Comparison of endothelial function of coronary artery bypass grafts in diabetic and nondiabetic patients: Which graft offers the best?

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Abstract

Objective: Diabetes associated endothelial dysfunction, which determines both long and short term graft patency, is not uniform in all coronary artery bypass surgery (CABG) grafts. Herein this study, we aimed to investigate the degree of endothelial dysfunction in diabetic radial artery (RA), internal mammarian artery (IMA) and saphenous vein (SV) grafts *in vitro* tissue bath system.

Methods: This is a prospective experimental study. Fifteen diabetic and 15 non-diabetic patients were included to the study. A total number of 96 graft samples were collected; 16 graft samples for each graft type from both diabetic and non-diabetic patients. Arterial grafts were harvested with pedicles and SV grafts were harvested by 'no touch' technique. Vasodilatation response of vascular rings to carbachol, which induces nitric oxide (NO) mediated vasodilatation, was designated as the measure of endothelial function.

Results: The IMA grafts had the most prominent NO mediated vasodilatation in both diabetic and non-diabetic patients, concluding a better preserved endothelial function than SV and RA. The 'no- touch' SV and RA grafts had similar vasodilatation responses in non-diabetic patients. In diabetic patients, on the other hand, RA grafts exhibited the least vasodilatation response (ie. worst endothelial function), even less vasodilatation than 'no touch' SV grafts ($p<0.0001$).

Conclusion: Deteriorated function of RA grafts in diabetic patients, even worse than SV grafts made evident by this study, encourages the use of 'no touch' technique as the method of SV harvesting and more meticulous imaging of RA before its use as a graft in diabetic patients.

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Keywords: endothelial function, coronary artery bypass grafts, tissue bath study

Introduction

The burden of 'diabetes epidemic' is growing with aging population, industrialization, increasing prevalence of obesity and physical inactivity. This also increases the number of patients with cardiovascular disease; which is the major complication of diabetes mellitus (DM) with more extensive, diffuse, multi-vessel coronary artery involvement (1).

Nowadays, diabetic patients constitute 20-30% of patients undergoing coronary artery bypass grafting (CABG) surgery (2). Considering current evidence that favor CABG as mode of revascularization in most diabetics and also the fact that DM it is a significant independent predictor of graft failure; the choice of CABG conduit in diabetic patients is of major concern (3, 4). Internal mammarian artery (IMA) is the gold standard graft for both diabetic and non-diabetic patients (5). The choice between the saphenous vein (SV) and radial artery (RA) on the other hand is more controversial with many conflicting data. Utilization of "no touch" saphenous vein grafts, which is shown to have better preservation of endothelial function than conventionally harvested veins, has further shuffled the topic.

In our study, we aimed to assess diabetes-induced endothelial dysfunction in coronary artery bypass grafts and determine the most suitable conduit in diabetic patients. Thus, we designed an experimental study to compare the nitric oxide (NO) dependent vasodilatation responses of IMA, RA and SV grafts of diabetic and non-diabetic (control) patients in in-vitro tissue bath system.

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Methods

Patient characteristics

An experimental prospective study. After obtaining approval from local Ethics Committee, 15 patients with Type 2 diabetes mellitus (DM) and 15 non-diabetic patients who were assigned to elective 3 or 4 vessel CABG surgery and gave informed consent, were enrolled into the study. All patients that was included info the study was on insulin teraphy. Patients with a history of RA cannulation, subclavian stenosis, inadequate ulnar circulation, previous forearm surgery, need for an arterio-venous fistula or in patients with apparent clinical evidence of diseased RA in whom the use of RA is not appropriate were excluded from the study. Of 30 patients, 24 were male and 6 were female. Mean age of the patients was 65.80±13 (min 39-max 73). The demographic and preoperative characteristics of patients are presented in Table 1. All diabetic patients were insulin treated with long standing diabetes. Mean duration of diabetes was 8.06±4.74 years and mean HbA1C level of the diabetic patients was 8.56±2.65% indicating poorly controlled disease.

Graft harvesting

Internal mammarian artery, SV and RA were collected and used in all of the patients. Adequacy of ulnar collateral circulation was evaluated through modified Allen's test before harvesting RA. In modified Allen's test, the patient is instructed to clench the fist while the examiner compresses radial and ulnar arteries. Then the ulnar artery is released as patient relaxes the hand. The return of palmar blush within 5-10 seconds is considered positive (normal) modified Allen's test (6). All grafts (SV, RA and IMA) were harvested using 'no-touch' technique along with their pedicles as previously explained (7). No vasodilatory agent was applied before placement of the graft into the Krebs solution. The SV grafts were harvested with 'no touch' technique with minimal handling and without inflation to avoid any damage. The abundant parts of grafts were then placed into +4° C Krebs solution (in mM; NaCl 122, KCl 5, $CaCl_2$ 1.25, $NaHCO_3$ 25, $MgSO_4$ 1.2, KH_2PO_4 1 and Glucose 11.5) and transferred to the laboratory immediately.

Tissue bath system

In vascular laboratory, the grafts were cleaned off from adjacent fat and adventitial tissues and were sliced into 3mm-wide vascular rings under microscope. Several pieces of vascular rings were prepared from abundant parts of each graft. The samples were then suspended into the classical tissue bath system with steel hooks. The upper end of the hook was attached to a tension transducer and the lower end was kept stable. Twenty milliliters of Krebs solution found in the tissue bath reservoir was continuously oxygenated with 95% O_2 and 5% CO_2 and was replaced every 20 minutes to keep the samples alive. An active tension of 2 to 4 gr was applied to all of the samples for a minimum of 60 minutes before entrainment with 100 mEq of Potassiim chloride (KCl) solution. Only the samples with tissue integrity and viability were used for the study. A total of 48 graft samples; 16 SV, 16 IMA and 16 RA samples from diabetic patients constituted group 1 and 48 graft samples; 16 SV, 16 IMA and 16 RA samples from non-diabetic patients constituted group 2 (control group).

Table 1. Demographic data of patients

	Group 1 (Diabetic) n:15	Group 2 (Non-diabetic) n:15	*P*
Age, years	56.13±12.37	63.0±7.75	0.328
Sex, female %	4 (26.7%)	5 (33.3%)	0.409
EF, %	52.80±8.90	57.06±4.66	0.241
EUROSCORE	3.26±1.27	1.73±1.79	0.227
HT, %	6 (40%)	4 (26.8%)	0.475
Smk, %	7 (46.7%)	7 (46.6%)	0.189
EF - ejection fraction; HT - hypertension; Smk - smoking			

All vascular rings were then washed thoroughly with Krebs solution and 10^{-6}M phenilephrine hydrochloride (Sigma) was added to tissue bath to achieve submaximal vasoconstriction. Carbachol (carbamylcholine chloride-Sigma, Taufkirchen, Germany), an acetylcholine receptor agonist, was used to assess nitric oxide (NO) dependent vasodilatation response. Carbachol is a potent cholinergic (parasympathomimetic) agent that stimulates both muscarinic and nicotinic receptors resulting in vasodilation which is mediated by release of NO consequent to the activation of M3 receptors on endothelial cells (8). Carbachol was administered starting from a concentration of 10^{-8}M, in two minutes intervals with half logarithmic dose increments until a concentration of 10^{-4}M. The responses of vascular rings were recorded in terms of vasodilatation or vasoconstriction relative to the basal state achieved by phenilephrine. The data were transferred into analysis programmed (MAY-MASTER, MP36, Commat, Ankara-Turkey) with the help of Transducer Acquisition System (MAY IOBS-99, FDT-05, Commat, Ankara-Turkey).

Statistical analysis

The data were analyzed using Graphpad Prism Software (Demo 6 Version) by which concentration -response curves were obtained. Data were compared using OneWay ANOVA. The demographic variables were analyzed using chi- square and t-test (SPSS 19 for Mac New York, USA). A p value of <0.05 was considered to be statistically significant.

Results

The measure of vasodilatation in grafts were recorded as percent vasodilatation of submaximal vasoconstriction achieved by phenylephrine. The responses in both groups are presented in Table 2. Firstly, vasodilatation response of each graft was compared between the diabetic and non-diabetic patients. In SV grafts (Fig. 1a), the amount of vasodilatation was 51.44±8.08% in

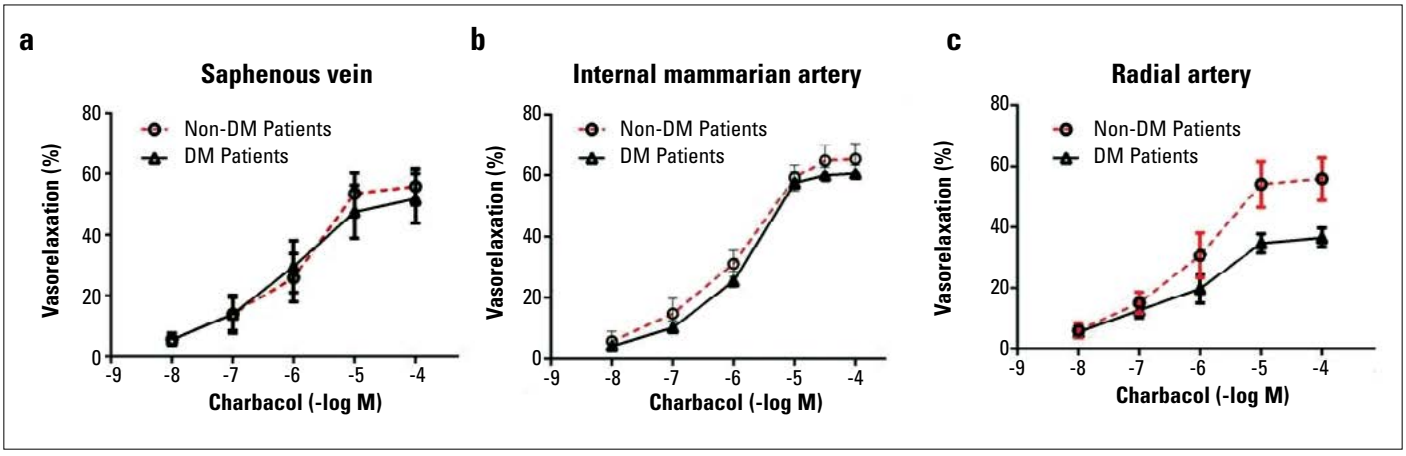

Figure 1. a-c. Comparison of vasodilatation responses of diabetic and nondiabetic patients in Saphenous vein (a) p=0.6667; internal mammarian artery (b) p=0.801 and radial artery (c) p<0.0001

Table 2. Maximal vasodilatation responses of coronary artery bypass grafts

	Group 1 (Diabetic) 48 samples	Group 2 (Non-diabetic) 48 samples	*P*
SV (n:16 each)	51.44±8.08%	55.92±6.03%	*P*=0.6667
IMA (n:16 each)	60.65±2.98%	65.53±9.98%	*P*=0.801
RA (n:16 each)	36.55±3.15%	55.8±6.99%	*P*<0.0001

IMA - internal mammarian artery; RA - radial artery; SV - saphenous vein

Table 3. Dual comparisons of each graft

Bonferroni's multiple comparisons	Mean difference	95% confidence interval of difference	*P*
(DM+) IMA vs (DM+) RA	24.10	18.3 to 30.17	<0.0001
(DM+) IMA vs (DM+) SV	8.776	2.705 to 14.85	0.0005
(DM+) IMA vs(DM-) IMA	-4.876	-10.95 to 1.196	>0.05
(DM+) IMA vs (DM-) RA	4.842	-1.229 to 10.91	>0.05
(DM+) IMA vs (DM-) SV	4.734	-1.337 to 10.81	>0.05
(DM+) RA vs (DM+) SV	-15.33	-21.40 to -9.254	<0.0001
(DM+) RA vs (DM-) IMA	-28.98	-35.05 to -22.91	<0.0001
(DM+) RA vs (DM-) RA	-19.26	-25.33 to -13.19	<0.0001
(DM+) RA vs (DM-) SV	-19.37	-25.44 to -13.30	<0.0001
(DM+) SV vs (DM-) IMA	-13.65	-19.72 to -7.581	<0.0001
(DM+) SV vs (DM-) RA	-3.934	-10.01 to 2.137	>0.05
(DM+) SV vs (DM-) SV	-4.042	-10.11 to 2.029	>0.05
(DM-) IMA vs (DM-) RA	9.718	3.646 to 15.79	<0.0001
(DM-) IMA vs (DM-) SV	9.610	3.539 to 15.68	0.0005
(DM-) RA vs (DM-) SV	-0.1075	-6.179 to 5.964	>0.05

DM -, +diabetic; DM - non-diabetic; IMA - internal mammarian artery; RA - radial artery; SV - saphenous vein

diabetic patients and 55.92±6.03% in non-diabetic patients with no statistically significant difference (p=0.6667). Similarly, the vasodilatation responses of IMA graft samples were 60.65±2.98% in diabetic patients 65.53±9.98% in non-diabetic patients, still with no statistically significant difference (p=0.801) (Fig. 1b). In RA grafts (Fig. 1c), on the other hand, the amount of vasodilatation was significantly lower in diabetic patients than non-diabetics (p<0.0001) (36.55±3.15% in diabetics vs. 55.81±6.99% in non-diabetics). Maximal vasodilatation of all grafts are presented in Fig. 2.

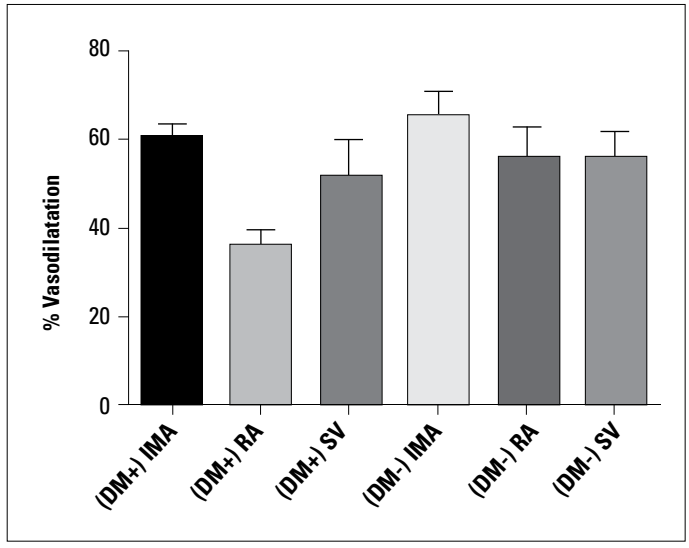

Figure 2. Maximal vasodilatation responses of all grafts
DM - diabetes mellitus; IMA - internal mammarian artery; RA - radial artery; SV - saphenous vein

Secondly, the three types of conduits (IMA, SV, RA) were compared within the diabetic and non-diabetic groups to determine the best graft in different populations. Not surprisingly, the IMA grafts had the most prominent endothelium derived vasodilatation in both groups (Fig. 3a, b). In non-diabetic patients, the RA and SV grafts had similar vasodilatation responses, but in diabetics, the NO-induced vasodilatation was significantly lower in RA grafts than in SV grafts. The log EC50 values of grafts were -4.904 for IMA, -4.495 for SV and -3.39 for RA in diabetic patients and -5.132 for IMA, -4.776 for RA and -4.730 for SV grafts in non-diabetic patients. Dual comparisons of each graft are summarized in Table 3.

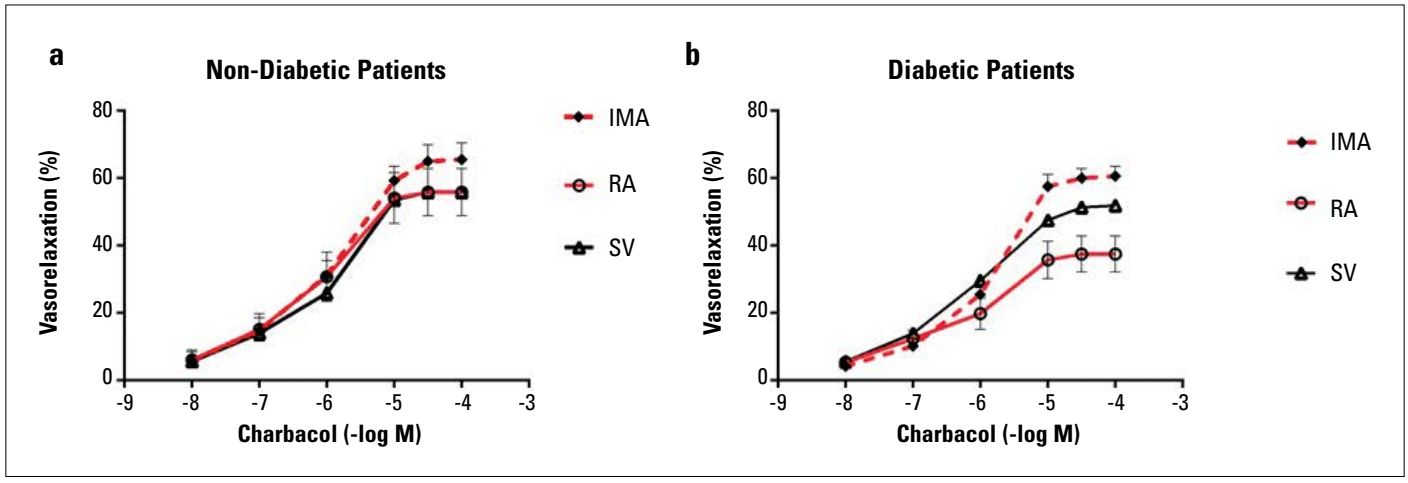

Figure 3. Comparison of vasodilatation responses of all three grafts in nondiabetic patients (3a) and diabetic patients (3b)
IMA - internal mammarian artery; RA - radial artery; SV - saphenous vein

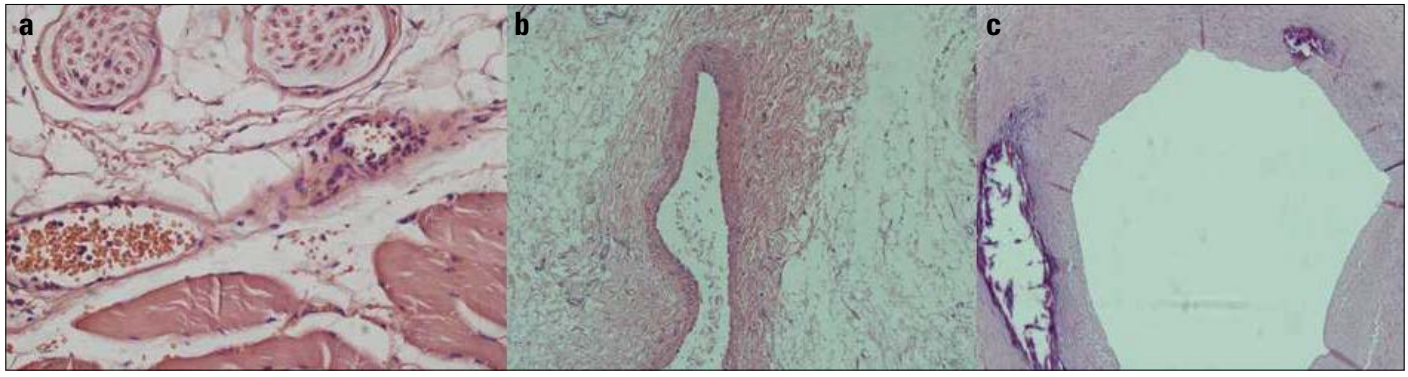

Figure 4. a-c. Sections from diabetic CABG grafts; 4a-SV shows no signs of atherosclerosis, 4b-IMA shows no signs of atherosclerosis, 4c-RA exhibiting intimal thickening and medial calcification

In Figure 4, sections from diabetic SV, IMA and RA graft samples stained with Hematoxylin-Eosin expose, if any, signs of atherosclerosis like intimal thickening or plaque formation. Figure 4a and 4b are from diabetic SV and IMA respectively, showing minimal or no signs of atherosclerosis, while figure 4c is from diabetic RA showing intimal thickening with scattered regions of medial calcification.

Discussion

Even the most optimistic assumptions estimate the prevalence of diabetes to more than double until 2030 (1). Since diabetes is known to increase the risk of coronary artery disease 2 to 6 fold and result in more extensive, diffuse, multivessel coronary artery involvement, the number of diabetic patients undergoing CABG is expected to rise (9). Unfortunately, numerous studies revealed that both short-and long-term mortality and morbidity of diabetic patients undergoing CABG surgery are higher than the non-diabetics (10, 11). One of the culprit mechanisms is shown to be lower nitric oxide (NO) levels due to hyperglycemia induced activation of protein kinase C in diabetic patients (12, 13). Broeders et al. (14) have exposed that the long term patency of the CABG grafts is positively correlated with endothelial NO production. This is in parallel with studies demonstrating that lower levels of NO synthesis resulted in both reduced graft patency and accelerated atherosclerosis following CABG (12, 13).

Internal mammarian artery is associated with better patency and survival rates in both diabetic and non-diabetic patients and therefore is the gold standard conduit in CABG (5).The IMA has an innate resistance to atherosclerosis which is believed to be due to preserved metabolic function of endothelium and better NO secretion (5, 15). The undisputed superiority of IMA grafts in both diabetic and non-diabetic patients was proven once again in our study. Better endothelial function of IMA grafts seems to oppose the metabolic effects of hyperglycemia more than any other graft.

The question of second best, on the other hand, is still uncertain. In the non-diabetic population, many surgeons prefer RA to SV in accordance with the evidence provided by reports on higher mid and long term patency rates of RA than SV grafts (16-18). Still, others prefer a more conservative approach since recent reports comparing RA and SV demonstrated conflicting results (19). In a meta-analysis that included 6 trials (1860 patients), Zhang et al. (20) concluded that RA could not always be considered better than SV since highly variable patency rates of this friable conduit fail to establish the superiority of RA grafts in terms of

outcomes or exclude the possibility of bias. Several prospective randomized trials also failed to show the superiority of RA over SV grafts (21, 22).

The choice of the right conduit is more challenging in rapidly growing diabetic population. Most studies that addressed this question compared RA or SV to IMA. The present study is the first to evaluate and compare endothelial function of RA, 'no touch' SV and IMA grafts in diabetic and non-diabetic patients. Lorusso et al. (23) have demonstrated that the morphologic and functional, mainly endothelium dependent vasodilatation, in SV grafts had deteriorated in diabetic patients while these were preserved in IMA grafts. In our study, the vasodilatation response of SV grafts in diabetic patients was slightly lower than the response in non-diabetic patients. However this did not reach statistical significance. The main explanation of this diminished difference in endothelial dysfunction of SV between diabetic and non-diabetic patients, may be the technique used in harvesting procedure of the saphenous vein. 'No touch' technique, which minimizes the damage to endothelium and vasa vasorum during harvesting and tissue handling, was employed in the present study. This method was shown to contribute substantially to the performance and patency of the SV grafts both in vivo and in vitro. Dreifalt et al. (24, 25) have also demonstrated a higher patency rate for 'no touch' SV than RA at 36 months of follow up. Our results also encourage the use of "no touch" technique as the method of SV harvesting.

Cardiovascular risk factors have different atherosclerotic consequences on different arterial beds. Kaufer et al. (26) have found that risk factors like sex, age, diabetes or peripheral vascular disease correlated only with the disease in RA but not in IMA. Likewise, age and diabetes were the strongest predictors of intimal thickness index in RA in the study of Ruengsakulracg et al. (27). *In vitro* studies have established the association of diabetes with impaired endothelial function and decreased NO bioavailability in RA grafts. Atherosclerotic process in diabetic patients was morphologically and functionally shown to be ahead of non-diabetic RA (28, 29). Optical coherence tomographic imaging of otherwise 'normal' RA revealed plaques in 76% of diabetic patients undergoing CABG surgery (30). These studies raises the question if presence of diabetes compromises the advantageous effects of RA. In present study, our findings were compatible with previous studies and indicated that the RA functionally did worse in diabetics than non-diabetics; indeed worse than any other graft in our specific study population (insulin treated long standing diabetic patients with poor gylcemic control).

The most striking finding in this study was the better performance of SV grafts than RA grafts in insulin-treated diabetic patients. This can partly be explained by the meticulous technique used in SV harvesting and partly by the predisposition of the RA to aggressive atherosclerosis of diabetic patients. The diabetic population in this study had diabetes for 8.06±4.74 years with a mean HbA1C of 8.56±2.65%, which could also have influenced the results of RA grafts. The histological analysis of the RA segments showed calcified deposits which were not evident during procurement. These findings provide evidence that an otherwise normal looking RA is usually functionally and histologically impaired.

Although there is no consensus regarding the preharvest evaluation of RA, simple Doppler US seems inadequate to determine the graft quality. Detailed evaluation of RA particularly in diabetics with high quality imaging methods like optical coherence tomography enables intravascular characterization of any plaque and precludes use of a diseased conduit (31).

Study limitations

As an in vitro tissue bath study, our study has limitations concerning extrapolation of influence of early atherosclerotic signs observed in RA graft samples to in vivo graft patency or clinical outcomes. The fact that the diabetic population in our study had long standing-poorly controlled insulin-treated diabetes also compromises the generalizability of these results to all diabetic patients. Discharged distal portion of RA grafts were used for the purpose of the study which could have also affect the results. Larger studies about the use of 'no touch' SV grafts and RA grafts in diabetic patients should be carried out before drawing conclusions on the use of arterial grafts in diabetic patients.

Conclusion

This study is the first to evaluate and compare the endothelial function of most commonly used CABG conduits, namely IMA, RA and SV in insulin treated diabetic patients to that in non-diabetics. The NO dependent vasodilatation in IMA and SV grafts did not differ significantly between diabetic and non-diabetic patients, with distinctly better vasodilatation in IMA grafts. The vasodilatation response in RA grafts were similar to SV grafts in non-diabetic patients but significantly lower in diabetic patients indicating that the RA did worse than any other graft in insulin treated diabetic patients. This study emphasizes the need of more data on the use of RA grafts in advanced diabetic vascular disease.

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