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Effects of carvedilol on vascular reactivity in human left internal mammary artery

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Abstract. – OBJECTIVE: Surgical treatment choice for coronary artery disease is coronary artery bypass grafting (CABG) surgery. Left internal mammary artery (LIMA) is frequently used as an arterial graft in CABG operations. Perioperative spasm of LIMA can result in increased morbidity and mortality. Pharmacological interventions are routinely used for prevention and treatment of LIMA spasm. In this study, we aimed to investigate the effects of carvedilol, an alpha- and beta-adrenergic receptor blocker, on responses to endogenous vasoconstrictors which play a role in graft spasm and the possible interaction between carvedilol and diltiazem/papaverine which are vasodilators commonly used in CABG surgery.

PATIENTS AND METHODS: Isolated LIMA rings collected from patients undergoing CABG operation were suspended in an organ bath. Concentration-dependent responses to norepinephrine (NE), serotonin (5-HT) and diltiazem were examined before and after carvedilol incubation (10^{-6} M, 1 hour). Maximum relaxation response to papaverine (10^{-4} M) was compared in LIMA rings incubated with 0.05% dimethyl sulfoxide (DMSO, placebo) or carvedilol (10^{-6} M).

RESULTS: Carvedilol did not affect the maximal contractile response to NE; however, it significantly reduced the sensitivity of LIMA to NE. Carvedilol increased contractile response and sensitivity to 5-HT. Promisingly, carvedilol increased the vasodilatory effects of diltiazem and papaverine.

CONCLUSIONS: Our study suggests that carvedilol may be administered perioperatively in combination with diltiazem or papaverine to prevent or resolve LIMA graft spasm.

Key Words:
Carvedilol, Internal mammary artery, Vascular reactivity, Human.

Introduction

Coronary artery bypass grafting (CABG) surgery is the main revascularization strategy in selected patients who have coronary artery disease[1]. Spasm of the arterial graft in CABG surgery is a major clinical problem, and it must be managed properly to avoid fatal scenarios. These spasms have a complex underlying mechanism, which involves type of the graft, mechanical and/or nerve stimulus, vasoconstrictor substances[2], hypothermia[3], and metabolic diseases[4]. Selection of the graft is one of the most important steps for CABG surgery. Basically, there are three types of arteries that are classified functionally as somatic, splanchnic, and limb arteries[5]. Among these, somatic arteries have the most favorable endothelial functions[6]. From this aspect, left internal mammary artery (LIMA) is the most frequently used artery which has long-term patency rate and survival benefits.

Spasm of LIMA can be observed during preparation of the graft, or after coronary anastomosis due to surgical stimulus[7]. Perioperative LIMA spasm can cause hemodynamic instability and transmural anterior myocardial infarction, which increases perioperative mortality and morbidity[8,9]. Although there is no standardized strategy for the management of the spasm of arterial grafts[10], pharmacological interventions and mechanical dilatation of LIMA are frequently used methods. The most commonly used topical pharmacological agents are papaverine, nitroglycerine, and diltiazem, which were evaluated in many previous studies[11-14]. In this respect, carvedilol may be a promising agent to prevent LIMA spasms in CABG surgeries.

Carvedilol is a lipophilic vasodilator and a non-selective β-blocker. Carvedilol is well-tolerated as it lacks intrinsic sympathomimetic activity[15]. This third generation β-blocker inhibits binding of norepinephrine (NE) to β_1-adrenergic and β-$_2$-adrenergic receptors as traditional β-blockers do. Moreover, apart from the traditional β-blockers it also inhibits binding of NE to α_1-adrenergic receptors[16,17]. As a consequence, it has a superior hemodynamic effect by both maintaining cardiac output and decreasing β-adrener-

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gic tonus[18]. In addition to its antihypertensive benefits, carvedilol also increases coronary flow. Thus, it is indicated in patients with coronary artery disease or patients who had myocardial infarction[19-21]. The predominant α-adrenergic receptor subtype is the α_1-subtype in this artery[22]. Since carvedilol affects both α- and β-adrenergic receptors, it has a potential to resolve LIMA spasms complicating CABG surgeries.

The aim of this study is to evaluate the effects of carvedilol on endogenous vasoconstrictors NE and serotonin (5-HT), which are both proven to cause graft spasm of LIMA. Diltiazem or papaverine is frequently used as vasodilator agent in clinical practice to prevent and treat graft spasm. Therefore, possible interactions between carvedilol and diltiazem or papaverine were also evaluated in this study.

Patients And Methods

Selection of Patients

The remaining segments of LIMA from patients who had undergone CABG surgery were used in organ chamber experiments. The mean age of the patients was 72±2. Since diabetes, calcium channel blockers and beta-blockers may affect the results, diabetic patients and patients who had used calcium channel blockers and/or beta-blockers in 48 hours before surgical intervention were excluded.

Preparation of Vessels

The vessel specimen was harvested without using any vasodilatory agents and placed immediately into cold (4°C) Dulbecco's Modified Eagle's Medium/F12 (DMEM/F12) cell culture medium and transferred to the laboratory. The vessels were cleaned off adherent connective tissues and cut into rings of 2-3 mm in length. The endothelial layers of the rings were gently removed by scratching with straight forceps in order to exclude the effects of endothelium-derived relaxant and/or hyperpolarizing factors. Four rings from each artery segment were used. LIMA rings were mounted on L-shaped stainless steel hooks and suspended in 10 ml organ chambers (PanLab, Barcelona, Spain) containing Krebs buffer (pH=7.4, composition in mM: NaCl, 118; KCl, 4.7; $CaCl_2$, 2.5; KH_2PO_4, 1.2; $MgSO_4$, 1.2; $NaHCO_3$, 25; glucose, 11.1). The solution was continuously gassed with 95% O_2 and 5% CO_2, and kept at 37°C. LIMA rings were gradually stretched to resting tension of 2 g, which was previously determined as optimal resting tension based on the length-tension relationship. Rings were then allowed to equilibrate for 1 hour during which buffer solution was changed every 15 min. Contractile force changes were measured with an isometric force transducer (ADInstruments, Colorado Springs, CO, USA) and recorded by a computer program (LabChart 7.0, ADInstruments, Colorado Springs, CO, USA).

At the end of the stabilization period, rings were constricted with NE ($10^{-5.5}$ M), and response to acetylcholine (ACh; 10^{-6} M) was measured to assess endothelium-dependent relaxation. Graft segments that were confirmed to be lacking functional endothelium were then subjected to different experimental protocols explained below. Each agonist was washed out by changing the chamber solution three times within 30 min before addition of the next agonist throughout the experiment.

Experimental Protocol

To study the effects of carvedilol on endogenous vasoconstrictors that are thought to play a role in graft vasospasm, concentration-dependent NE (10^{-9}-10^{-4} M) or 5-HT (10^{-9}-$10^{-4.5}$ M) responses were obtained in vessel segments before and after 10^{-6} M carvedilol incubation (1 hour). Since carvedilol was dissolved in dimethyl sulfoxide (DMSO), concentration-dependent contractile response to NE (10^{-9}-10^{-4} M) was also determined in the absence or presence of DMSO (0.05%, v/v, 1 hour) in another ring to serve as control. To study the effects of concurrent use of carvedilol with diltiazem, which is clinically used for the treatment of graft spasm, concentration-response curves to diltiazem (10^{-9}-10^{-4} M) were taken in rings pre-contracted with NE ($10^{-5.5}$ M) before and after 10^{-6} M carvedilol incubation (1 hour). Lastly, relaxation response to papaverine (10^{-4} M) in arteries pre-contracted with NE ($10^{-5.5}$ M) was taken. All drugs were dissolved in distilled water; except for carvedilol which was dissolved in DMSO, and further diluted with 0.9% NaCl as needed. All chemicals except diltiazem (Diltiazem, Mustafa Nevzat, Istanbul, Turkey) were purchased from Sigma-Aldrich Co., St. Louis, MO, USA.

Ethics

The experimental protocol was approved by the Ethical Committee of Izmir University (Protocol Number: 2016/57). The research was carried out in accordance with Declaration of Helsinki of the World Medical Association. Informed consent was obtained from all individual participants included in the study.

Statistical Analysis

All data were expressed as mean ± SEM. $p \leq 0.05$ was considered statistically significant. Means were compared by paired Student's t-test. Values of maximal effect (E_{max}) and 50% effective concentration (EC_{50}) were derived for each cumulative concentration-response curve with iterative non-linear curve fitting (GraphPad Prism 5, La Jolla, CA, USA). The means of the negative logarithm of EC_{50} values (pD_2 values) were compared. All contraction responses were normalized with dry weight of the rings. Relaxation responses were normalized to single dose NE pre-contraction.

Results

Effect of Carvedilol on Norepinephrine-Induced Contractions

Incubation of LIMA rings with carvedilol (10^{-6} M) for 1 hour reduced contractile response to NE at concentrations of 10^{-5} M and $10^{-5.5}$ M ($p \leq 0.01$ and $p \leq 0.05$, respectively). However, carvedilol did not affect maximal contractile response to NE (Figure 1). On the other hand, carvedilol significantly reduced sensitivity to NE (NE pD_2 values before and after carvedilol incubation: 5.12± 0.15 and 2.22±0.84, respectively, $p \leq 0.05$).

In control arteries, DMSO (0.05%, v/v) incubation did not change NE-induced maximum contraction response (0.25±0.04 g/mg contraction and 0.32±0.03 g/mg contraction before and after DMSO incubation, respectively).

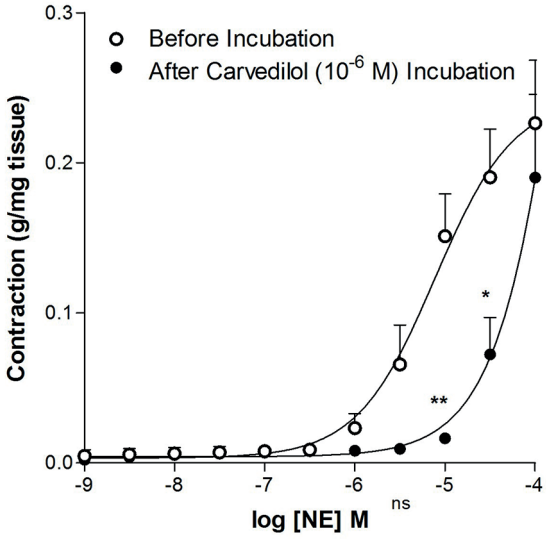

Figure 1. Effects of carvedilol incubation on NE-induced contractions. Cumulative dose-response curves to NE (10^{-9}-10^{-4} M) were determined before (○) and after (●) carvedilol incubation (10^{-6} M, 1 hour) (n=6). Data are expressed as mean ± SEM. *$p \leq 0.05$, ** $p \leq 0.01$: before vs after incubation; Paired Student's *t*-test.

Effect of Carvedilol on Serotonin-Induced Contractions

Incubation of LIMA rings with carvedilol (10^{-6} M) for 1 hour, increased maximum contractile response to 5-HT ($p \leq 0.05$, Figure 2). Also, carvedilol significantly increased sensitivity to 5-HT (pD_2 values before and after carvedilol incubation: 5.42± 0.35 and 5.99±0.27, respectively, $p \leq 0.05$).

Effect of Carvedilol on Diltiazem-Induced Relaxations

Incubation of LIMA rings with carvedilol (10^{-6} M) for 1 hour increased maximum relaxation response to diltiazem ($p \leq 0.01$, Figure 3).

Effect of Carvedilol on Papaverine-Induced Relaxations

Incubation of LIMA rings with carvedilol (10^{-6} M) for 1 hour, increased relaxation response to papaverine when compared to placebo incubation group ($p \leq 0.01$, Figure 4).

Discussion

The results of this study revealed that carvedilol decreases the sensitivity of LIMA to NE; thus, it might decrease the incidence of LIMA graft spasm. We also showed that carvedilol increases the vasodilator effects of routinely used anti-spasmogenic drugs diltiazem and papaverine on LIMA. By these characteristics, preoperative administration of carvedilol until achieving maximal serum doses may provide favorable outcomes during and after CABG surgery.

Nowadays, LIMA grafts are the most frequently used grafts in CABG surgeries, which have 90% long-term patency rates over 10 years[23]. Moreover, release of high amounts of nitric oxide (NO) in LIMA when compared to other graft types also contributes to high patency rates over a long period[24]. But, despite these favorable characteristics, CABG surgeries may still be complicated by the spasms in LIMA. These spasms increase the mortality and morbidity related to the surgery. Up to date, many mechanisms were postulated as the cause of LIMA spasms, and there is not a single definite way of spasm progression. Physical manipulations, electrocautery stimulation and release of spasmogenic agents such as thromboxane A_2

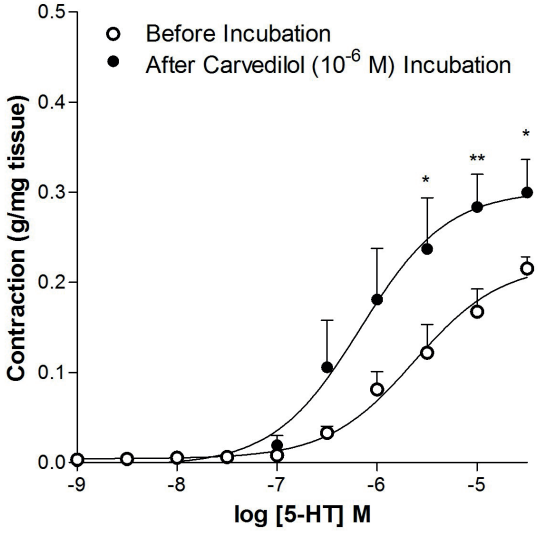

Figure 2. Effects of carvedilol incubation on 5-HT-induced contractions. Cumulative dose-response curves to 5-HT (10^{-9}-$10^{-4.5}$ M) were determined before (○) and after (●) carvedilol incubation (10^{-6} M, 1 hour) (n=6). Data are expressed as mean ± SEM. $^{*}p \leq 0.05$, $^{**}p \leq 0.01$: before *vs.* after incubation; Paired Student's *t*-test.

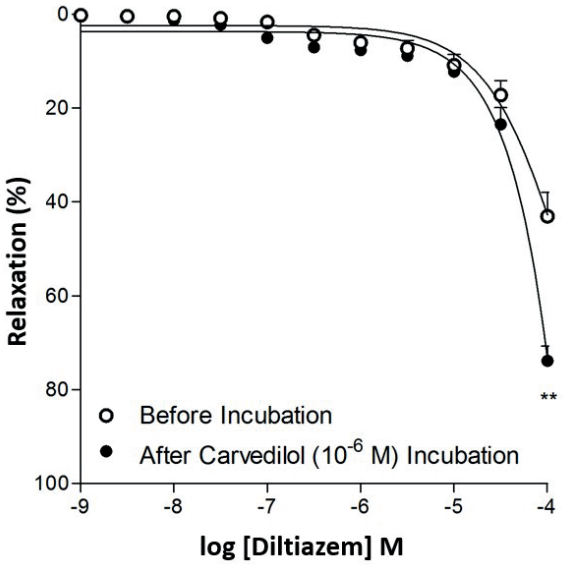

Figure 3. Effects of carvedilol incubation on diltiazem-induced relaxations. Cumulative dose-response curves to diltiazem (10^{-9}-10^{-4} M) were determined in rings precontracted with NE before (○) and after (●) carvedilol incubation (10^{-6} M, 1 hour) (n=6). Data are expressed as mean ± SEM. $^{**}p \leq 0.01$: before *vs.* after incubation; Paired Student's *t*-test.

(TXA_2) following the initial damage are among the pronounced topics on this issue[25]. For the very first times of LIMA utilization as a graft in CABG surgeries, spasm of the artery was a prevalent issue, but new techniques developed to overcome this problem over time[26,27]. Pharmacological interventions are widely used applications to prevent graft spasms. Agents used for this purpose include nitroglycerine, phosphodiesterase inhibitors, and intraluminal calcium channel blockers, which are all effective to increase arterial blood flow in LIMA[28,29]. In this study, we showed that carvedilol may also be used in combination with diltiazem or papaverine as a promising agent to prevent or treat perioperative LIMA spasms. Due to its favorable characteristics as a vasodilatory antihypertensive agent that also maintains coronary flow combination therapy might be preferable in refractory LIMA spasm.

Since arterial spasms are major causes of perioperative mortality and morbidity, there has been a substantial amount of research about the spasmogenic agents in arteries. These agents include endothelium-derived factors such as endothelin-1, prostaglandins such as TXA_2 and prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$), α-receptor agonists such as NE, platelet-derived factors such as 5-HT, and other factors such as histamine[30,31]. These endogenous vasoconstrictors are all possible precipitating agents of arterial spasm. But, there are also some mechanisms that prevent arterial vasoconstriction, which maintain the tonus of arterial wall in equilibrium. The most prominent of these is the presence of an intact endothelium[10]. Intact endothelium releases some anti-spasmogenic substances such as NO, endothelium-derived hyperpolarizing factor (EDHF), and prostacyclin (PGI_2)[32,33]. In our study, we have removed the endothelium in order to evaluate the sole effects of carvedilol on preventing vasospasm, by

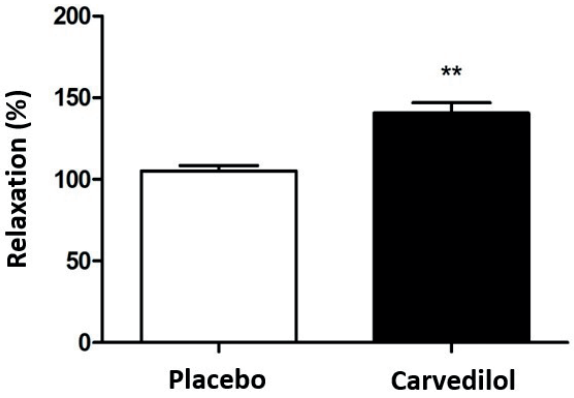

Figure 4. Effects of carvedilol incubation on papaverine-induced relaxations. Relaxation responses to papaverine (10^{-4} M) were determined in rings precontracted with NE in rings incubated either with DMSO (0.05% v/v, 1 hour) or carvedilol (10^{-6} M, 1 hour) (n=6). Data are expressed as mean ± SEM. $^{**}p \leq 0.01$: placebo *vs.* carvedilol incubation; Paired Student's *t*-test.

eliminating endothelium-derived vasodilatation. This also leds to increased vasoconstrictor effects of above mentioned vasospastic factors. These factors were postulated to cause vasoconstriction even in the presence of an intact endothelium[34]. Since the vascular endothelium was denuded in our study, the observed vasodilatation enhancing effects of carvedilol should be interpreted as consequences of smooth muscle adrenergic receptor blockage and not endothelium-dependent mechanisms.

Previous data suggest that arterial smooth muscle of LIMA has dominant α_1-adrenoreceptors, and minimal α_2- or β-adrenoceptor functions[22,35]. These receptors have varying sensitivity to different agents when compared with other arterial grafts[36]. Since carvedilol blocks α_1-adrenergic receptors unlike other conventional β-blocker agents, blockage of α_1-adrenoreceptors seems to be contributing to the enhancement of vasorelaxation responses to diltiazem and papaverine. This mechanism also leads to the reduction of sensitivity of LIMA to NE in carvedilol pre-treated arteries in our study. Even if it is not very prominent, LIMA also has β-adrenoceptors. Rozec et al[37] reported in their study that LIMA has also β_3-adrenoreceptors on endothelium, which has not been classified as a target for carvedilol. Nevertheless, since the LIMA samples used in our study had no endothelium, we can suggest that carvedilol could only exert its effects over α_1- and β_2-adrenergic receptors in vascular smooth muscle.

Carvedilol increased contractile response and sensitivity to 5-HT in our study. Previous studies showed that acute coronary events significantly increase 5-HT levels in coronary artery sinus, which deteriorate the clinical prognosis of vasoconstriction related cardiac events[38]. Moreover, mechanical interventions such as coronary angiography and angioplasty may also stimulate coronary vasospasm over 5-HT receptors[39]. Therefore, activation of these 5-HT receptors is significantly important for adverse events in coronary surgery. Since we found that carvedilol increases the 5-HT sensitivity and its vasoconstrictor effects in LIMA, patients undergoing treatments or procedures affecting 5-HT levels should be monitored and managed more carefully. Further studies may be warranted to investigate the effects of non-selective adrenergic blockage on 5-HT induced LIMA spasm. Until then, cautious use of adrenergic blockers might be advised in patients that are likely to have damaged endothelium, as 5-HT is proposed to have an enhanced contractile effect in endothelium-denuded arteries[34].

Conclusions

Preoperative application of carvedilol might be a promising add-on therapy to diltiazem or papaverine for reducing the dosage of either agent as well as decreasing the spasm incidence in LIMA grafts in CABG surgery.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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