

The comparative effects of esmolol and amiodarone on isolated coronary artery bypass grafts

Demet ÖZKARAMANLI GÜR^{1*}, Ozcan GÜR², Selami GÜRKAN²

¹Department of Cardiology, Faculty of Medicine, Namık Kemal University, Tekirdağ, Turkey

²Department of Cardiovascular Surgery, Faculty of Medicine, Namık Kemal University, Tekirdağ, Turkey

Received: 16.02.2018 • Accepted/Published Online: 19.08.2018 • Final Version: 31.10.2018

Background/aim: Esmolol and amiodarone are two most commonly used antiarrhythmic drugs in coronary artery bypass grafting (CABG) surgery. Nevertheless, blockade of beta-2 receptors by increasing doses raise concerns about possible vasospasms. We studied the vasoactive effects of amiodarone and esmolol on left internal mammary artery (LIMA), radial artery (RA), and saphenous vein (SV) grafts.

Materials and methods: After determining the presence of functional smooth muscle and endothelial layers, the responses of submaximally precontracted graft samples were recorded in a tissue bath system. A total of 96 graft samples from 40 patients were used: 16 LIMA, 16 RA, and 16 SV grafts for each drug. Esmolol and amiodarone were added to reservoirs separately, starting from a concentration of 10⁻⁸ M until a concentration of 10⁻⁴ M.

Results: Although both drugs caused vasodilatation, amiodarone exhibited a more potent vasodilatory effect than esmolol ($P < 0.0001$ for LIMA, $P = 0.0128$ for RA, and $P < 0.0001$ for SV). The vasodilatation rates with esmolol were $48.99 \pm 2.28\%$ in LIMA, $49.77 \pm 3.03\%$ in RA, and $41.90 \pm 4.05\%$ in SV grafts and with amiodarone they were $71.65 \pm 5.18\%$ in LIMA, $58.61 \pm 5.87\%$ in RA, and $65.07 \pm 4.09\%$ in SV grafts.

Conclusion: This in vitro study revealed that even increasing doses of both drugs induce vasodilatation of CABG grafts, with amiodarone having a more potent vasodilatory effect than esmolol.

Key words: Amiodarone, esmolol, coronary artery bypass grafts, tissue bath system

1. Introduction

Cardiac arrhythmias are among the most common complications of coronary artery bypass grafting (CABG) surgery (1). Post-CABG atrial fibrillation (AF) has an incidence rate of 15% to 50%, while the incidence rate of nonsustained ventricular tachycardia is 18% to 58% (2,3). Esmolol and amiodarone are the two most commonly used drugs in the perioperative period for treatment of both ventricular and supraventricular arrhythmias. Esmolol is a short-acting parenteral beta-blocker and a Vaughan Williams class II antiarrhythmic. Amiodarone is a unique class III antiarrhythmic. Recent studies recommend their administration preoperatively for prophylaxis of postoperative AF, yielding more frequent utilization (4–6).

The preference of one drug over another, however, is argumentative. Although amiodarone is an established peripheral vasodilator, it also possesses noncompetitive beta-blocker features (6). The vasoactive effects of increas-

ing the doses of amiodarone and esmolol on coronary conduits are questionable due to reported cases of amiodarone-induced coronary spasm and the fact that increasing doses of 'cardioselective' beta-blockers have vasospastic effects on the peripheral vasculature (7). To the best of our knowledge, there is no study that assesses whether the use of these drugs carries the risk of vasospasm and the early failure of CABG grafts. In this study, we aimed to assess this risk and compare the in vitro effects of esmolol and amiodarone on the left internal mammary artery (LIMA), radial artery (RA), and saphenous vein (SV) grafts in an in vitro tissue bath system.

2. Materials and methods

Forty consecutive patients (24 male, 16 female) undergoing CABG for 3-vessel disease were enrolled in the study after obtaining approval from the local ethics committee. Patients with diabetes mellitus, peripheral

* Correspondence: dozkarm@yahoo.com

arterial disease, chronic renal failure, severe valvular or ventricular dysfunction defined by an ejection fraction of <50%, and prior beta-blocker or amiodarone use were excluded. An equal number of patients were assigned to each group: 20 patients (12 males and 8 females) for the esmolol group and 20 patients (12 males and 8 females) for the amiodarone group. All patients gave informed consent and took similar medications defined by the cardiovascular team before the surgery. The vascular grafts were harvested as described previously (8). The graft samples were not treated with any pharmacological agent during or after harvesting. The tissue samples from the LIMA, RA, and SV grafts obtained during CABG were placed into 4 °C Krebs solution (with a molar composition of 122 mmol/L NaCl, 5 mmol/L KCl, 1.25 mmol/L CaCl₂, 25 mmol/L NaHCO₃, 1.2 mmol/L MgSO₄, 1.0 mmol/L KH₂O₄, and 11.5 mmol/L glucose) and transported to the vascular laboratory where they were sliced into vascular rings 3 mm wide and suspended in a tissue bath system. Only viable vascular rings with functional endothelium and smooth muscle layers were used in the study. Out of 96 viable graft samples, an equal number of grafts was studied for each drug. More specifically, 16 LIMA, 16 RA, and 16 SV samples were studied in the esmolol group and 16 LIMA, 16 RA, and 16 SV samples were studied in the amiodarone group.

2.1. Tissue bath system

The reservoirs in the tissue bath system were filled with 20 mL of 37 °C Krebs solution, which was continuously oxygenated with a gas mixture composed of 95% O₂ and 5% CO₂ and changed every 20 min to keep the tissues alive. The upper ends of the vascular rings were attached to the force transducer and the lower ends were kept stable. The viability and contractile function of the vascular smooth muscle layer were tested through vasoconstrictor response to 10⁻⁶ M phenylephrine, a potent α₁ agonist, added to the bath system. Next, 10⁻⁷ M carbachol (Sigma-Aldrich), a cholinergic agonist, was used to induce endothelium-dependent vasodilatation, which consequently proved the presence of an intact endothelial layer. After determining the functionality of the tissue samples, those with both functional muscular and endothelial layers were washed thoroughly and kept in Krebs solution without any drug for 30 min before the experiment.

Before adding the study drug into the bath system, the grafts were submaximally constricted with 10⁻⁶ M phenylephrine to make any vasodilator or vasoconstrictor responses to esmolol and amiodarone obvious.

Esmolol (Brevibloc, premixed 250 mL, Eczacıbaşı-Baxter, İstanbul, Turkey) was added into the reservoir to achieve a concentration of 10⁻⁸ M, and the dose was incremented half logarithmically in 2-min intervals until its concentration in the reservoir reached 10⁻⁴ M. The

effective plasma concentration of esmolol is 1.56 × 10⁻⁴ to 9.93 × 10⁻⁴ mg/mL, corresponding to 5.3 × 10⁻⁷ M to 3.4 × 10⁻⁶ M esmolol composition in the tissue bath. The responses of the vascular rings to the increased doses of esmolol were recorded.

Amiodarone (Cordarone, 150 mg IV amp, Sanofi Aventis, İstanbul, Turkey) was studied in the graft samples using the same protocol as that used for esmolol. The concentration of amiodarone in the reservoir was increased from 10⁻⁸ M to 10⁻⁴ M half logarithmically in 2-min intervals. The therapeutic plasma level of amiodarone, which was defined as 2.5 µg/mL, is equivalent to 3.67 × 10⁻⁶ M tissue bath concentration and was also covered in the study. The data were transferred to a computer with the help of the Transducer Acquisition System (MAY IOBS 99, FDT 05, Ankara, Turkey) and stored using MAY-MASTER MP36 analysis software. Finally, the concentration-response curves were constructed for each drug.

2.2. Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics 20 for Mac (IBM Corp., Armonk, NY, USA) and GraphPad Prism Version 4 software (GraphPad Software Inc., La Jolla, CA, USA). The continuous variables were presented as mean ± standard deviation (SD) and categorical variables were represented as percentages. The continuous variables was compared by independent samples t-test, and the categorical variables, such as smoking status, hypertension, and hyperlipidemia, were compared by chi-square test. The analysis of the data regarding the vascular responses to the drugs was conducted by one-way ANOVA, and the concentration-response curves were constructed by GraphPad Prism software. P < 0.05 was considered to be statistically significant.

3. Results

No significant differences were observed between the demographic variables of the patients in the esmolol and amiodarone groups. There were equal numbers of male and female patients in each group with similar cardiovascular risk factors (Table 1). The vasodilatation responses to esmolol and amiodarone were recorded in submaximally precontracted graft samples. Table 2 shows the ratio of vasodilatation responses and log EC₅₀ values of different graft samples treated with the two drugs. Log EC₅₀, which is the logarithmic half maximal effective concentration, represents the potency of the drugs.

When the samples of LIMA, RA, and SV grafts were analyzed in terms of their response to esmolol treatment, all of the graft samples exhibited similar amounts of vasodilatation. The vasodilatation rates with esmolol were 48.99 ± 2.28% in LIMA, 49.77 ± 3.03% in RA, and 41.90 ± 4.05% in SV grafts. The log EC values of esmolol in the LIMA, RA, and SV grafts were -5.810, -5.500, and

Table 1. The demographic characteristics of patients.

	Esmolol group	Amiodarone group	P-value
Age (min-max)	64.5 ± 8.9 (51-82)	64.3 ± 9.5 (46-80)	0.93
Smoking status	3 (15%)	5 (25%)	0.43
Hypertension	18 (90%)	14 (70%)	0.11
Hyperlipidemia	16 (80%)	19 (95%)	0.15

Independent samples t-test was used to compare age. Smoking status, hypertension, and hyperlipidemia were compared by the chi-square test

-5.440, respectively. There were no statistically significant differences among the graft types.

The vasodilatation rates with amiodarone were 71.65 ± 5.18% in LIMA, 58.61 ± 5.87% in RA, and 65.07 ± 4.09% in SV grafts. The log EC values of amiodarone in LIMA, RA, and SV grafts were -5.290, -5.090, and -4.840, respectively. Although LIMA graft samples had numerically higher vasodilatation rates, there were no significant differences among the graft types. Between the two drugs, on the other hand, amiodarone exhibited a more potent vasodilatory effect in all three graft types than esmolol (P < 0.0001 for LIMA, P = 0.0128 for RA, and P < 0.0001 for SV grafts) (Figure).

4. Discussion

In this study, we addressed the question of whether increasing the doses of commonly used drugs, esmolol (a cardioselective beta-blocker) and amiodarone (a vasodilator with noncompetitive beta-blocker features), induces vasospasm in arterial and venous conduits. This question has two implications:

Table 2. Vasodilatation responses to esmolol and amiodarone.

Graft type	Esmolol Vasodilatation Log EC		Amiodarone Vasodilatation Log EC		P-value
	Log EC		Log EC		
LIMA	48.99 ± 2.28	-5.81	71.65 ± 5.18	-5.29	0.0001
RA	49.77 ± 3.03	-5.50	58.61 ± 5.87	-5.09	0.0128
SV	41.90 ± 4.05	-5.44	65.07 ± 4.09	-4.84	0.0001

LIMA: Left internal mammary artery, RA: radial artery, SV: saphenous vein, Log EC: logarithmic half-maximal effective concentration.

1) Unfavorable vasospastic effect of either drug can result in fatal graft failure and thus should be avoided.

2) Any favorable effect, such as vasodilatation, may facilitate the selection between the two drugs in the treatment of dysrhythmias.

Our study showed that both drugs induce dose-dependent vasodilatation of all CABG grafts, including RA grafts. However, the vasodilatory effect of amiodarone was significantly higher than that of esmolol, which is of particular benefit in the perioperative period.

We used esmolol, an ultrashort-acting second-generation beta-blocker, as the prototype beta-blocker for several reasons. As an antiarrhythmic and an antihypertensive drug, it has an elimination half-life of 9 min that makes it a favorable choice in immediate postoperative patients when rapid recovery from beta-blockage is crucial (9,10). Nevertheless, its use is not confined to the postoperative period since trials demonstrated that esmolol reduces myocardial oxygen consumption, metabolic demands, and thus myocardial damage when given before cardioplegia or as an additive to cardioplegia solutions (11). Although it exerts primarily a beta-1 selectivity at low doses, higher doses carry the

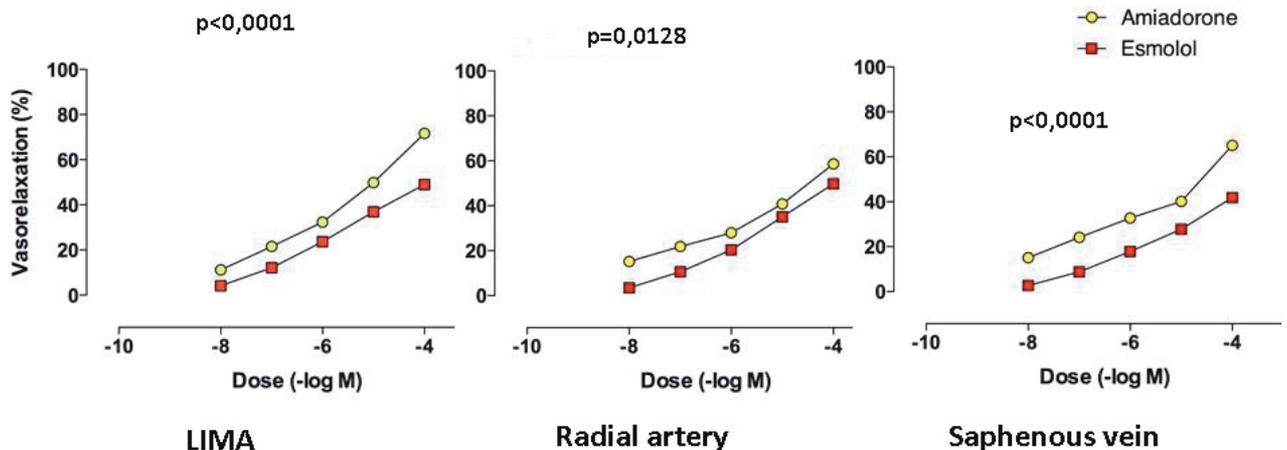


Figure. Concentration-response curves of esmolol and amiodarone.

risk of beta-2 receptor blockade provoking coronary and vascular spasm. Beta-blockers are shown to attenuate the expected coronary vasodilatory response to exercise and enhance the coronary vasoconstrictor response to cold stress (12,13).

Esmolol also lacks the peripheral vasodilatory features of the third-generation beta-blockers (14). In our study, we showed that esmolol had vasodilatory effects on all CABG grafts. This effect is particularly obvious in arterial grafts and is of interest for RA grafts, since this conduit is notorious for its susceptibility to vasospasms. The possible mechanism of this acute vasodilatory effect is nitric oxide (NO)-dependent vasodilatation as explained by Arnalich-Montiel et al., who demonstrated that esmolol induces acetylcholine-mediated NO-dependent vasodilatation in the coronaries of hypertensive rats (15). Similarly, in an in vivo human study of coronary arteries, esmolol infusion was shown to increase the minimal luminal diameter and decrease the endothelial shear stress in patients with moderate coronary stenosis (16). Our findings support the literature and reveal that the antiischemic features of esmolol may go beyond the reduction of heart rate, cardiac index, or ejection fraction and may be related to coronary vasodilatation as well.

Amiodarone, a class III antiarrhythmic agent with sodium, calcium, and potassium channel blocking properties, is also a noncompetitive alpha- and beta-blocker (17). In contrast to esmolol, it has a long elimination half-life of 25 to 50 days and established coronary and peripheral vasodilatory effects. The exact mechanism of vasodilatation, however, is not completely understood. Radhino et al. showed that amiodarone does

not modify smooth muscle contraction in rabbit aorta strips and proposed that the vasodilatory action is not through calcium channel blockade (18). Animal studies of amiodarone have shown that the coronary vasodilatation induced by amiodarone is highly dependent on NO. Additionally, amiodarone caused endothelium-dependent vasodilatation in human vessels both in vivo and in vitro (19,20). Polysorbate 80, the solvent of the intravenous amiodarone formulation, is also known to contribute vasodilatory effects (21).

While both drugs are thought to provoke NO-mediated vasodilatation, the significantly higher potency of amiodarone over esmolol can be attributed to its additional antioxidative and antiinflammatory features and to its vasodilatory solvent (22).

Although LIMA grafts are known to possess better endothelial function and more NO release when compared to the other grafts, there was no statistically significant difference among specific graft types with regard to amount of vasodilatation in the esmolol or amiodarone groups (23). In other words, LIMA grafts did not perform better than other grafts. The explanation seems to be related to the distal and more spastic segment of LIMA that was used for the purpose of this study.

This in vitro study showed that increasing doses of both esmolol and amiodarone caused vasodilatation in all CABG graft samples. Considering the more potent vasodilatory effect of amiodarone, it may be a more favorable antiarrhythmic drug than esmolol.

Although in vitro data suggest that both drugs induce vasodilatation, their safety and efficacy in the perioperative period should be further addressed in clinical trials.

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