

Continued cigarette smoking after coronary artery bypass surgery reduces endothelium-dependent vasodilation in internal thoracic artery grafts

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Key words:
Coronary bypass surgery; Endothelium; Smoking.

Background. Cigarette smoking is known to promote endothelial dysfunction, thus it can be responsible for an impaired endothelium-dependent vasomotility in arterial grafts late after coronary surgery.

Methods. Twenty consecutive patients (mean age 64.5 years), previously submitted to coronary bypass surgery with the internal thoracic artery, underwent quantitative angiography of the implanted graft at long-term follow-up (mean time 2.5 years). To assess both endothelium-dependent and independent vasomotility, angiograms were acquired before and after selective infusions of acetylcholine (10^{-6} mmol/ml) and nitroglycerine (500 μ g). The predictive value of risk factors, including previous and continued smoking, for an impairment in endothelium-dependent vasomotility was assessed.

Results. Continued smoking ($p = 0.038$), but not a previous history of smoking ($p = 0.55$) was the only predictor of a reduced endothelium-dependent vasodilation. While previous smokers and non-smokers showed a similar response to acetylcholine, current smokers showed a reduced endothelium-dependent vasodilation vs non-smokers (94.8 ± 2.6 vs $99.6 \pm 2.3\%$ of the maximal vasodilative capacity, $p = 0.001$).

Conclusions. Although maintained, the vasodilative response to acetylcholine appears reduced in internal thoracic artery grafts of patients who continued smoking long term after coronary bypass surgery. Whether this could affect the long-term outcome of these patients has to be further investigated.

(Ital Heart J 2001; 2 (2): 139-141)

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Received July 26, 2000;
revision received
September 28, 2000;
accepted November 3,
2000.

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Background

Cigarette smoking has a deleterious effect on coronary arteries since it is responsible for atherosclerosis, thrombogenicity, and vasoconstriction¹. Cigarette smoking also worsens the outcome of patients after coronary surgery (CABG) by jeopardizing the integrity of venous grafts². Currently, there is a tendency to use the internal thoracic artery (ITA) as a first-choice conduit for CABG. The ITA shows an excellent angiographic patency, providing a good long-term event-free survival³. To investigate the effect of previous and/or continued cigarette smoking on this graft, we studied ITA's vasomotor response to acetylcholine, an endothelium-dependent vasodilator, by means of quantitative angiography.

Methods

Twenty consecutive patients (mean age 64.5 ± 7.5 years), with no evidence of angi-

na and good left ventricular function (ejection fraction $> 40\%$) were submitted to an angiographic follow-up (mean time 2.5 ± 0.9 years) after CABG with pedicled ITA. Patients gave informed consent and the protocol was approved by the Institutional Review Board. Among the study group, 10/20 patients (previous smokers) had a history of smoking before CABG: 6 of them (current smokers) continued smoking at the time of follow-up. No patient started smoking after CABG.

Baseline angiograms of the ITA graft were acquired in a fixed radiological view, then acetylcholine was injected into the ITA in three increasing dosages (10^{-8} , 10^{-7} and 10^{-6} mmol/ml \times 3 min each) under electrocardiographic and blood pressure monitoring. Angiograms were repeated within 1 min of each infusion and after a subsequent administration of nitroglycerine (500 μ g). End-diastolic frames were chosen and the mean diameter of the proximal part of the ITA

was calculated by quantitative analysis (Quantocor QCA 3.0, Pie Medical Imaging, Maastricht, The Netherlands) for baseline, post-acetylcholine (highest dose achieved) and post-nitroglycerine sequences.

As nitrates are considered endothelium-independent vasodilators, post-nitroglycerine mean diameter was taken as the maximal vasodilative capacity of the ITA: the endothelial contribution to vasodilation was then calculated for each patient as the ratio (in percentage) between post-acetylcholine (highest dose achieved) and post-nitroglycerine mean diameters, normalized for baseline diameters.

Statistical analysis was performed by means of the Statistical Package for the Social Science version 8.0 for Windows (SPSS Inc., Carey, NC, USA). Descriptive statistics are expressed as mean values \pm SD or as percentages. Univariate regression analysis was performed to evaluate the influence of clinical features, medications, or risk factors on endothelium-dependent vasodilation, included as a continuous variable. Variables with a probability value of < 0.20 were selected for multivariate regression analysis. Analysis of variance was performed for assessing statistical differences between groups (previous and current, smokers and non-smokers).

Results

All patients tolerated the highest acetylcholine dose (10^{-6} mmol/ml) without any significant side effects.

At univariate analysis, continued smoking ($p = 0.038$), but not a previous history of smoking before surgery ($p = 0.55$) was the only predictor of an endothelium-dependent vasodilation impairment, thus a multivariate analysis was not performed. Smokers and non-smokers showed similar characteristics regarding clinical features, medications or risk factors (Table I).

Previous smokers vs non-smokers showed comparable baseline values and maximal vasodilative capac-

ity of the ITA and endothelium-dependent vasodilation was not significantly different between the two groups (97.0 ± 3.9 vs $98.9 \pm 2.2\%$ of the maximal vasodilative capacity, $p = 0.20$). Current smokers vs non-smokers also showed comparable baseline values and maximal vasodilative capacity of the ITA, but endothelium-dependent vasodilation was significantly lower in current smokers than in non-smokers (94.8 ± 2.6 vs $99.6 \pm 2.3\%$, $p = 0.001$, 95% confidence interval -7.1 to -2.1) (Fig. 1).

Discussion

This study demonstrates that, though ITAs maintain a vasodilative response to acetylcholine infusion in the presence of coronary atherosclerosis and after CABG, continued smoking, but not a previous history of smoking before surgery, predicts a reduction in endothelium-dependent vasodilation of the arterial graft.

Cigarette smoking is known to reduce the production of nitric oxide, alter rheology at the endothelial surface and upregulate the expression of leukocyte adhesion molecules. Smoking can enhance the oxidation of circulating low-density lipoproteins, thus leading to the development of atherosclerosis. It is also able to promote thrombosis onto the dysfunctional endothelium. In the clinical setting this translates into an increased incidence of cardiac adverse events⁴.

Previous studies have reported that smokers have a worse outcome after CABG, due to an increased hazard for perioperative complications, graft occlusion and re-intervention². Referring to the unfavorable results and hypothesizing a waste of health care resources, some authors have even suggested not offering CABG to smokers⁵.

Although smoking can be held responsible for myocardial and coronary damage occurring before surgery, a previous history of smoking before CABG does not seem a major determinant for a future impairment of the

Table I. Clinical features, medications and other risk factors for previous and current, smokers and non-smokers.

	Previous		Current	
	Smokers (n=10)	Non-smokers (n=10)	Smokers (n=6)	Non-smokers (n=14)
Age (years)	64.4 \pm 5.8	64.5 \pm 9	64.5 \pm 7.3	64.5 \pm 7.8
Follow-up (months)	25.1 \pm 18.3	35.4 \pm 19.8	21.8 \pm 17.7	34.5 \pm 19.3
Sequential anastomosis	3 (30%)	4 (40%)	3 (50%)	4 (29%)
LVEF (%)	51.5 \pm 9.2	51.9 \pm 9.5	51.4 \pm 8.9	52.1 \pm 9.7
ACE-inhibitor use	3 (30%)	4 (40%)	3 (50%)	4 (29%)
Statin use	3 (30%)	5 (50%)	2 (33%)	6 (43%)
History of				
Hypercholesterolemia	3 (30%)	6 (60%)	2 (33%)	7 (50%)
Systemic hypertension	3 (30%)	3 (30%)	2 (33%)	4 (29%)
Diabetes mellitus	2 (20%)	0	1 (16%)	1 (7%)
MI in the grafted area	2 (20%)	2 (20%)	1 (16%)	3 (21%)

LVEF = left ventricular ejection fraction; MI = myocardial infarction.

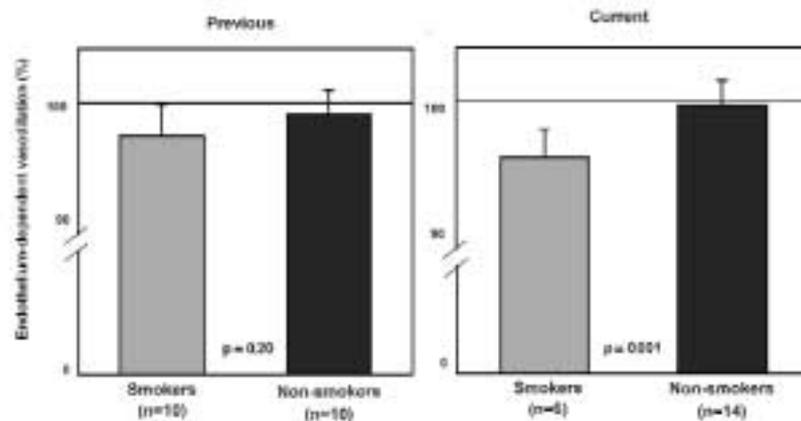


Figure 1. Endothelium-dependent vasodilation (as percentage of the maximal vasodilative capacity) of internal thoracic artery grafts in smokers and non-smokers.

arterial graft integrity. In a previous study we found that both endothelium-dependent and independent vasomotility of arterial conduits are correlated with the age of the patient but do not deteriorate over time after surgery⁶. Even in the presence of diffuse atherosclerosis, and differently from coronary arteries, which show an aberrant vasoconstrictive response to acetylcholine, ITAs vasodilate regardless of any risk factor, including smoking before surgery.

However, in patients who continued smoking after surgery endothelium-dependent vasodilation is mildly but significantly impaired: whether this finding might negatively influence the long-term outcome in those patients receiving arterial grafts is questionable, also due to the small dimensions of our study group. Nevertheless, an effort should be made in convincing patients who undergo CABG of the beneficial effect of stopping smoking with the aim at preserving the integrity of the implanted grafts.

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