

## Choice of medication for radial artery vasodilation in patients awaiting coronary artery bypass grafting

*Koroner arter bypass greftleme ameliyatına alınacak hastalarda radial arter vazodilatasyonu için ilaç seçimi*

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**Background:** In this study, the vasodilatory effects of calcium antagonists and beta-blockers were investigated.

**Methods:** After obtaining Faculty Ethics Committee approval and written informed consent from the patients, 72 adult patients (50 males, 27 females; mean age 62.9±9.3 years; range 37 to 75 years) who will undergo elective coronary artery bypass grafting (CABG) surgery were included in this study. We evaluated the vasodilatory effect of diltiazem alone (group 1), nifedipine alone (group 2), amlodipine alone (group 3), nebivolol alone (group 4) and nifedipine in combination with metoprolol (group 5). Seventy-seven patients who would undergo isolated CABG using radial artery were prospectively randomized to oral agents four or five days before operation. The dilatation of the lumen diameter and area of the radial artery were evaluated with high-resolution ultrasonography just before and 4-5 days after medical treatment.

**Results:** Diltiazem alone group (p=0.058) and nifedipine in combination with metoprolol group (p=0.067) did not show a significant increase in the lumen diameter and area after medical treatment compared to the pretreatment values. Statistically significant increases in lumen diameter and area were observed in nifedipine (p=0.007), amlodipine (p=0.003) and nebivolol (p=0.047) groups.

**Conclusion:** Our results demonstrate that calcium channel antagonists are not equally effective in radial artery vasodilatation. Nifedipine, amlodipine and nebivolol appear to be the most effective agents in reducing radial artery spasm. Nebivolol is a beta-blocker and also has a potent vasodilatory effect on radial artery vasospasm.

**Key words:** Coronary artery bypass grafting; hypertension/etiology; nitric oxide; radial artery.

**Amaç:** Bu çalışmada kalsiyum antagonistleri ve betablokörlerin vazodilatatör etkileri araştırıldı.

**Çalışma planı:** Fakülte Etik Kurul onayı ve hastaların yazılı bilgilendirilme onamı alındıktan sonra elektif koroner arter bypass greftleme (KABG) ameliyatı planlanan 72 erişkin hasta (50 erkek, 27 kadın; ort. yaş 62.9±9.3 yıl; dağılım 37-75 yıl) bu çalışmaya dahil edildi. Tek başına diltiazem (grup 1), tek başına nifedipinin (grup 2), tek başına amlodipinin (grup 3), tek başına nebivololün (grup 4) ve nifedipinin metoprolol ile kombinasyonunun (grup 5) vazodilatatör etkileri değerlendirildi. Radial arter kullanılarak izole KABG ameliyatına giden ardışık 77 hasta ileriye dönük olarak ameliyattan dört ila beş gün önce oral ajanlara randomize edildi. İlaç tedavisinden hemen önce ve tedaviden 4-5 gün sonra radial arterin lumen çapı ve alanındaki dilatasyonu yüksek çözünürlüklü ultrasonografi ile değerlendirildi.

**Bulgular:** Tek başına diltiazem grubu (p=0.058) ve metoprolol ile kombine edilen nifedipin grubu (p=0.067), ilaç tedavisinden önceki lümen çap ve alanları ile kıyaslandığında anlamlı bir artış göstermedi. Nifedipin (p=0.007), amlodipin (p=0.003) ve nebivolol (p=0.047) grubunda lümen çap ve alanında istatistiksel olarak anlamlı artışlar gözlemlendi.

**Sonuç:** Sonuçlarımız kalsiyum kanal antagonistlerinin radial arterin vazodilatasyonunda aynı derecede etkili olmadığını göstermektedir. Nifedipin, amlodipin ve nebivolol radial arter spazmının azaltılmasında en etkili ajanlar gibi görünmektedir. Nebivolol bir beta-blokerdir ve aynı zamanda radial arter vazospazmı üzerinde güçlü bir vazodilatör etkiye sahiptir.

**Anahtar sözcükler:** Koroner arter bypass greftleme; hipertansiyon/etyoloji; nitrik oksit; radial arter.

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The radial artery (RA) is increasingly used as a conduit for coronary artery bypass grafting (CABG) due to reports of long-term patency, accessibility, encouraging mid-term results and the need for additional conduits.<sup>[1-3]</sup> The potential disadvantage of the radial artery is its increased tendency to spasm because of its greater muscular content compared with other arteries.<sup>[4,5]</sup> Vasodilators such as calcium-channel antagonists, especially diltiazem, may be used to prevent perioperative and postoperative radial artery spasm.<sup>[1,6,7]</sup>

The use of a potent vasodilator with minimal side effects is an important parameter for the successful use of the radial artery as a conduit in CABG surgery. We investigated and reported the vasodilatory effect of calcium antagonists and beta-blockers in this study.

## PATIENTS AND METHODS

### Patients

After obtaining Faculty Ethics Committee approval and written informed consent, 72 adult patients (50 males, 27 females; mean age 62.9±9.3 years; range 37 to 75 years) with coronary artery disease who had been admitted to the Department of Cardiothoracic Surgery of Turgut Özal Medical Center for elective CABG were included in this randomized double-blind study. They were divided into five groups; group 1 was treated with diltiazem (90 mg/per day) alone, group 2 was treated with nifedipine (30 mg/per day) alone, group 3 was

treated with amlodipine (10 mg/per day) alone, group 4 was treated with nebivolol (5 mg/per day) alone and group 5 was treated with nifedipine (30 mg/per day) in combination with metoprolol (100 mg/per day). They were prospectively randomized to oral agents four or five days before operation. The exclusion criteria included emergent operation, unstable angina and the patients who stopped treatment because of side effects such as hypotension and bradycardia. The demographic data was similar in all groups as seen in table 1. The effect of each drug on the radial artery was evaluated after 4-5 days administration by a blinded evaluator.

### Radial artery measurements

An ultrasound device (color Doppler Acuson 128 XP/10 with 7-MHz linear transducer, (Acuson, Mountain View, CA, USA) was used for high-resolution ultrasound measurements and color Doppler images. The measurements of the radial artery lumen diameter were taken before and after drug administration by a blinded evaluator. For each patient, optimal radial artery images were obtained between 2 and 5 cm above the radial styloid. This location was marked, and all images were obtained at the same location.

### Statistical methods

All analyses were conducted with SPSS 10.0 software (SPSS Inc, Chicago, Illinois USA). Continuous variables were presented as mean ± standard deviation; categorical

**Table 1. Patients demographics**

	Group 1 diltiazem (n=15)		Group 2 nifedipine (n=16)		Group 3 amlodipine (n=15)		Group 4 nebivolol (n=15)		Group 5 nifedipin+metaprolol (n=16)		p
	n	Mean±SD	n	Mean±SD	n	Mean±SD	n	Mean±SD	n	Mean±SD	
Gender (men)	12		10		12		7		9		NS
Age		64±10		627±6		62±11		66±8	6	1±10	NS
Smoking	7		7		5		4		7		NS
Hypertension	5		10		4		6		8		NS
Hyperlipidemia	9		6		4		12		7		NS
Obesity	5		4		3		6		5		NS
COPD	4		0		1		3		1		NS
Diabetes	3		3		3		4		4		NS
Previous MI	9		14		10		10		9		NS
Body mass index		25±3		25±4		24±4		25±4		26±4	NS
Body surface area		1.7±0.2		1.7±0.2		1.8±0.3		1.7±0.1		1.8±0.3	NS
LVEDP		18±5		18±6		16±4		16±5		18±5	NS
LVPS		10±2		11±2		9±1		10±2		10±2	NS
Systolic pressure		119±2		116±2		124±2		114±2		118±2	NS
Diastolic pressure		70±8		69±9		73±1		72±8		71±9	NS
Heart rate		78±7		77±1		78±1		78±8		76±9	NS
# of vessel disease		2.6±0.6		2.4±0.7		2.2±0.8		2.6±0.6		2.4±0.8	NS

COPD: Chronic obstructive pulmonary disease; MI: Myocardial infarction; LVEDP: Left ventricle end diastolic pressure; LVPS: Left ventricle performance score; SD: Standard deviation; NS: Non significant.

**Table 2. Radial artery diameter before and after treatment (mm)**

	Group 1	Group 2	Group 3	Group 4	Group 5
	diltiazem	nifedipine	amlodipine	nebivolol	nifedipine+metoprolol
	Mean±SD	Mean±SD	Mean±SD	Mean±SD	Mean±SD
Before treatment	3.5±0.7	3.3±0.7	3.6±0.6	4.2±0.8	3.0±0.7
After treatment	3.6±0.6	3.6±0.7	4.0±0.6	4.5±0.7	3.2±0.9
<i>p</i>	0.058	<b>0.007</b>	<b>0.003</b>	<b>0.047</b>	0.067

variables were presented as numbers. Normality for continued variables in groups was determined by the Shapiro Wilk test. Because the variables did not show normal distribution ( $p < 0.05$ ), comparisons of groups were performed with the Kruskal-Wallis analysis of variance test and pre-post comparisons with paired observations were analyzed by using the Wilcoxon test. The Fisher's exact test and Pearson Chi-square test were used for comparison of discrete variables between studied groups. In all statistical comparisons the *p* values  $< 0.05$  were reported significant.

## RESULTS

The results for the demographic features in the five treatment groups are shown in table 1. There were no statistically significant differences among groups with mean age, mean body surface area, mean body mass index, mean left ventricle end diastolic pressure and left ventricle performance score.

Table 2 summarizes the radial artery diameter before and after treatment (mm) and table 3 summarizes the radial artery cross-sectional area ( $\text{mm}^2$ ) before and after treatment. The respective mean pre-treatment and post-treatment RA diameter in each group follows: 3.5±0.7 and 3.6±0.6 mm in the diltiazem group ( $p=0.058$ ); 3.3±0.7 and 3.6±0.7 mm in the nifedipine group ( $p=0.007$ ); 3.6±0.6 and 4.0±0.6 mm in the amlodipine group ( $p=0.003$ ); 4.2±0.8 and 4.5±0.7 mm in the nebivolol group ( $p=0.047$ ) and 3.0±0.7 and 3.2±0.9 mm in the nifedipine + metoprolol group ( $p=0.067$ ). The respective mean pre-treatment and post-treatment RA cross-sectional area in each group follows: 0.15±0.22 and 0.16±0.23  $\text{mm}^2$  in the diltiazem group ( $p=0.05$ ); 0.09±0.05 and 0.14±0.13  $\text{mm}^2$  in the nifedipine group ( $p=0.004$ ); 0.11±0.04 and 0.14±0.04  $\text{mm}^2$  in the amlo-

dipine group ( $p=0.002$ ); 0.14±0.06 and 0.17±0.05  $\text{mm}^2$  in the nebivolol group ( $p=0.069$ ) and 0.07±0.03 and 0.08±0.04  $\text{mm}^2$  in the nifedipine + metoprolol group ( $p=0.103$ ).

As shown, when compared the radial artery diameter and cross-sectional area before and after the treatment the significant and most increased values were found in nifedipine, amlodipine and nebivolol groups. In diltiazem group the radial artery diameter and cross-sectional area increased but it was not statistically significant. The radial artery diameter and cross-sectional area were increased also in nifedipine + metoprolol group but it was not statistically significant. When compared the results of nifedipine, amlodipine and nebivolol groups there were no differences found.

## DISCUSSION

The radial artery is increasingly used as a conduit for CABG due to reports of long-term patency, accessibility, encouraging mid-term results and the need for additional conduits.<sup>[1-3]</sup> There are also some disadvantages of using the radial artery as a conduit; it is prone to vasospasm in the early postoperative period.<sup>[4,8,9]</sup> Neurohormonal system activation, which includes elevated endothelin and norepinephrine, occurs after CABG and may contribute to early RA vasospasm.<sup>[10-15]</sup> The main subject is the choice of vasodilators used on radial conduits.<sup>[16-19]</sup> In our study we compared the effects of diltiazem, nifedipine, amlodipine, nebivolol and nifedipine + metoprolol for radial artery spasm when used preoperatively. There are three kinds of calcium-channel antagonists which affect voltage-sensitive calcium channels- dihydropyridines, benzothiazepins and phenylalkylamines.<sup>[20]</sup> Both nifedipine and amlodipine have dihydropyridine rings that may be responsible for their

**Table 3. Radial artery cross-sectional area before and after treatment ( $\text{mm}^2$ )**

	Group 1	Group 2	Group 3	Group 4	Group 5
	diltiazem	nifedipine	amlodipine	nebivolol	nifedipine+metoprolol
	Mean±SD	Mean±SD	Mean±SD	Mean±SD	Mean±SD
Before treatment	0.15±0.22	0.09±0.05	0.11±0.04	0.14±0.06	0.07±0.03
After treatment	0.16±0.23	0.14±0.13	0.14±0.04	0.18±0.05	0.08±0.04
<i>p</i>	0.052	<b>0.004</b>	<b>0.002</b>	<b>0.049</b>	0.103

SD: Standard deviation.

increased vascular selective properties, and this class of calcium channel antagonist also produces less severe effects on myocardial conduction and activation.<sup>[20-24]</sup> Diltiazem is a 1,5-benzothiazepine that binds to a subunit of L-type calcium channel.<sup>[19]</sup> L-type blockade in the heart results in negative inotropic and chronotropic effect that induces bradycardia, especially when used with beta-blockers.<sup>[17]</sup>

Nebivolol is a  $\beta$ 1-selective adrenergic receptor antagonist, which is also the precursor of nitric oxide. Nitric oxide is a potent vasodilator which is released from endothelial cells of arteries. Metoprolol is a beta-blocker which can be used for management of ischemic heart failure in combination with calcium channel blockers.

As shown in table 2 and 3, when comparing the radial artery diameter and cross-sectional area before and after treatment the significant and most increased values were found in the nifedipine and amlodipine groups. When comparing the results of nifedipine and amlodipine groups there were no significant differences found. These results were concordant with the results reported in the literature.<sup>[20-24]</sup>

The radial artery diameter and cross-sectional area were also increased in the nebivolol group and it was statistically significant, with equal increases in radial artery diameter and cross-sectional areas compared with the results of the nifedipine and amlodipine groups. Nebivolol produces vasodilation in the human forearm vascular bed via the L-arginine/nitric oxide pathway.<sup>[25]</sup> For the peripheral vasodilator effects of nebivolol, prospective and wide studies must be done. Nebivolol can also be used as part of a combined ischemic and hypertension therapy. Metoprolol is a beta-blocker which can be used for management of ischemic heart failure in combination with calcium channel blockers. This was the basis for treating a group of our patients with metoprolol and nifedipine combination. In this group the radial artery diameter and cross-sectional area were increased but it was not statistically significant. Still and all, we can also use nifedipine + metoprolol combination therapy in coronary artery disease patients undergoing CABG without any radial spasmodic side effects.

In the diltiazem group the radial artery diameter and cross-sectional area were also increased but it was not statistically significant. Diltiazem's advantage is its infusion form and today most clinics use diltiazem infusion routinely to prevent perioperative radial artery spasm and cardiac rhythm control.

If the patient populations have preoperative waiting times, the preoperative therapy with these drugs will increase the activity of perioperative and postoperative

vasodilator treatment. For the vasodilator treatment of patients who had radial artery as a conduit for CABG we suggest the use of nifedipine and amlodipine from the calcium-channel antagonist group because of their more effective results and nebivolol from the beta-blocker group, which has an unquestionable place in postoperative CABG treatment as an alternative. Further investigations should be done for evaluating the peripheral vasodilator effects in the human forearm vascular bed via the L-arginine/nitric oxide pathway and beta-blocker effects in treatment of patients who had radial artery as a conduit for CABG with a greater number of patients and long treatment period. Although we used nebivolol alone in our study, the combination treatment with nifedipine and amlodipine may have better results.

#### Declaration of conflicting interests

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

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