

In Vitro Effects of Dopamine on Internal Thoracic Artery Graft Used in Coronary Artery Bypass Surger

Dopaminin Koroner Arter Bypass Cerrahisi Operasyonlarında Kullanılan İnternal Torasik Arter Grefti Üzerine İn Vitro Etkileri

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Objective: The aim of this study was to investigate in vitro effects of dopamine on internal thoracic artery (ITA) graft.

Material and Methods: Between December 2003- June 2005, 32 patients (2 women and 30 men, mean age; 59.26±8.34, range 37-75 years old) who were subjected to coronary artery bypass grafting (CABG) operation in our clinic were enrolled in this study. ITA remnants were suspended in an isolated organ bath. Constrictor or relaxant responses to dopamine were recorded isometrically.

Results: Dopamine in the concentration range of 10⁻⁹ M-10⁻⁷ M produced a mild relaxant effect on phenylephrine-precontracted ITA, and at higher concentrations than 10⁻⁷ M it produced a constrictor response. Ther relaxant effect of dopamine was partially antagonized by L-NAME (nitric oxide synthase inhibitor, 10⁻⁶ M), propranolol (10⁻⁶ M), and cis-α-flupentixol (dopaminergic receptor antagonist, 10⁻⁶ M), but not by metoclopramide (D₂-dopaminergic receptor antagonist). The constrictor effect of dopamine was partially antagonized by phenolamine, prazosin and, yohimbine.

Conclusion: It was concluded that, while dopamine produces a vasodilator response at the lower concentrations, it causes a constrictor effect on ITA at the higher concentrations. Both a β-adrenergic and a nitric oxide mediated mechanism (via D₁-dopaminergic receptor) may play a role in the relaxant effect of dopamine on ITA at the lower concentrations. Constrictor response to dopamine at the higher concentrations on ITA may be produced by the activation of α₁- and α₂-adrenergic receptors.

Key words: Internal thoracic artery; coronary artery bypass surgery; dopamine.

Amaç: Bu çalışmanın amacı dopaminin internal torasik arter (İTA) grefti üzerine etkilerini, invitro araştırmaktır.

Gereç ve Yöntemler: Aralık 2003- Haziran 2005 tarihleri arasında kliniğimizde koroner arter bypass greft (CABG) operasyonu olan toplam 32 hasta (2'si kadın 30'u erkek, ortalama yaş; 59.256±8,34, 37-75 yaşları arası) çalışmaya alındı. İn vitro organ banyosunda hastaların İTA'larından arta kalan parçacıklar üzerinde dopaminin oluşturduğu kasıcı ve gevşetici yanıtlar isometrik olarak kaydedildi.

Bulgular: Dopamin 10⁻⁹ M-10⁻⁷ M konsantrasyon aralığında fenilefrinle önceden kastırılmış İTA'da hafif bir gevşeme yanıtı, sonrasında artan konsantrasyonlarında (>10⁻⁷ M) kasılma yanıtı gerçekleştirdiği gözlemlendi. Dopaminin gevşetici etkisinin kısmen L-NAME (nitrik oksit sentaz inhibitörü, 10⁻⁶ M), propranolol (10⁻⁶ M) ve cis-α-flupentiksol (dopaminergic reseptör antagonisti, 10⁻⁶ M) ile kısmen azaldığı fakat metoklopramidin (D₂-dopaminergic reseptör antagonisti) dopaminin kaynaklı gevşemeye etki yapmadığı gözlemlendi. Dopaminin İTA'daki kasıcı etkisi kısmen fentolamin, prazosin ve yohimbin ile antagonize edildiği gözlemlendi.

Sonuç: Sonuç olarak dopamin düşük konsantrasyonlarda İTA'da vazodilatasyon yanıtını oluştururken daha yüksek konsantrasyonlarda İTA'da vasokonstriksiyon yanıtını oluşturmaktadır. β-adrenergik ve nitrik oksit aracılı mekanizma (D₁-dopaminergic reseptör yoluyla) dopaminin düşük konsantrasyonlarında İTA'da oluşturduğu gevşetici etkide rol alabilir. Dopaminin yüksek konsantrasyonlardaki İTA'da oluşturduğu kasıcı etki α₁- ve α₂-adrenergik reseptörlerin aktivasyonu ile oluşturulmaktadır.

Anahtar sözcükler: İnternal torasik arter; koroner arter bypass cerrahisi; dopamin

INTRODUCTION

Coronary artery bypass grafting (CABG) operation is widely performed to improve coronary circulation in patients who have coronary artery disease. Nowadays, CABG operations are widely performed with full arterial revascularization. On the other hand, various veins could be used as a graft with or without arterial grafts in CABG operations, e.g., greater saphenous vein, lesser saphenous vein and cephalic vein.^[1] Internal thoracic artery (ITA) grafts are sensitive to vasoactive agents. Physiological and structural features of grafts are very important for short and long-term success of operations. It was known that approximately 30% initial segment, 40-60% middle segment, and remaining last segment of ITA have elasticomuscular, elastic and elasticomuscular structures, respectively. Therefore, vasospasm of ITA might be occurred easily. As well, perioperative medical treatment plays a role in the development of vasospasm. To have knowledge of pharmacological properties of drugs, which are applied to the patients during perioperative period, are important to prevent vasospasm and to provide relaxation when necessary. Thereby, improving in graft flow and preventing of structural damages were provided. If medical treatment could not be appropriately performed, perioperative vasospasm may occur and long-term grafts patency decreases. As a part of medical treatment during perioperative period, dopamine is applied for frequently renoprotective ($3 \mu\text{g}/\text{kg}/\text{min}$), and rarely inotropic support ($3-10 \mu\text{g}/\text{kg}/\text{min}$) in selected patients who underwent coronary artery bypass surgery. Dopamine may exert some important dilator or constrictor effects on ITA graft tissues. The aim of this study was to investigate *in-vitro* effects of dopamine on ITA strips in organ bath.

MATERIALS AND METHODS

Between December 2003-June 2005, the internal thoracic artery (ITA) remnants were obtained from 32 patients (2 women and 30 men, mean age; 59.26 ± 8.34 , range; 37-75 years old) who were subjected to CABG operation in our clinic. This study had been approved by the "Local Ethics Committee" of our faculty. After having obtained informed consents, patients are enrolled in this study. No patient had diabetes mellitus. ITA was harvested as pedicle with electrocautery. Titanium clips were used to bind side branch of ITA. The artery was cut after bifurcation of ITA and distal ITA was ligated. ITA samples were taken before the papaverin application. ITA samples were putted in a cold Krebs solution, and then transferred to cardiovascular laboratory Department of Pharmacology at Trakya University Medical Faculty. The samples transferred to laboratory were cut in approximately 2 mm length rings. The rings were suspended between two stainless-steel L-shaped hooks in a 10 ml organ bath filled with Krebs-Henseleit solution which had following composition (mM): NaCl: 122, KCl: 5, CaCl_2 : 1.25, NaHCO_3 : 25.0, MgSO_4 : 1.2,

KH_2PO_4 : 1, glucose: 11.5. Organ bath was maintained at 37°C and aerated with $95\% \text{O}_2 + 5\% \text{CO}_2$. Each preparation was fixed, using a silk thread, to an isometric force transducer (FDT 10-A, COMMAT, Turkey), which was connected to Transducer Acquisition System (COMMAT TDA-10-A, COMMAT, Turkey) and POLWIN 97 software. The preload tension was set at 2 g and maintained throughout the experiment. After equilibration period of 90 minutes, the vascular rings were tested for viability of vascular endothel. Substantial relaxation with acetylcholine (ACh) (10^{-6}M) in phenylephrine (phe) (10^{-6}M) precontracted rings was accepted as an evidence of intact endothelium. Constrictor or relaxant responses of ITA remnants to dopamine were recorded isometrically.

The data were expressed as mean \pm standart error of the mean. The concentration-response curves were analysed by a computer program (Graphpad Prism 4 Demo software, San Diego, CA). Non linear regression analysis (variable slope) was applied on dose-response graphics. Graphs were compared each other with F test. Values of p less than 0.05 were considered statistical significant. This study was done in accordance with the Helsinki Declaration and it was supported by Trakya University Scientific Research Foundation.

Drugs: Acetylcholine chloride, phenylephrine hydrochloride, dopamine hydrochloride, cis- α -flupentixol, propranolol hydrochloride, N ω -nitro-L-arginine methyl ester (L-NAME) hydrochloride, metoclopramide hydrochloride, phentolamine hydrochloride, prazosin hydrochloride and yohimbine hydrochloride were purchased from Sigma.

RESULTS

At the beginning of the study, cumulative dopamine dose response experiments were performed. Cumulative dopamine concentrations from 10^{-9}M to 10^{-1}M were produced in organ bath, and relaxant contractile responses were recorded in precontracted with phenylephrine and in non-contracted ITA strips, respectively (Figure 1). As can be seen in figure 1, dopamine responses in ITA depend on dopamine concentrations; at the concentration range from 10^{-9}M to 10^{-7}M (Figure 1), dopamine causes mild relaxation in phenylephrine precontracted ITA, whereas at the concentration range from 10^{-7}M to 10^{-3}M , dopamine produces contraction (Figure 1). In order to investigate whether relaxant effect of dopamine depends on nitric oxide released from vascular endothelium, cumulative dopamine dose response experiments were repeated in the existence of a nitric oxide synthase inhibitor, N ω -nitro-L-arginine methyl ester (L-NAME) hydrochloride, at the 10^{-6}M concentration (Figure 2). The existence of L-NAME decreased relaxant effect of dopamine indicating a NO: Nitric oxide (NO) -mediated mechanism ($p < 0.0001$).

To investigate a possible role of β -adrenergic receptors in the effects of dopamine, cumulative dose respons-

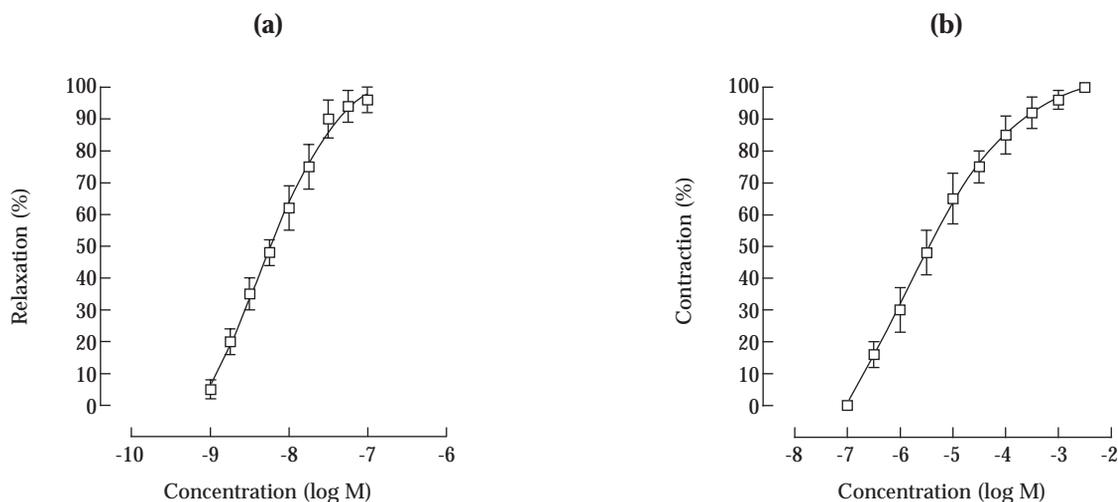


Figure 1. In vitro dopamine [□] related vasodilation (a) and vasoconstriction (b) on ITA.

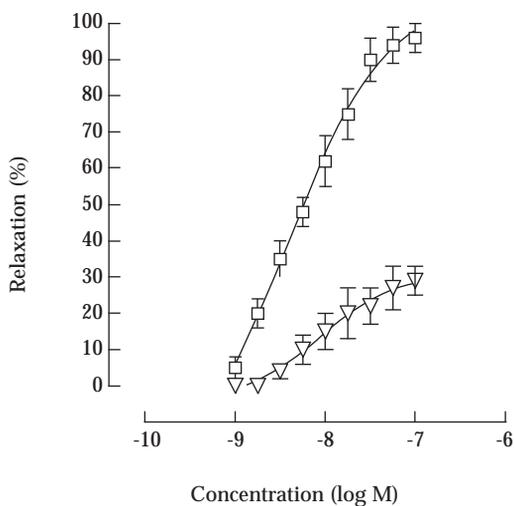


Figure 2. In vitro relaxant response to dopamine on ITA: dopamine alone [□]; L-NAME (10^{-6} M) [▽].

es were obtained in the existence of a non-selective β -adrenergic receptor blocker, propranolol hydrochloride, at the 10^{-6} M concentration (Figure 3). Propranolol partially antagonized the relaxant effect of low dopamine concentrations ($p < 0.0001$), suggesting a partial β -adrenergic receptor mediated mechanism, while it had no effect on constrictor response. The role of dopaminergic receptors in the relaxant effect of dopamine was also investigated. While dopamine D_2 -receptor antagonist, metoclopramide hydrochloride, at the concentration of 10^{-6} M had no effect on relaxant response for dopamine (Figure 4), a non-selective dopaminergic receptor

antagonist, cis- α -flupenthixol, at the 10^{-6} M concentration partially reduced the relaxant effect (Figure 5, $p < 0.0001$), suggesting a contributing mechanism mediated by D_1 -dopaminergic receptor to the β -adrenergic receptor mediated mechanism.

In order to investigate the role of α -adrenergic receptors in the contractile effect of dopamine, cumulative dose responses were obtained in the existence of non-selective α -adrenergic receptor blocker, phentolamine hydrochloride, at the concentrations from 10^{-8} M to 10^{-6} M (Figure 6). Phentolamine dose dependently antagonized contractile responses of dopamine ($p < 0.0001$), showing α -adrenergic mechanism in contractile response of dopamine in ITA. To describe α -adrenergic receptor subtypes specific effects of dopamine, dose-response experiments were performed in the existence of α_1 - and α_2 -specific antagonists (prazosin hydrochloride and yohimbine hydrochloride, respectively) alone and together. As can be seen in Figure 7, both prazosin (10^{-6} M) and yohimbine (10^{-6} M) antagonized contractile response to dopamine only partially, and when they were applied together to organ bath (for each antagonist 10^{-6} M), higher decrease in contractile response to dopamine was obtained.

DISCUSSION

Coronary artery bypass grafting is performed by autogenous grafts especially arterial grafts. In present, ITA is an arterial graft, which is mostly used. It has been known that endothelial function has a role on continuation of vascular tonus by releasing vasodilator and vasoconstrictor agents.^[2] Endothelial dysfunction exists in cardiovascular disease,^[3] and NO production and releasing is associated with endothelial function and vasospasm.^[4] NO production and release are higher in ITA than saphenous vein,^[3,4] therefore, ITA has superior

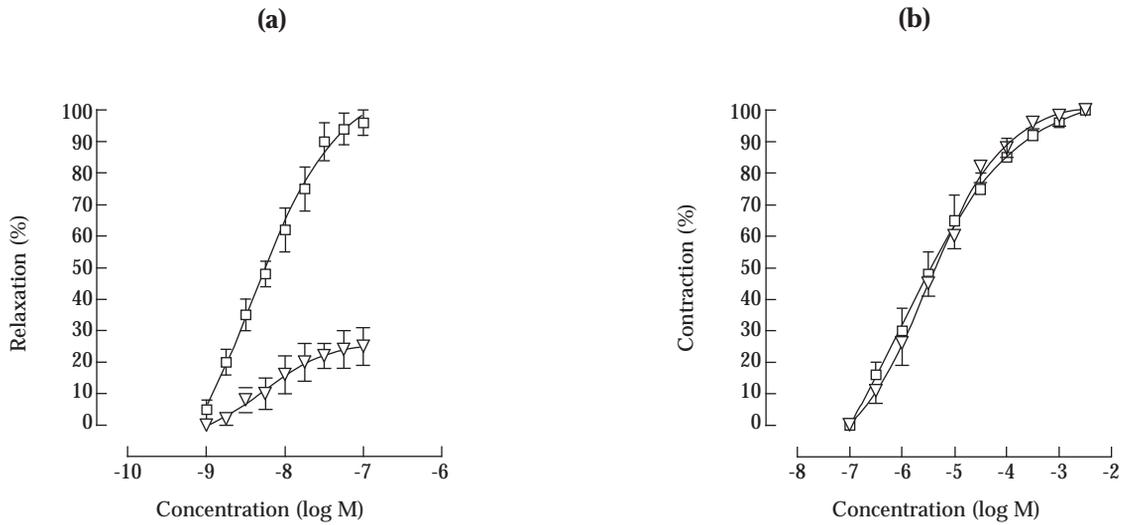


Figure 3. In vitro relaxant response to dopamine on ITA: (a) dopamine alone [□], with propranolol (10^6 M) [▽]; (b) dopamine alone [○], with propranolol (10^6 M) [▽].

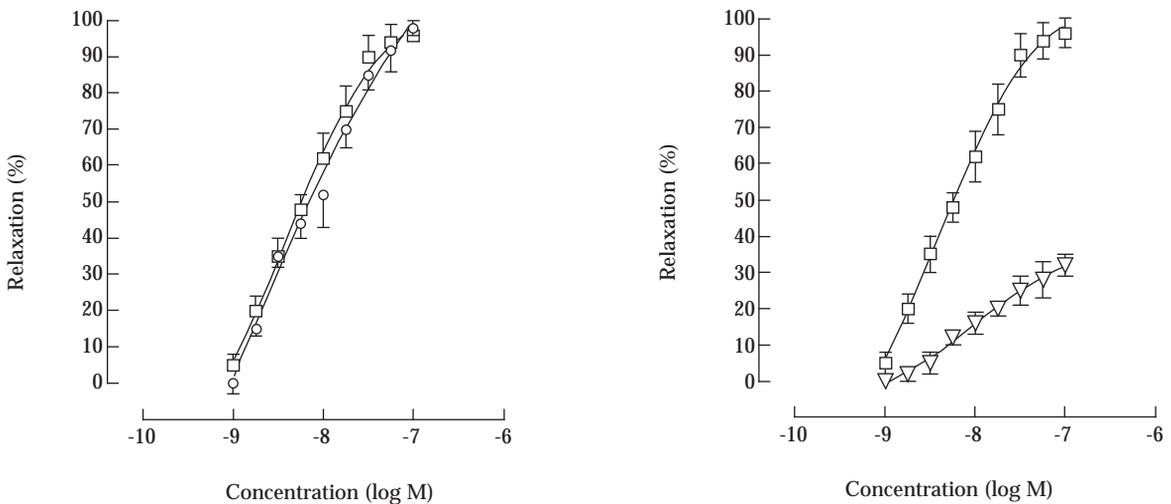


Figure 4. In vitro relaxant response to dopamine on ITA: dopamine alone [□]; metoclopramide (10^6 M) [○].

Figure 5. In vitro relaxant response to dopamine on ITA: dopamine alone [□]; α -flupenthixol (10^6 M) [▽].

outcomes of patency than saphenous vein.^[5-7] As well, atherosclerosis is seen as delayed in ITA to native coronary artery.^[8] On the other hand, it has small caliber and sensitivity to vasospasm.^[9] Latter is important problem in perioperative period. Vasospasm is one of the most important factors that cause graft failure and morbidity in undergoing coronary artery bypass (10,2). Injury of graft during harvesting and implantation stages may disturb the vasodilation mechanism in perioperative period. Following the vasospasm, blood flow in ITA is markedly decreased, and it may cause hemodynamic

problems,^[10] which are related perioperative morbidity, postoperative myocardial failure and death.^[11,12] Furthermore, vasospasm of graft can affect early and late graft patency,^[3,12] and it may cause perioperative morbidity and mortality in patient with coronary artery bypass operation.^[13]

He et al.^[14] reported in an in-vitro study that endothelium denuded ITA preparations show more vasoconstrictor response to noradrenaline than ITA preparations with intact endothelium. Besides, Chardigny et al.^[15] reported similar results to He et al. that vasoconstrictor

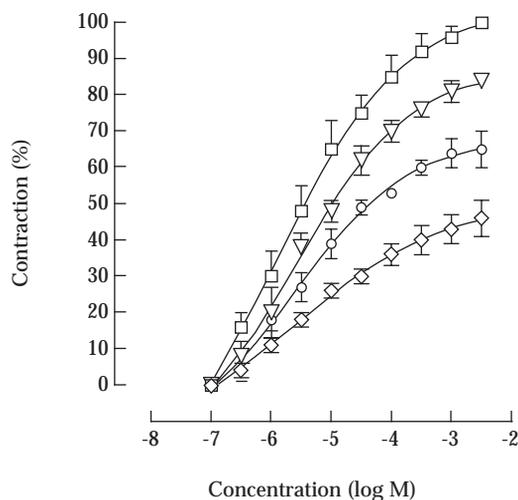


Figure 6. *In vitro* constrictor response to dopamine on ITA: dopamin alone [□]; with phentolamine (10^6 M) [▽], (10^7 M) [○], (10^6 M) [◇]).

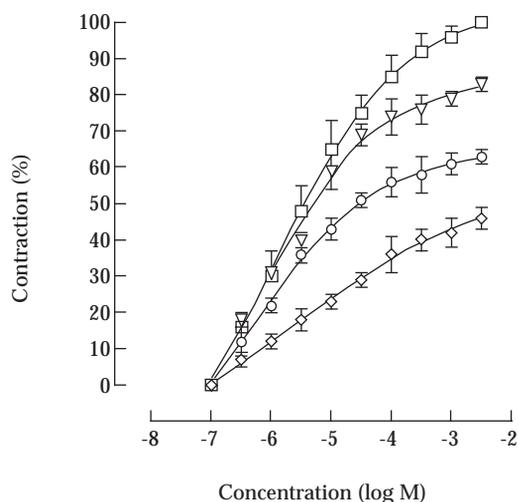


Figure 7. *In vitro* constrictor response to dopamine on ITA: dopamin alone [□]; with yohimbine (10^6 M) [○]; with prazosin (10^6 M) [▽]; with yohimbine (10^6 M) + prazosin 10^6 M [◇].

tor response to noradrenaline in ITA is augmented by endothelial injury. Lüscher et al.^[16] detected that acetylcholine causes endothelium-related vasodilation on ITA preparations. In our study, vasodilator effect of low dose dopamine was decreased after adding L-NAME to organ bath, or after adding non-specific dopaminergic-receptor antagonist cis- α -flupenthixol (but not D_2 -selective antagonis metoclopramide), or after adding non-specific β -adrenergic receptor blocker (propranolol). Based on the observation the fact that non-specific dopaminergic antagonist has some antagonistic effect on vasodilator response to dopamine on ITA, but D_2 -specific antagonist has not such effect, it can be speculated that D_1 -receptors may mediate relaxant effect of dopamine. As a result, these findings indicate that both a β -adrenergic and a nitric oxide mediated mechanism (via D_1 -dopaminergic receptor) may play a role in the relaxant effect of dopamine on ITA. Radioligand binding and light microscopy techniques showed the existence of D_1 and D_2 receptors on the rabbit pulmonary artery^[17] and only D_1 receptors rat renal artery.^[18] As well, Mori et al.^[19] have been observed D_1 related vasodilation on rabbit pulmonary artery, which is reduced by cis- α flupenthixol (non-selective D_1 receptor blocker) in an organ bath study. It was suggested that vascular effects of dopamine are produced by specific dopamine receptors in cardiovascular system.^[20,21] Available data showed that activation of D_1 receptors (which are located on vascular smooth muscle postsynaptically) cause vasodilation and stimulation of D_2 receptors (which are located on vascular smooth muscle presynaptically) cause inhibition of vasoconstriction.^[5,21] It has been reported that dopamine related vasodilation in human cardiovascular system is primarily

mediated by D_1 receptors.^[22] As well, D_1 receptors have been detected in human renal, mesenteric, cerebral blood vessels, and it has been reported that these receptors subserved vasodilation.^[23] Yamuchi et al.^[24] reported that low-dose dopamine induces vasodilation via D_1 receptors, but high-dose dopamine produces vasoconstriction, and isoproterenol causes a weak dose-related vasodilation in human pulmonary artery. D_1 receptors had also been detected in rabbit pulmonary artery.^[19] Katai et al.^[25] have been reported that SCH 23390, a DA_1 receptor antagonist, decreased dopamine related vasodilation on ITA in an *in-vitro* study. In addition to, there are some studies reported that dopamine causes vasoconstriction on ITA.^[26,27] Like our study, Forster et al.^[28] showed that dopamine related vasodilation of human basilar artery was decreased by cis- α -flupenthixol. Also, sulpirid (selective D_2 receptor antagonist) had no effect on relaxant response of ITA. It was reported that α - ve β -adrenergic receptors exist in human ITA.^[29] β -adrenoreceptors have little role on ITA and thus, usage of β -blockers did not cause important vasospasm.^[30] Rosenfeldt et al.^[30] have found that isoproterenol, β_1 - and β_2 -adrenoreceptor agonist, related maximum vasodilation is about 24%. In another study with human ITA, which was precontracted with KCl, isoproterenol produced a relaxant response about 13% of KCl contraction, and it was fully antagonized by propranolol.^[31]

It was known that while α adrenoreceptors play a role in vasoconstriction, β adrenoreceptors play a role in vasodilation. There were some studies showing α adrenergic receptor agonists such as noradrenaline, methoxamine, phenylephrine cause vasoconstriction in ITA.^[32-34]

Also, α_1 receptors are more prominent in ITA than α_2 receptors.^[30,31,35] But He et al.^[35] have found that methoxamine (MO) and norepinephrine (NE) causes vasoconstriction on ITA, and the contractions induced by both MO and NE were totally abolished by α_1 -antagonist prazosin but not α_2 -antagonist yohimbine. As a result, they offered that in the human ITA the postjunctional α -adrenoceptors are predominantly of the α_1 -subtype. In the another study, Katai et al.^[24] showed that dopamine produces vasoconstriction in the concentrations higher than 0.1 mM. In our study, ITA vasoconstriction with dopamine doses higher than 0.1 mM was seen, and α_1 and α_2 receptor blockers decreased this response. Our data indicates that this vasoconstriction response may be mediated by stimulation of α_1 and α_2 receptors with dopamine. It was known that low (0-3 $\mu\text{g}/\text{kg}/\text{min}$), middle (3-5 $\mu\text{g}/\text{kg}/\text{min}$), and high (10 $\mu\text{g}/\text{kg}/\text{min}$) doses of dopamine infusions predominantly affect dopamine receptors, β -receptors, α -adrenergic receptors, respectively, on ITA graft. Thus, stimulation of these receptors determines the response of ITA to dopamine.^[19,24,36] Dopamine produces a vasodilator response at the lower concentrations and therefore, dopamine is used commonly as renoprotective agent. However, Türkay et al. reported that dopamine given at renal doses dose not protect renal tubular function in patients with normal heart and kidney functions undergoing coronary surgery and they do not recommend the use of dopamine for routine renal prophylaxis in this patients.^[37] In another study, it is reported that if low flow in ITA was detected during the operation, this graft tends to occlusion in in long period.^[38] As well, like other arterial grafts, any agent, which causes vasospasm on ITA, causes significantly decrease in graft flow.^[39] This condition may induce perioperative morbidity and mortality.^[13]

In conclusion, it was found that dopamine produces a vasodilator response at the lower concentrations, whereas at the higher concentrations it causes a constrictor effect on ITA. Both a β -adrenergic and a nitric oxide mediated mechanism (via D_1 -dopaminergic receptor) may play a role in the relaxant effect of dopamine on ITA at the lower concentrations. Constrictor response to dopamine at the higher concentrations on ITA may be produced by the activation of α_1 - and α_2 -adrenergic receptors.

Conflict of Interest

No conflict of interest declared by the authors.

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