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Original Article

Vasodilation Responses to Non-Selective α-Adrenergic Blockage of Coronary Bypass Grafts in Diabetic and Non-Diabetic Patients: In Vitro Study

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Background: Adrenergic tonus is increased in atherosclerotic coronary arteries. In this study, we aimed to demonstrate in vitro effects of phentolamine, a reversible nonselective alpha (α) adrenergic blocker, on coronary artery bypass grafts (CABG) and compare its effects in diabetic and nondiabetic patients.
Methods: A total number of 30 patients (15 diabetic and 15 nondiabetic) who were assigned to elective CABG surgery were enrolled into the study. For both groups of patients, 16 internal mammarian artery (IMA) samples, 16 saphenous vein (SV) samples and 16 radial artery (RA) samples were collected and studied in the tissue bath system. The vasodilatation responses to increasing doses of phentolamine were recorded.
Results: When grafts were compared in terms of amount of vasodilatation to phentolamine, IMA had the most prominent vasodilatation followed by RA and SV respectively. Although the vasodilatation responses in nondiabetic patients were numerically higher than diabetic patients, there was no statistically difference between the groups.
Conclusion: Phentolamine, a nonselective α adrenergic blocker, is proven to have equal vasodilatory effects in diabetic and nondiabetic CABG grafts and can safely be used both intravenously and topically in the perioperative period.

Keywords: phentolamine, coronary artery bypass graft, vasodilatation

Background

Coronary atherosclerosis is usually accompanied by increased adrenergic tonus that predisposes coronary vasoconstriction.[1,2] In the case of moderate to severe coronary stenosis, increased α adrenergic tonus induces myocardial ischemia. In the presence of ischemia and congestive heart failure; the number of β1 adrenergic receptors decrease and the α adrenoceptors increase and externalize further attenuating ischemia.[3]

Blockage of the α-adrenergic system results in inhibition of vasoconstriction induced by endogenous catecholamines in vascular smooth muscle, and suppression of insulin secretion and lipolysis.[1]

Although neglected in the contemporary medical practice, the use of α adrenergic blockers in reducing coronary resistance is well established.[4–6] Additionally, they were once used as vasodilatory agents in the presence of increased levels of catecholamines as in the case of heart failure or in low output states following open heart surgery.[7,8]

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In this study, we sought to investigate in vitro effects of phentolamine, a reversible nonselective α adrenergic blocker, on coronary artery bypass grafts to elucidate the variability of adrenergic tonus among different graft types. Secondly, the grafts samples from diabetic and nondiabetic patients were compared to uncover the effect of diabetes mellitus on adrenergic tonus of bypass grafts.

Materials and Methods

Patient selection

A total number of 30 patients (15 diabetic and 15 nondiabetic) who were planned to undergo elective coronary artery bypass grafting (CABG) surgery were prospectively enrolled into the study between January 2013–July 2013. Patients diagnosed with Type 2 diabetes mellitus were included as diabetic group. Before initiating the study, the ethics committee of our faculty approved the study and informed consent was obtained from all patients.

The diabetic patients constituted the Group 1 and nondiabetic patients constituted Group 2. For both groups of patients, 16 pieces of internal mammarian artery (IMA), 16 radial artery (RA) and 16 saphenous vein (SV) graft samples were collected. The demographic and operative data of the patients are presented in **Table 1**.

Graft preparation

After excision of grafts for CABG, the surplus distal ends were used for the purpose of study. Both IMA and RA grafts were harvested together with the adjacent tissue with the aid of scissors and/or electrocautery. For the collection of the RA grafts, nondominant arm with adequate ulnar collateral circulation, assessed by Allen's test, was selected. Radial artery was not used in patients with the history of RA cannulation, subclavian stenosis, inadequate ulnar circulation or need for a future arteriovenous fistula. The SV grafts were excised without pedicle. No vasodilatory agent was used during preparation of the grafts.

Tissue bath system

The graft samples from IMA, RA and SV were transferred from operating room to the vascular laboratory in +4°C Krebs Solution (Composition: 122 mmol/l sodium chloride (NaCl), 5 mmol/l potassium chloride (KCl), 1.25 mmol/l calcium chloride ($CaCl_2$), 25 mmol/l sodium hydrogen carbonate ($NaHCO_3$), 1.2 mmol/l magnesium sulphate ($MgSO_4$), 1.0 mmol/l monopotassium phosphate (KH_2PO_4), and 11.5 mmol/l glucose) in 5 min. The reservoirs in the tissue bath system were filled with 20 ml of 37°C Krebs solution which was continuously oxygenated with Carbogene gas of 95% O_2 and 5% CO_2 and changed every 20 minutes to keep the tissues alive. After removal of adjacent fatty tissues and adventitia, the grafts were sliced into 3 mm wide vascular rings and were suspended into the tissue bath system through steel hooks. The upper ends were attached to the transducer and the lower ends were kept stable. The vascular rings were entrained by 2–3 gr of active tension which was applied for 60 min and by KCl. Then the tissues were sub maximally contracted by 10–6 M phenylephrine (Sigma) in order to elucidate the any vasodilation response to phentolamine mesilate (Regitin Ampule; Novartis, Bern, Switzerland). Phentolamine was then added to the tissue bath system cumulatively starting from a concentration of 10–10 M in 2 min intervals and the dose was incremented half logarithmically until a concenration of 10–4 M was achieved. The data were transferred to the computer with the help of the Transducer Acquisition System (MAY IOBS 99, FDT 05; Commat, Ankara, Turkey) and stored with MAY-MASTER MP36 analysis software.

Statistical Analysis

The demographic variables were analyzed by SPSS 19 for Mac, and a p value <0.05 was considered to be statistically significant. Concentration-response curves were obtained by Graphpad Prism 6 Software Demo Version. Nonlinear regression analysis and One Way ANOVA was applied to the graphics.

Results

The demographic data of diabetic and non-diabetic patients were similar with no statistically significant difference (**Table 1**).

After submaximal vasoconstriction of graft samples from diabetic (Group 1) and non-diabetic patients (Group 2) by phenilephrine, vasodilatation responses induced by incrementing doses of phentolamine were recorded. The data on percent vasodilatation and log EC50 (logarithmic half maximal effective concentration) values of different graft types are presented in **Table 2**.

When the samples from IMA, RA and SV grafts were compared in terms of amount of vasodilatation response to phentolamine, IMA graft samples exhibited the most pronounced vasodilatation in both groups. The %vasodilatation responses with phentolamine were 95.12% ± 5.69% for IMA, 85.8% ± 7.33% for RA and 63.06% ± 4.72%

Table 1 Preoperative characteristics and operative data of patients

	Group 1 DM	Group 2 NON-DM	p values
Age	63.53 ± 9.17	62.73 ± 9.21	>0.05
Euroscore	4.53 ± 1.24	2.53 ± 0.83	>0.05
HT	12 (80%)	12 (80%)	>0.05
Preop EF	56.66 ± 6.1	53.13 ± 8.42	>0.05
COPD	2 (13.3%)	3 (20%)	>0.05
No.of grafts	2.66 ± 0.89	2.53 ± 0.83	>0.05
CBT	66.46 ± 24.45	65.13 ± 24.58	>0.05
CCT	38.33 ± 14.22	37.66 ± 13.85	>0.05
ICU Stay	2.26 ± 0.59	2.13 ± 0.35	>0.05
Hospital Stay	5.93 ± 1.33	5.06 ± 0.25	>0.05

DM: diabetes melitus; HT: hypertension; EF: ejection fraction; COPD: chronic obstructive pulmonary disease; CBT: cardiopulmonary bypass time; CCT: cross clamp time; ICU: intensive care unit

Table 2 Vasodilatation responses to phentolamine

	Diabetic		Nondiabetic		p values
	%VD	logEC50	%VD	logEC50	
IMA	95.12 ± 5.69	–6.464	109.91 ± 11.65	–6.063	0.717
RA	85.8 ± 7.33	–6.261	91 ± 6.99	–6.261	0.862
SV	63.06 ± 4.72	–5.994	70.18 ± 6.03	–2.816	8.890

%VD: percent vasodilatation; IMA: internal mammarian artery; RA: radial artery; SV: saphenous vein

for SV. The log EC values in diabetic patients were –6.464 for IMA, –6.261 for RA and –5.994 for SV. For non-diabetic patients on the other hand, %vasodilatation responses with phentolamine were 109.91% ± 11.65% for IMA, 91.73% ± 6.99% for RA and 70.18% ± 6.03% for SV. The log EC values in non-diabetic patients were –6.063 for IMA, –6.261 for RA and –2.816 for SV. Although the %vasodilatation responses in non-diabetic patients were numerically higher than diabetic patients, there was no statistically difference between the two groups. **Figures 1–3** demonstrates the concentration-response curves of IMA, RA and SV grafts in Groups 1 and 2 respectively.

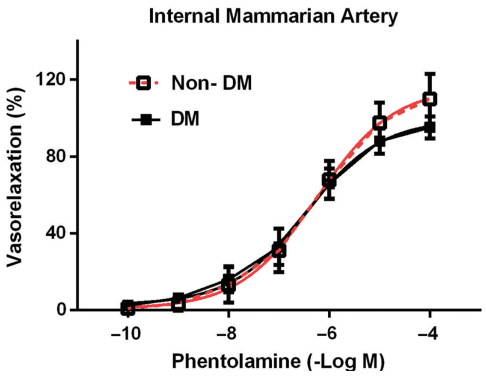

Fig. 1 Vasodilatation response curves of internal mammarian arteries.

Discussion

Alpha adrenergic system regulates the tonus of arterial and venous vasculature.[2,3] Activation of α-1 aderenoceptors causes an increase in intracellular Ca^{+2} in vascular smooth muscle and results in vasoconstriction and increase in blood pressure. Alpha-2 adrenoceptors, on the other hand are mainly presynaptic causing a biphasic blood pressure response when activated; a hypotensive response after a short period of hypertensive phase which is believed to be the result of its distinguished subtypes.[9]

In this study, we have tried to demonstrate the effects of nonselective α adrenergic blockage (by phentolamine) on CABG grafts in diabetic and non-diabetic patients.

Animal and human studies revealed that α 2 adrenergic receptors are mainly situated at microvascular circulation, while α 1 adrenergic receptors are more abundant at epicardial coronary arteries.[10,11] Endothelial dysfunction in atherosclerotic coronary arteries is shown to increase α adrenergic tonus through rising the number of receptors. Baumgart, et al. have documented that α agonists stimulate vasoconstriction in both conduit and resistant arteries

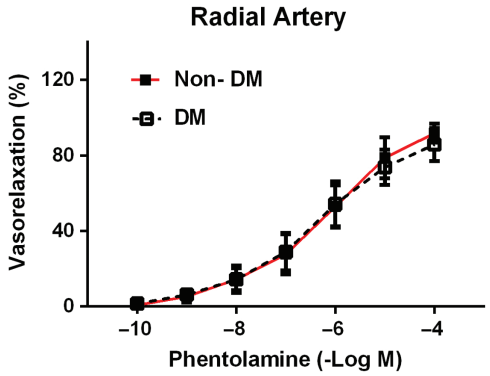

Fig. 2 Vasodilatation response curves of radial arteries.

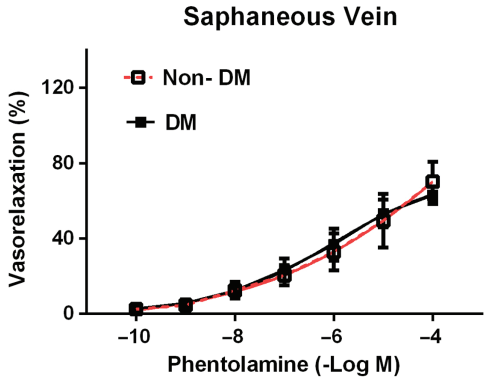

Fig. 3 Vasodilatation response curves of saphenous veins.

in patients with coronary artery disease aggravating ischemia.[1] Moreover, both nonselective and selective α 1 blockage are shown to prevent vasoconstriction induced by cold pressors, exercise or cigarette smoking.[12]

Studies to characterize the specific adrenoceptor types in IMA, SV and RA revealed that, RA and IMA grafts are well equipped with α 1 receptors and a relatively thicker layer of smooth muscle, while SV grafts possess both α 1 and α 2 adrenoceptors but little smooth muscle.[13] In our study, we showed that the vasodilatation response to phentolamine was most prominent in the IMA grafts, followed by RA and SV grafts.

Diabetes Mellitus (DM) is associated with accelerated atherosclerosis mainly as a result of severe endothelial dysfunction.[14] In particular, in type 2 DM, vascular smooth muscle dysfunction and increased circulating levels of edothelin-1 contributes to coronary vasoconstriction.[15–17] Thus, α adrenergic tonus is expected to be more prominent in diabetic patients. Through this study, we aimed to compare the response to nonselective α blockage in diabetic and non-diabetic patients. Although the vasodilatation response to phentolamine was numerically higher in non-diabetic patients, we could not demonstrate any statistically significant difference between the two groups. Main explanation for this finding is the mechanism of vasodilatation caused by α antagonists which is via smooth muscle. Therefore, deranged endothelial function in diabetics may not necessarily influence the adrenergic tonus of the vessel.

Another factor contributing to the diminished difference between diabetic and non-diabetic patients is the fact that the α adrenoceptors increase in number only in atherosclerotic vessels. Thus, IMA, RA and SV grafts are preserved with better vascular tone.[1]

Phentolamine is currently used as a parenteral vasodilatory agent in hypertensive crisis of pheochromacitoma, cocaine associated myocardial ischemia, in high systemic vascular resistance states of severe congestive heart failure and hypertensive and/or low output states after cardiac surgery.[1] All these medical conditions represent high levels of circulating chatecholamines. Present study has showed that, phentolamine can safely be used postoperatively in the need for a vasodilator agent. Moreover, it can also be used locally to treat graft spasm in both arterial and venous grafts.

In order to determine the efficacy of phentolamine at receptor level, both endothelialized and de-endothelialized tissue samples should have been used. This is one of the limitations of our study. The other limitation is the relatively small sample size.

Conclusion

In conclusion, phentolamine, a nonselective blocker, is proven to have equal vasodilatory effects in diabetic and nondiabetic CABG grafts and can safely be used both intravenously and topically in the perioperative period.

Disclosure Statement

None declared.

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