.

Statistical Analysis

Results were expressed as mean $\pm$ standard error unless otherwise stated. Differences between continuous variables were determined using Unpaired Student's t-test. Associations between categorical variables were assessed using Chi-square or Fisher's exact tests. Paired Student's t-test was used to analyze intra-individual changes in LV dimensions from baseline values. All tests were 2-sided and a p level of < 0.05 was considered statistically significant. All analyses were conducted with the statistical package SPPS for Windows (Release 13.0 SPSS Inc, Chicago, IL).

RESULTS

Baseline Characteristics

Eleven patients with a history of idiopathic cardiomyopathy agreed to participate in the study. 3 patients continued on beta-blockers (2 on bisoprolol; 1 on carvedilol) and 8 patients stopped beta-blockers (all on bisoprolol). They were all of Chinese ethnicity and the majority was male. They were all in New York Heart Association functional class I when they entered the study. The patients who were taken off the beta-blockers were significantly younger (51.9 years versus 74.3 years) and had a significantly larger body surface area (1.82 kg/m^2 versus 1.53 kg/m^2). The mean time interval between the onset of heart failure to recruitment into the study was 23.3±5.6 months. The prior duration of heart failure before entering the study was the same in both groups and both groups of patients had the same length of exposure to beta-blockers. All the patients were on an ACE inhibitor or angiotensin receptor blocker, 36% were on spironolactone and 73% were on digoxin on the onset of the study (refer to Table 1) and there were no changes in medications over the follow-up period. Over the 1 year period of follow-up, 2 patients in the BBOFF group and 1 patient in the BBON group did not turn up for the 12^{th} month follow-up evaluation. At baseline, the mean heart rate was 72±8 bpm, and the mean blood pressure was 143/81 mmHg. The baseline heart rate and blood pressure were similar between both study groups.

Table1

Clinical Parameter	BBON (n=3)	BBOFF (n=8)	P Value
Duration of heart failure (SE), months	21.0 (9.0)	23.9 (6.9)	0.85
Age, mean (SE),y	74.3 (2.3)	51.9 (3.8)	0.008
Men, n (%)	3(100)	7(88)	0.52
Diabetes, n (%)	0(0)	2(25)	0.34
Hypertension, n (%)	2(66.7)	4(50)	0.62
Hyperlipidemia, n (%)	2(66.7)	3(37.5)	0.39
Cerebrovascular accident, n (%)	1(33.3)	1(12.5)	0.43
Revascularization, n (%)	0(0)	0(0)	n.a.
Creatinine, mean (SE), umol/L	112 (12)	124 (19)	0.74
Height, mean (SE), cm	158 (1.8)	167 (3.4)	0.13
Weight, mean (SE), kg	53.7 (4.1)	83.5 (9.7)	0.11
BSA, mean (SE), m2	1.53 (0.04)	1.82 (0.11)	0.08
SBP, mean (SE), mmHg	137 (1.0)	145 (6.8)	0.61
DBP, mean (SE), mmHg	89 (3.0)	79 (4.4)	0.3
Heart rate, mean (SE), bpm	76 (2.0)	71 (3.1)	0.5
New York Heart Association functional class I n, (%)	3(100)	8(100)	n.a.
ACE-I/ARB, n (%)	3(100)	8(100)	n.a.
Spironolactone, n (%)	1(33.3)	3(37.5)	1.00
Digoxin, n (%)	3(100)	5(62.5)	0.49

Table 2

Parameter	Baseline			3 months			6 months			12 months		
	No.	Mean (S.E.)	P value	No.	Mean (S.E.)	P value	No.	Mean (S.E.)	P value	No.	Mean (S.E.)	P value
LVEDVI, mL/m^2												
BBON	3	64.2±19.7	0.58	3	34.0±5.1	0.02	3	31.8±3.8	0.04	2	35.7±8.2	0.40
BBOFF	8	50.9±5.0		8	47.0±2.8		7	46.2±2.2		6	46.2±5.7	
LVESVI, mL/m^2												
BBON	3	31.1±7.9	0.42	3	13.4±1.2	0.03	3	12.6±1.8	0.04	2	13.0±1.6	0.25
BBOFF	8	22.9±3.2		8	19.2±2.4		7	20.3±2.4		6	19.1±4.5	
LVEF, %												
BBON	3	49.9±6.0	0.43	3	59.8±2.5	0.68	3	59.7±6.6	0.68	2	62.5±4.0	0.63
BBOFF	8	56.0±3.1		8	57.5±4.8		7	56.2±4.2		6	58.7±6.2	

Changes in Heart Rate and Blood Pressure

After 12 months of follow-up, the mean systolic blood pressure decreased significantly from the baseline of 145±7 mmHg to 132±4 mmHg (p=0.03) in the BBOFF group. The mean diastolic blood pressure decreased slightly from the baseline of 79±4 mmHg to 76±2 mmHg, which was not significantly different. The mean heart rate in the BBOFF group was unchanged at 12 months when compared to baseline (71±3 bpm versus 75±5 bpm). In the BBON group, the mean systolic blood pressure decreased from the baseline of 137± 1 mmHg to 130±6 mmHg, which was not significantly different. The mean diastolic pressure was not significantly changed from baseline to 12 months (89±3 mmHg versus 84±8 mmHg). Although the mean heart rate in the BBON group decreased from a baseline of 76±2 bpm to 66±4 bpm, the difference did reach significance (p=0.13).

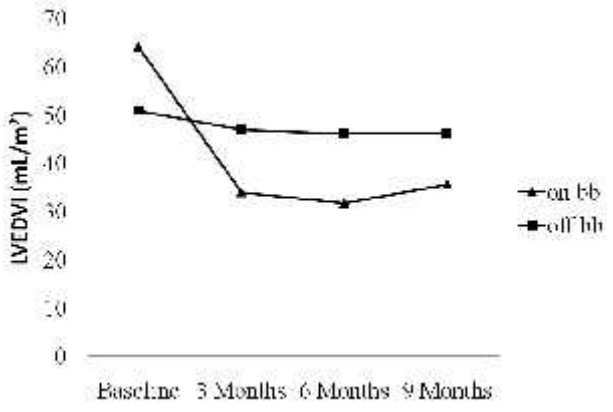

Figure 1 A

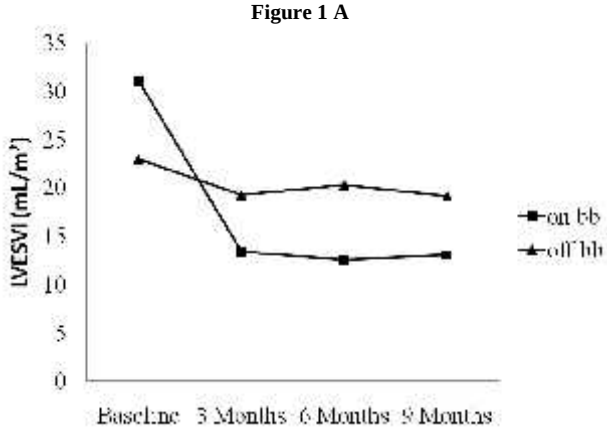

Figure 1 B

Changes in LV dimensions

The LV dimensions in the BBON group were slightly larger and LVEF slightly lower at baseline compared to the BBOFF group which was not significant. However, over the follow-up of 12 months, the LV dimensions in the BBOB group were significantly smaller than the BBOFF group at 3 months and 6 months follow-up. The LV dimensions in the BBON group tended to be smaller than in the BBOFF group at 12 months but it was not statistically significant. This could be due to the small number of patients left in the study. The LVEF between the 2 groups were not significantly different at any of the follow-up time points (refer to Table 2).

Mean change in LV dimensions from baseline did not differ significantly at 3, 6 or 12 months in either the BBON or BBOFF groups (refer to Table 3). Represented in a graphical manner (Figure 1A and Figure 1B), the LVEDVI and LVESVI continued to decrease in the BBON group for a period of one year. Conversely, the LVEDVI and LVESVI remained almost the same over the same period in the BBOFF group. Mean change from baseline in LVEDVI and LVESVI at 3, 6 or 12 months in the BBON or BBOFF groups is displayed graphically (Figures 2A and 2B).

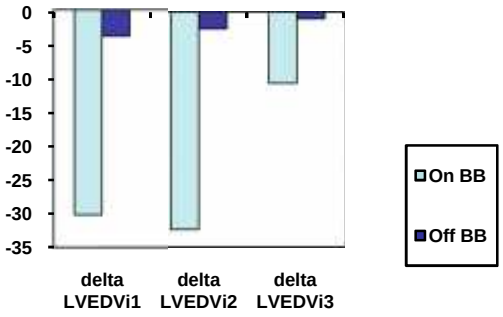

Figure 2A

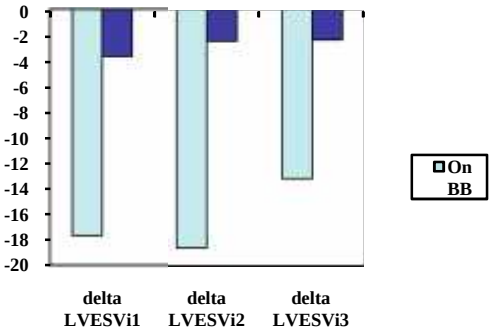

Figure 2B

Table 3

	Baseline to 3 months			Baseline to 6 months			Baseline to 12 months		
	Mean Change	95% CI	P vs Baseline	Mean Change	95% CI	P Vs Baseline	Mean Change	95% CI	P vs Baseline
LVESVI, mL/m2									
BBON	-17.7	-50.3 to 14.9	0.14	-18.5	-46.2 to 9.1	0.10	-13.2	-129.6 to 103.2	0.39
BBOFF	-3.72	-12.8 to 5.3	0.37	-2.48	-10.5 to 5.5	0.48	-2.38	-10.1 to 5.3	0.46
LVEDVI, mL/m2									
BBON	-30.2	-124.1 to 63.7	0.30	-32.4	-128.2 to 63.4	0.28	-10.6	-88.7 to 67.5	0.33
BBOFF	-3.93	-17.6 to 9.7	0.52	-2.46	-9.9 to 5.0	0.45	-0.99	-14.7 to 12.7	0.86
LVEF, %									
BBON	-5.8	-47.8 to 36.3	0.62	-5.7	-44.6 to 33.2	0.59	-11.1	-222.3 to 200.1	0.63
BBOFF	-1.44	-12.3 to 9.4	0.76	-1.36	-15.5 to 12.8	0.82	-2.59	-17.4 to 12.2	0.67

Clinical Outcomes

None of the patients in either the BBON or BBOFF group had deterioration in New York Heart Association functional class during the study period of 12 months. They remained in New York Heart Association functional class I throughout the study period. There were also no hospitalizations for heart failure or any cardiac events for patients in either study group. There were no deaths in either study group during the 12 month follow-up period.

DISCUSSION

There is a wealth of data supporting the beneficial effects of beta-blockers in particular carvedilol on LV remodeling which appears to be incremental to that of ACEI's in patients with both ischemic and non-ischemic cardiomyopathy [2]. However, there is a paucity of data on whether or not either beta-blockers or ACEI's should be continued once the LV function and/or clinical status has normalized.

The results of our study show that stopping beta-blockers did not result in a loss of the LV reverse remodeling effect up to a duration of 12 months. Conversely, in those patients where beta-blockers was not stopped, the LV reverse remodeling effect continued, with a further decrease in both LVEDVI and LVSEVI with its maximum effect seen at 3 months from onset of the study.

A review of the literature revealed only one previous study addressing this issue [6]. In that study, 24 patients with idiopathic dilated cardiomyopathy who had normalisation of LV function and clinical status 6 months after treatment with metoprolol had their metoprolol stopped. 16 patients (67%) had deterioration in their clinical status and LV function at 12 months and underwent readministration of metoprolol with subsequent improvement in both clinical status and LV function. Only 8 patients (33%) had maintained normal clinical status and LV function at 12 months. In our study however, all subjects maintained normal clinical status and LV function up to 12 months after stopping beta-blockers. Differences between the 2 study populations with regards to aetiology of heart failure, type of beta-blocker used, duration of beta-blocker therapy and concomitant use of ACEI could in part explain the discrepancy between the 2 studies in the outcome of subjects who were taken off beta-blockers. While patients with chronic active myocarditis were specifically excluded from Waagstein F's study, they were not excluded for our study.

Chronic active myocarditis patients may represent a subset of dilated cardiomyopathy patients with a better prognosis in whom spontaneous recovery of LV function may occur [7]. Failure to exclude patients with chronic active myocarditis could therefore have resulted in a more favourable outcome in our study.

Type of beta-blocker used was also different in the 2 studies. All subjects in Waagstein F's study were on metoprolol, whereas the majority of our study patients were on bisoprolol (n=10) and 1 patient was on carvedilol. Several studies have evaluated the comparative effects of different beta-blockers on LV remodeling in patients with chronic heart failure [8,9]. In all these studies, carvedilol (a non-selective vasodilating beta-blocker with alpha-blocking properties) was superior to metoprolol (a cardioselective beta-blocker) in promoting reverse LV remodeling. Only 2 previous studies have evaluated the effects of bisoprolol (a cardioselective beta-blocker) on LV remodeling in patients with chronic heart failure and the results were conflicting, with 1 study [10] demonstrating a trend towards reverse LV remodeling, whereas in the other study [11], early treatment failed to prevent adverse LV remodeling in post-AMI patients. However, the progressive decrease in LVEDVI and LVESVI in our study subjects in whom bisoprolol was continued was reassuring, and supported the favorable effects of beta-blockers on LV remodeling in patients with chronic heart failure.

Duration of beta-blocker therapy was also different between the 2 studies. In Waagstein F's study, patients were on beta-blockers for only 6 months, whereas in our study, subjects were on beta-blockers for a mean duration of 24 months before beta-blockers were discontinued. The longer duration of beta-blocker therapy in our study patients could have resulted in further reverse LV remodeling and hence the better clinical outcome.

Lastly, Waagstein F's study was performed at a time when treatment with vasodilators was relatively rare. Indeed only 2 out of 33 patients were on ACEI's. On the contrary, all our study subjects were on either ACEI (n=8) or ARB (n= 3). Randomized trial data demonstrate that complete neurohormonal blockade using a combination of both beta-blocker and ACEI had the most potent effect on reverse LV remodeling, superior to that achieved with either beta-blocker or ACEI alone [2]. The additive effects of the combination of both beta-blocker and ACEI on the LV remodeling process in

our study subjects could also have contributed to the more favorable prognosis.

It is difficult to ascertain how much of the improvement in our study subjects could be attributed to spontaneous recovery or beneficial effects of drug therapy on the LV remodeling process. As was elegantly demonstrated in Waagstein's study, the deterioration during beta-blocker withdrawal in most patients and subsequent improvement after reinstitution strongly support a cause and effect relationship between clinical improvement and beta-blocker treatment in these patients.

Study Limitations

Our study was non-randomized, unblinded and the sample size was small. Follow-up duration was also short.

CONCLUSIONS

Our study shows that discontinuing bisoprolol after 24 months of treatment is safe and does not result in adverse LV remodeling in non-ischemic cardiomyopathy patients with normalization of LV function and clinical status, up to a duration of 12 months. Larger prospective studies are required to confirm the findings of our study and to identify the subset of non-ischemic cardiomyopathy patients in whom it is safe to discontinue beta-blockers and also to further define the optimal duration of beta-blocker treatment.

References

1. McMurray JJV, Pfeffer MA, Swedberg K, Dzau VJ. Which inhibitor of the rennin-angiotensin system should be used in chronic heart failure and acute myocardial infarction? Circulation 2004;110:3281-3288.
2. Udelson JE. Ventricular remodeling in heart failure and the effects of β-blockade. *Am J Cardiol* 2004; 93(suppl):43B-48B.
3. Cioffi G, Stefenelli C, Tartantini L, Opasich C. Chronic left ventricular failure in the community: prevalence, prognosis, and predictors of the complete clinical recovery with return of cardiac size and function to normal in patients undergoing optimal therapy. *J Card Fail* 2004; 10:250-257.
4. Frigerio M, Roubina E. Drugs for left ventricular remodeling in heart failure. *Am J Cardiol* 2005; 96(suppl):10L-18L.
5. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA *et al*. Recommendations for chamber quantification: a report from the American Society of Echocardiography's guidelines and standards committee and the chamber quantification writing group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. *J Am Soc Echocardiogr* 2005; 18:1440-1463.
6. Waagstein F, Caidahl K, Wallentin I, Bergh CH, Hjalmarson A. Long-term beta-blockade in dilated cardiomyopathy. Effects of short- and long-term metoprolol treatment followed by withdrawal and readministration of metoprolol. Circulation 1989; 80:551-563.
7. Fuster V, Gersh BJ, Giuliani ER, Tajik AJ, Brandenburg RO, Frye RL. The natural history of idiopathic dilated cardiomyopathy. *Am J Cardiol* 1981; 47:525.
8. Gilbert EM, Abraham WT, Olsen S, Hattler B, White M, Mealy P *et al*. Comparative hemodynamic, left ventricular functional, and antiadrenergic effects of chronic treatment with metoprolol versus carvedilol in the failing heart. Circulation 1996; 94:2817-2825.
9. Metra M, Giubbini R, Nodari S, Boldi E, Modena MG, Dei Cas L. Differential effects of beta-blockers in patients with heart failure: a prospective, randomized, double-blind comparison of the long-term effects of metoprolol versus carvedilol. Circulation 2000; 102:546-551.
10. Dubach P, Myers J, Bonetti P, Schertler T, Froelicher V, Wagner D *et al*. Effects of bisoprolol fumarate on left ventricular size, function, and exercise capacity in patients with heart failure: analysis with magnetic resonance myocardial tagging. *Am Heart J* 2002; 143:676-683.
11. Yoshitomi Y, Kojima S, Yano M, Sugi T, Matsumoto Y, Kuramochi M. Long-term effects of bisoprolol compared with imidapril on left ventricular remodeling after reperfusion in acute myocardial infarction: an angiographic study in patients with maintained vessel patency. *Am Heart J* 2000; 140:E27.

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