Laboratory Investigation

Comparative Efficacy of Nebivolol and Metoprolol

to Prevent Tachycardia-Induced Cardiomyopathy in a Porcine Model

Alireza Nazeri, MD
MacArthur A. Elayda, MD, PhD
Ana Maria Segura, MD, MPH
Raymond F. Stainback, MD
Joanna Nathan, MD
Vei-Vei Lee, MS
Christina Bove, DVM
Luiz Sampaio, MD
Brian Grace, BS
Ali Massumi, MD
Mehdi Razavi, MD

Key words: *Anti-arrhythmia agents/therapeutic use; arrhythmias, cardiac/prevention & control; cardiomyopathies/physiopathology; disease models, animal; heart rate/drug effects; metoprolol; nebivolol; receptors, adrenergic, beta/drug effects; swine; tachycardia/drug effects/prevention & control/physiopathology*

From: *Center for Clinical Electrophysiology Research and Innovation (Drs. Bove, Massumi, Nathan, Nazeri, and Razavi) and Departments of Biostatistics and Epidemiology (Dr. Elayda and Ms Lee), Cardiology (Drs. Elayda, Sampaio, and Stainback), Cardiovascular Pathology (Dr. Segura), and Cardiovascular Surgical Research (Dr. Bove and Mr. Grace), Texas Heart Institute, Houston, Texas 77030*

Dr. Bove is now at the Veterinary Teaching Hospital, Colorado State University, Fort Collins, Colorado.

Address for reprints: *Mehdi Razavi, MD, Center for Cardiac Arrhythmias and Electrophysiology, Texas Heart Institute, 6624 Fannin St., Suite 2480, Houston, TX 77030*

E-mail: *mehdirazavi1@gmail.com*

Chronic tachycardia is a well-known cause of nonischemic cardiomyopathy. We hypothesized that nebivolol, a β-blocker with nitric oxide activity, would be superior to a pure β-blocker in preventing tachycardia-induced cardiomyopathy in a porcine model.

Fifteen healthy Yucatan pigs were randomly assigned to receive nebivolol, metoprolol, or placebo once a day. All pigs underwent dual-chamber pacemaker implantation. The medication was started the day after the pacemaker implantation. On day 7 after implantation, each pacemaker was set at atrioventricular pace (rate, 170 beats/min), and the pigs were observed for another 7 weeks. Transthoracic echocardiograms, serum catecholamine levels, and blood chemistry data were obtained at baseline and at the end of the study. At the end of week 8, the pigs were euthanized, and complete histopathologic studies were performed.

All the pigs developed left ventricular cardiomyopathy but remained hemodynamically stable and survived to the end of the study. The mean left ventricular ejection fraction decreased from baseline by 34%, 20%, and 20% in the nebivolol, metoprolol, and placebo groups, respectively. These changes did not differ significantly among the 3 groups (P=0.51). Histopathologic analysis revealed mild left ventricular perivascular fibrosis with cardiomyocyte hypertrophy in 14 of the 15 pigs.

Both nebivolol and metoprolol failed to prevent cardiomyopathy in our animal model of persistent tachycardia and a high catecholamine state. ***(Tex Heart Inst J 2016;43(6):477-81)***

As their names imply, pacing- and tachycardia-induced cardiomyopathies (PTICMs) result from ongoing right ventricular (RV) pacing and from ventricular or supraventricular tachyarrhythmia, respectively. These cardiomyopathies manifest themselves as ventricular systolic dilation and dysfunction and result in heart failure-related symptoms, most of which can be reversed by normalizing the heart rate. Pacing of the RV has led to left ventricular (LV) dysfunction and progression of congestive heart failure (CHF). Investigators have shown that rate control with negative chronotropic agents significantly improves systolic function.[1,2]

Patients with chronic tachycardia are often prescribed β-blockers to slow the heart rate and prevent tachycardia-induced cardiomyopathy. Long-term β-blocker use has improved symptoms and increased survival rates in patients with CHF[3]; however, it is not clear whether β-blockers benefit such patients by modulating chronotropy, inotropy, or both—or by some other mechanism.

Nebivolol (BYSTOLIC®; Forest Laboratories, LLC, an affiliate of Allergan, Inc.; New York, NY), a 3rd-generation cardioselective β-blocker, induces peripheral vasodilation by increasing the production of endothelial nitric oxide (NO).* Nitric oxide has been shown to augment the parasympathetic effects of acetylcholine, both by increasing its release and by augmenting its stimulatory effect on the production of guanylyl.[4]

L-arginine is a precursor of NO and, therefore, also promotes vasodilation. In patients with heart failure, dysfunction in the L-arginine–NO pathway leads to de-

*Forest Laboratories (New York, NY) provided the nebivolol used in the study but was not involved in the study design; in the collection, analysis, or interpretation of data; in the writing of the report; or in the decision to submit the article for publication.

This manuscript is dedicated to the memory of Dr. Ali Massumi, who died before its publication. He will be missed by all.

creased myocardial perfusion and increased endothelial dysfunction, which partly explains the reduced exercise capacity of patients with CHF. Doutreleau and colleagues[5] showed that L-arginine supplementation improved endurance and exercise tolerance in patients with stable CHF: compared with a placebo group, patients who took L-arginine had a significant decrease in their average heart rate throughout exercise and the recovery period.

We speculated that the effects of this NO release, combined with the established therapeutic effects of β-blockade on chronic tachycardia, might make nebivolol a promising pharmacologic tool for treating patients with CHF. Therefore, we tested the relative efficacy of nebivolol and a pure β-blocker, metoprolol, in a porcine model, hypothesizing that nebivolol would be superior in preventing tachycardia-induced cardiomyopathy.

Materials and Methods

Fifteen healthy Yucatan pigs underwent implantation of dual-chamber pacemakers (Medtronic, Inc.; Minneapolis, Minn). The pigs were then randomly assigned to groups of 6, 6, and 3, respectively, to be given nebivolol, metoprolol, or placebo once daily, beginning 2 days after pacemaker implantation. Our objective was to lower each pig's heart rate by 10% to 15% from baseline (the mean heart rate on the 2nd day after pacemaker implantation). We began with a dose of 10 mg of nebivolol or 25 mg of metoprolol, with the intent to increase the dose if the target heart rate was not achieved. However, in all cases, these doses were sufficient to achieve the targeted heart rate and appeared to be safe.

To simulate tachycardia, the pacemaker was set at atrioventricular pace (rate, 170 beats/min) on day 7 after implantation, and the pigs were observed for another 7 weeks. The intention was to sustain a high ventricular rate without causing hemodynamic compromise due to atrioventricular dyssynchrony, and to test the effect of the β-blocker in reducing the catecholamine surge caused by sustained tachycardia. Two-dimensional and Doppler echocardiographic studies were performed at baseline and at the end of week 8. We measured serum basic metabolic values, as well as serum levels of brain natriuretic peptide, fibrinogen, epinephrine, norepinephrine, angiotensin-converting enzyme, renin, and C-reactive protein, at baseline and at the end of the study. At the end of week 8, the pigs were euthanized, and complete histopathologic studies were performed. The study was conducted in accordance with the "Guide for the Care and Use of Laboratory Animals."

The collected data were analyzed with use of SAS statistical software version 9.2 (SAS Institute, Inc.; Cary, NC). Two-way analysis of variance was used to compare the changes in the outcome variables among the 3 groups. Our primary endpoint was the degree of decline in LV ejection fraction (LVEF) from baseline to week 8. A P value <0.05 was considered to be significant.

Results

All the pigs remained hemodynamically stable and survived to the end of the study. All developed LV cardiomyopathy. The mean LVEF decreased from baseline by 34%, 20%, and 20% in the nebivolol, metoprolol, and placebo groups, respectively. These changes did not differ significantly among the 3 groups ($P=0.51$). Echocardiographic and chemistry findings (Table I) showed changes from baseline in inflammatory- and autonomic-response blood markers in each group, but these changes were not significantly different among the groups. There was mild LV perivascular fibrosis with cardiomyocyte hypertrophy in 14 of the 15 pigs (6 nebivolol, 5 metoprolol, and 3 placebo). The remaining pig, which was in the metoprolol group, had severe multifocal inflammatory changes, including extensive myocardial fibrosis and necrosis in the LV.

Discussion

The chief finding of the current study is that, outside of any direct effects on heart rate, β-blockers might not be protective against PTICM. This finding suggests that the salutary effects of β-blockers on PTICM are probably not substantial enough to manifest themselves as a reduction in LVEF. This is in direct contradistinction to ischemic and nonischemic cardiomyopathies, against which these drugs are clearly effective.

The reasons for this finding are not obvious. Like other forms of systolic heart failure, PTICM involves a downregulation of β-receptors.[6] Thus, one would expect that, like other nonischemic cardiomyopathies, PTICM would respond to β-blockade with a rebound in β-receptor density. Although we did not analyze β-receptor density, the absence of LVEF improvement and the trend toward higher plasma levels of adrenergic neurohormonal markers in the β-blockade groups than in the placebo group suggest that administering metoprolol or nebivolol did not lead to improvement in β-receptor density in the treatment groups. If anything, there was a trend toward less susceptibility to pacing-induced diminution of LVEF in the placebo group. Thus, our negative findings cannot be dismissed as an artifact of small sample size; rather, they suggest that administering β-blockers while rapid pacing is underway worsens hemodynamic values, as has been noted in clinical settings.

The PTICMs are heralded by alterations of cellular architecture, including fibrosis.[7] In our study, no salutary effects of β-blockers on fibrosis were noted. Our study results support other studies of RV pacing that

TABLE I. Relevant Echocardiographic, Inflammatory, and Autonomic Response Findings in the 3 Groups (N=15)

Variable	**Nebivolol** (n=6)		**Metoprolol** (n=6)		**Placebo** (n=3)		*P* Value
	Baseline	**Final**	**Baseline**	**Final**	**Baseline**	**Final**	
Echocardiographic							
LVEF	0.74 ± 0.05	0.40 ± 0.2	0.69 ± 0.06	0.48 ± 0.22	0.73 ± 0.06	0.53 ± 0.25	0.51
RVEF	0.74 ± 0.05	0.40 ± 0.2	0.68 ± 0.07	0.45 ± 0.25	0.73 ± 0.06	0.55 ± 0.26	0.55
LVEDD (cm)	3.8 ± 0.7	3.4 ± 0.5	4 ± 0.5	4.1 ± 0.6	4 ± 0.4	3.9 ± 0.1	0.22
LVESD (cm)	1.9 ± 0.6	2.7 ± 0.6	2.2 ± 0.3	2.7 ± 1	2.2 ± 0.3	2.3 ± 0.8	0.48
Inflammatory							
Creatine kinase (U/L)	383.7 ± 149.5	168.2 ± 69.4	494.3 ± 201.5	124.7 ± 38.7	250 ± 20.4	186.3 ± 65	0.1
Fibrinogen (mg/dL)	514 ± 330.6	471 ± 362.5	352.8 ± 155.4	485.5 ± 241.4	358 ± 16.8	342 ± 30.9	0.32
CRP (mg/L)	1 (0.03–4.9)	2.6 (0.08–5.4)	0.4 (0.01–1)	2.8 (0.13–6.6)	0.28 (0.06–83.9)	0.28 (0.01–0.79)	0.1
Norepinephrine (pg/mL)	4.2 (1.5–6.8)	5 (2.2–7.1)	3.9 (0.001–6.9)	2.9 (0.001–8.4)	1.8 (0.001–3.2)	0.2 (0.001–0.5)	0.48
Epinephrine (pg/mL)	1.7 (0.8–2.6)	3.8 (2.7–6)	2.7 (0.5–8.2)	3.6 (0.001–6)	0.7 (0.4–1)	3.2 (0.3–8.7)	0.74
ACE (U/L)	191 (12–258)	171.3 (72–240)	197.3 (1.7–267)	208.3 (139–279)	206.3 (163–270)	238.6 (186–284)	0.72
BNP (pg/mL)	60 (45–74.3)	40.1 (26.4–75.5)	62.6 (31.6–99.6)	111.5 (29–448.1)	85 (49.5–147.8)	62 (24.5–105.2)	0.51
Autonomic							
Renin (pg/mL)	11.8 (1.4–60)	12.3 (0.7–46.7)	17.5 (0.01–60)	14.2 (0.07–60)	1.9 (0.4–2.7)	10.6 (1.7–27.9)	0.76
BUN (mg/dL)	12.8 ± 2.3	16.2 ± 4.3	13.5 ± 2.5	12.8 ± 4.9	15.6 ± 2.1	14.6 ± 1.2	0.26
Creatinine (mg/dL)	1 ± 0.2	1.1 ± 0.2	1 ± 0.2	1.1 ± 0.2	1 ± 0.2	1 ± 0.2	0.28
Calcium (mg/dL)	9.4 ± 0.5	8.6 ± 0.5	9.8 ± 0.5	8.8 ± 1	9.5 ± 0.1	9.5 ± 0.2	0.29
Magnesium (mEq/L)	2.4 ± 0.2	2.1 ± 0.3	2.3 ± 0.2	2.2 ± 0.5	2.5 ± 0.4	2.3 ± 0.4	0.82

ACE = angiotensin-converting enzyme; BNP = brain-type natriuretic peptide; BUN = blood urea nitrogen; CRP = C-reactive protein; LVEDD = left ventricular end-diastolic diameter; LVEF = left ventricular ejection fraction; LVESD = left ventricular end-systolic diameter; RVEF = right ventricular ejection fraction

Values are expressed as mean ± SD or as median and interquartile range. $P < 0.05$ was considered statistically significant.

have shown fibrosis in PTICM.[8] In one such study, the same rate of 170 beats/min was used to induce RV pacing-induced cardiomyopathy.[9] In our study, β-blockers did not reduce the extent of myocardial fibrosis; rather, the amount and uniformity of the fibrosis was what one would expect to see in this model of heart failure. This finding might have been due to the continued insult of rapid pacing and tachycardia or to the relatively brief duration of the study. In this context, it is important to point out that some of the strongest trends that we found were those pointing to decreased systemic inflammation (as indicated by C-reactive protein and creatine kinase levels) in the β-blockade groups in comparison with the placebo group at 8 weeks.

It should be noted that both metoprolol and nebivolol administration resulted in a nonsignificant attenuation of the renin surge normally associated with cardiomyopathy. Thus, although some of the neurohormonal effects of β-blockade were manifest, the salutary effects of such blockade were not apparent in any of the echocardiographic variables that we studied. This finding seems to support the hypothesis that intrinsic β-receptor and second-messenger dysfunction (and not simply downregulation) at the level of the myocardium

promotes the development of PTICM.[10] It might also explain why other study results have shown improved cardiac function with the use of inotropic agents in rapid RV pacing-induced cardiomyopathy.[11,12]

The levels of epinephrine and norepinephrine trended higher in both treatment groups than in the placebo group, probably indicating a response to long-term receptor blockade. This suggests that, although systemic activation of the sympathetic system is increased—probably through a renal trigger—during PTICM, the effect of β-blockade on the myocardium in animals undergoing active, rapid pacing is minimal. The reasons for this paucity of effect are unknown, but again, myocardial adrenergic receptor dysfunction seems a plausible explanation.

The response of serum epinephrine and norepinephrine levels to pacing was mixed. Our study showed an increase in epinephrine levels across all groups, whereas norepinephrine levels decreased in the metoprolol-treated pigs and, particularly, in the placebo-treated pigs. The significance and cause of these changes are uncertain.

This study has a few notable limitations. The greatest of these is that because it was an animal study, the number of data points was limited in comparison with those in larger clinical studies that established the efficacy of β-blockers for treating nonischemic cardiomyopathies. In addition, we did not study the effects of higher doses of nebivolol or metoprolol on preventing PTICM; because 10 mg of nebivolol and 25 mg of metoprolol sufficiently reduced heart rate by 10% to 15% in all the pigs, we did not use higher doses in any of them. Another limitation is that we did not study the course of PTICM recovery after pacing was discontinued. We did, however, initiate β-blockade one week before starting pacing. It appears that, in our limited sample, a one-week period of premedication was not sufficient to protect against PTICM. An additional limitation of this study was the titration of the medication, which would have better shown the drugs' clinical effects had it been done over 8 weeks instead of 1 week. Finally, we induced cardiomyopathy with a combination of RV pacing and tachycardia, which are both independent risk factors for cardiomyopathy. We chose this model to maximize the chance of inducing cardiomyopathy in each pig, thereby avoiding having to run more experiments than necessary (the 3-armed study design already necessitated a relatively large sample size), and because in many cases (such as premature ventricular contractions) the foci of ectopy may be associated with dyssynchronous ventricular contraction. However, the combined use of both pacing and tachycardia might have overwhelmed any protective effects specific to increased levels of NO.

Our findings indicate that neither nebivolol nor metoprolol was effective in mitigating the effects of PTICM. The overall outcomes in the placebo group were better than those in both medication groups, which raises the question of whether the side effects of these β-blockers affected the outcomes. In addition, these results suggest that, once the rate-controlling effects of nebivolol and metoprolol are negated, neither has significant effects on myocardial remodeling. This in turn supports the theory that the pathophysiology of PTICM involves fibrosis (which was equally prevalent among our 3 groups) and β-receptor and second-messenger dysfunction, as has been suggested in previous reports. Nonetheless, because this is a pilot study, our findings should be interpreted with caution regarding their clinical implications. Further research is warranted to evaluate the additional effect of NO enhancement of β-blockers in the prevention of tachycardia-induced cardiomyopathy. We plan to perform additional studies that will focus specifically on tachycardia (using atrial pacing only, so that ventricular activation occurs through the normal His-outline conduction system) and, separately, on ventricular pacing mechanisms (in the absence of tachycardia).

References

1. Falk RH. Is rate control or rhythm control preferable in patients with atrial fibrillation? Rate control is preferable to rhythm control in the majority of patients with atrial fibrillation. Circulation 2005;111(23):3141-50.
2. Redfield MM, Kay GN, Jenkins LS, Mianulli M, Jensen DN, Ellenbogen KA. Tachycardia-related cardiomyopathy: a common cause of ventricular dysfunction in patients with atrial fibrillation referred for atrioventricular ablation. Mayo Clin Proc 2000;75(8):790-5.
3. Waagstein F, Hjalmarson A, Varnauskas E, Wallentin I. Effect of chronic beta-adrenergic receptor blockade in congestive cardiomyopathy. Br Heart J 1975;37(10):1022-36.
4. Opie LH, Hasenfuss G. Mechanisms of cardiac contraction and relaxation. In: Bonow RO, Mann DL, Zipes DP, Libby P, editors. Braunwald's heart disease: a textbook of cardiovascular medicine. 9th ed. Philadelphia: Saunders; 2011. p. 459-86.
5. Doutreleau S, Mettauer B, Piquard F, Rouyer O, Schaefer A, Lonsdorfer J, Geny B. Chronic L-arginine supplementation enhances endurance exercise tolerance in heart failure patients. Int J Sports Med 2006;27(7):567-72.
6. Shite J, Qin F, Mao W, Kawai H, Stevens SY, Liang C. Antioxidant vitamins attenuate oxidative stress and cardiac dysfunction in tachycardia-induced cardiomyopathy. J Am Coll Cardiol 2001;38(6):1734-40.
7. Packer DL, Bardy GH, Worley SJ, Smith MS, Cobb FR, Coleman RE, et al. Tachycardia-induced cardiomyopathy: a reversible form of left ventricular dysfunction. Am J Cardiol 1986;57(8):563-70.
8. Spinale FG, Hendrick DA, Crawford FA, Smith AC, Hamada Y, Carabello BA. Chronic supraventricular tachycardia causes ventricular dysfunction and subendocardial injury in swine. Am J Physiol 1990;259(1 Pt 2):H218-29.
9. Paslawska U, Gajek J, Kiczak L, Noszczyk-Nowak A, Skrzypczak P, Bania J, et al. Development of porcine model of chronic tachycardia-induced cardiomyopathy. Int J Cardiol 2011;153(1):36-41.

10. Calderone A, Bouvier M, Li K, Juneau C, de Champlain J, Rouleau JL. Dysfunction of the beta- and alpha-adrenergic systems in a model of congestive heart failure. The pacing-overdrive dog. Circ Res 1991;69(2):332-43.
11. Cardinal R, Nadeau R, Laurent C, Boudreau G, Armour JA. Reduced capacity of cardiac efferent sympathetic neurons to release noradrenaline and modify cardiac function in tachycardia-induced canine heart failure. Can J Physiol Pharmacol 1996;74(9):1070-8.
12. Arora RC, Cardinal R, Smith FM, Ardell JL, Dell'Italia LJ, Armour JA. Intrinsic cardiac nervous system in tachycardia induced heart failure. Am J Physiol Regul Integr Comp Physiol 2003;285(5):R1212-23.