The Effect of Different β-Blockers on Vascular Graft Nitric Oxide Levels: Comparison of Nebivolol Versus Metoprolol

E. Bayar [a], G. Ilhan [b,*], C. Furat [b], C. Atik [a], Y. Arslanoglu [a], C. Kuran [a], B. Ozpak [c], M.E. Durakoglugil [d]

[a] Gaziantep University, Faculty of Medicine, Department of Cardiovascular Surgery, Gaziantep, Turkey
[b] Recep Tayyip Erdogan University, Faculty of Medicine, Department of Cardiovascular Surgery, Rize, Turkey
[c] Izmir Katip Celebi University, Ataturk Education and Research Hospital, Department of Cardiovascular Surgery, Izmir, Turkey
[d] Recep Tayyip Erdogan University, Faculty of Medicine, Department of Cardiology, Rize, Turkey

WHAT THIS PAPER ADDS

The aim of this study was to investigate the effects of the vasodilating β-blocker nebivolol and the cardioselective β-blocker metoprolol on nitric oxide levels at vascular graft endothelium and vasa vasorum compared to controls in patients undergoing coronary artery bypass graft surgery. According to our results, we think that nebivolol may be safer and preferable in order to diminish graft spasm in patients undergoing coronary artery bypass graft surgery due to the nitric oxide-mediated vasodilating effect.

Objectives: The aim of this study was to investigate the effects of the vasodilating β-blocker nebivolol and the cardioselective β-blocker metoprolol on nitric oxide (NO) levels at vascular graft endothelium and vasa vasorum compared to controls in patients undergoing coronary artery bypass graft surgery.

Methods: This was a prospective study. Fifty-five patients were divided into three groups: nebivolol group (group N, $n = 23$), metoprolol group (group M, $n = 16$), and control group (group A, $n = 16$). Group N received nebivolol 5 mg once daily, and group M received metoprolol 50 mg once daily for 15 days in the preoperative period. Control patients did not use β-blocker therapy. Tissue samples of both left internal mammary artery (LIMA) and saphenous vein grafts were investigated for NO activity using immunohistochemical methods.

Results: Demographic characteristics and risk factors were similar between groups. We observed the highest NO activity in group N in both endothelial and vasa vasorum samples of LIMA and saphenous veins. NO activity of metoprolol group was similar to controls.

Conclusions: According to our results, we think that nebivolol may be safer and preferable in order to diminish graft spasm in patients undergoing coronary artery bypass graft surgery due to the NO-mediated vasodilating effect.

Article history: Received 3 July 2013, Accepted 2 November 2013, Available online 10 November 2013

Keywords: Beta blocker, Coronary artery bypass graft surgery, Metoprolol, Nebivolol, Nitric oxide

INTRODUCTION

Ischemic heart disease occurs as a result of mismatch between myocardial oxygen demand and vascular supply. Coronary artery bypass graft (CABG) surgery is a widely utilized treatment of ischemic heart disease depending on the clinical condition. However, graft spasm, especially in arterial conduits, and graft stenosis still creates a major problem in patients undergoing CABG surgery.[1] Graft spasm can present with angina, acute hemodynamic collapse, ST segment elevation, or ventricular fibrillation, or a combination of these additional factors. Insufficient blood flow through arterial grafts may also cause a "hypoperfusion syndrome" manifested by left ventricular failure, increasing pulmonary wedge pressure, and by cardiac arrest. According to the literature, its incidence varies between 0.8 and 1.3%.[2] However, the incidence and mortality rates may be underestimated because it is mainly the surviving cases that are reported, and an exact diagnosis can only be achieved with coronary angiography.[2]

β1-adrenergic receptor blockers have become a hallmark in the management of patients after acute myocardial infarction.[3] In contrast to conventional selective β1 adrenergic receptor antagonists such as metoprolol-succinate, the selective β1 adrenergic receptor blocker nebivolol has been shown to possess additional actions—stimulating endothelial cell nitric oxide (NO) production, in particular, which is thought to be mediated by β3-receptor activation and by interaction with the estrogen receptor.[3] The release of the endothelium-derived relaxing factor NO has been suggested to mediate vasodilatory properties of nebivolol because nebivolol-induced vasodilation is almost completely blocked by inhibitors of NO synthase.[4]

* Corresponding author. G. Ilhan, Recep Tayyip Erdogan University, Faculty of Medicine, Department of Cardiovascular Surgery, Islampaşa Mah, 53100 Rize, Turkey.

E-mail address: drgknilhan@yahoo.com (G. Ilhan).

1078-5884/$ — see front matter © 2013 Published by Elsevier Ltd on behalf of European Society for Vascular Surgery.

http://dx.doi.org/10.1016/j.ejvs.2013.11.003

Vasodilation effects based on endothelial NO liberation following treatment with nebivolol have been demonstrated in peripheral macrovessels and in human coronary microvessels.[5] In addition, nebivolol has been shown to cause an increase in stroke volume, associated with a reduction in vascular resistance, resulting in a maintained cardiac output despite reduced heart rate.[6] These different effects of NO, resulting in increasing blood flow and considerable advantages in terms of the hemodynamic profile on cardiac output, may also contribute to graft spasm after CABG surgery. However, this activity seems not to be a class effect of β-blockers. Yet, no clinical data on CABG patients are available, but a rabbit model of carotid venous bypass grafting indicates that nebivolol might decrease the development of intimal hyperplasia.[7]

The aim of this study was to investigate the effects of the vasodilating β-blocker nebivolol and the cardioselective β-blocker metoprolol on NO levels at vascular graft endothelium and vasa vasorum compared with controls in patients undergoing CABG surgery.

MATERIALS AND METHODS

This study was approved by the local institutional review board. Written informed consent was obtained from all participants. Fifty-five consecutive patients who underwent CABG surgery between January and March 2007 were randomly divided into three groups by simple randomization constructed with tables of random numbers: nebivolol group (group N, $n = 23$), metoprolol group (group M, $n = 16$), and control group (group A, $n = 16$). Group N received nebivolol 5 mg once daily, and group M received metoprolol 50 mg once daily for 15 days in the preoperative period. Control patients did not use β-blocker therapy. Tissue samples of both left internal mammary artery (LIMA) and saphenous vein grafts were investigated for NO activity using immunohistochemical methods.

Patient selection

Patients were evaluated by physical examination, laboratory tests, transthoracic echocardiography, electrocardiography, and coronary angiography. Hypertension was defined as a mean systolic blood pressure $\geq$140 mmHg, diastolic blood pressure $\geq$90 mmHg, and/or use of antihypertensive medications. Hyperlipidemia was defined as total cholesterol level $>$240 mg/dL (6.2 mmol/L), the current use of lipid-lowering treatment, or both. Patients with New York Heart Association (NYHA) class IV heart failure, left ventricular ejection fraction $\leq$30%, previous CABG surgery, and patients older than 75 years, requiring emergency surgery and inotropic support were excluded. Patients having additional cardiac (valvular or congenital) and systemic (chronic obstructive pulmonary disease, and renal and hepatic failure) pathologies were also excluded.

Surgery

Anesthetic technique was standard for all patients. General anesthesia and intratracheal intubation were done. Median sternotomy was performed under general anesthesia. LIMA was prepared in suitable patients. Saphenous veins were readied in patients requiring more than one graft. Vascular samples of 1 cm length were taken from LIMA and saphenous vein grafts prior to systemic heparin administration during either conventional or off-pump CABG surgery. Venous or arterial grafts other than LIMA and saphenous veins were not used. Following sampling surgical procedure was completed as usual. Surgical technique (off-pump or conventional) were not taken into consideration.

Immunohistochemistry

Sampled vessels were preserved in 10% formalin solution at room temperature. Afterwards samples of vascular wall and vasa vasorum were evaluated for NO activity. Immunohistochemical staining was performed using the goat ImmunoCruz Staining System (sc-2053; Santa Cruz Biotechnology, Santa Cruz, CA, USA). Primary antibody was inducible nitric oxide synthase epitope-specific rabbit antibody (0.5 mL for 200 ng/mL). Samples were evaluated using light microscopes after preparation. NO activity was scored according to histopathological findings.

Immunohistochemical expression was quantified and scored by assessing a proportion of percentage as an intensity score according to Allred's scoring protocol.[8] The intensity of the immunostaining in the arteries was graded semiquantitatively from 0 to 2, with 0 corresponding to the absence of staining, 1 corresponding to the intermediate staining, and 2 representing strong staining. The grading was performed by a single investigator, who was unaware of the clinical and hemodynamic data.

Statistical analysis

Data were analyzed using SPSS version 13.0 for Windows (SPSS, Chicago, IL, USA). A normal distribution of the quantitative data was checked using the Kolmogorov–Smirnov test.

Table 1. Demographic and clinical characteristics of patients.

	Group A[a]	Group M[b]	Group N[c]	*p*
Gender (M/F)	9/7	12/4	10/13	.14
Age (y)	64 ± 8.93	63.2 ± 9.13	60.1 ± 1.7	.63
Hypertension (mmHg)	6/16 (37.5%)	7/16 (43.8%)	14/23 (60.8%)	.31
Diabetes mellitus	9/16 (56.2%)	6/16 (37.5%)	7/23 (69.6%)	.26
Hyperlipidemia	7/16 (43.8%)	10/16 (62.5%)	13/23 (56.5%)	.55
Number of coronary grafts ($n = 1$)	2	0	7	.09
Number of coronary grafts ($n > 1$)	14	16	16	.43

Note. M = male; F = female.
[a] Control group.
[b] Metoprolol group.
[c] Nebivolol group.