Evidence of Nitric Oxide Produced by the Internal Mammary Artery Graft in Venous Drainage of the Recipient Coronary Artery

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Background. **The endothelium of the internal mammary artery produces nitric oxide in greater quantity than other vessels employed in revascularization of the ischemic myocardium. The aim of this study was to measure the concentration of stable metabolite (nitrite) of the endothelium-derived nitric oxide in the venous drainage (anterior interventricular vein) of the recipient coronary artery, which was the left anterior descending branch. The sampling was carried out before and after anastomosis completion.**

Methods. **Nitrite levels in the anterior interventricular vein, before and after anastomosis completion, in the left internal mammary artery free flow, and in the subclavian vein were measured. Fluroscopy after 4-hydroxycoumarin nitrozation was utilized to measure nitrite content of blood samples in 50 consecutive, partly heparinized patients undergoing off-pump coronary bypass surgery. Nitrate content of all samples was removed by Cadmium pearls.**

Results. **One hundred and sixty-four samples taken from 41 patients were feasable to analyze. A significant increase of nitric oxide (nitrite) level was found in the anterior interventricular vein, when comparing concentrations measured before and after the anastomosis between the left internal mammary artery and the left anterior descending artery. Mean values in the anterior inteventricular vein before and after anastomosis completion were as follows: 44.8 μMol (SD 4.9) and 70.7 μMol (SD 8.1), respectively.**

Conclusions. **The increased production of nitric oxide by the internal mammary arterial graft may provide a perpetual vasodilatory response and partially protect the distal coronary vessel from atherosclerosis.**

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Studies on long-term patency rate of the internal mammary artery (IMA) bypass graft unequivocally reveal that atherosclerosis rarely develops in this artery [1–3]. Autopsy specimens of diffuse atherosclerotic coronaries of elderly people were compared with the internal mammary artery morphology of the same individual, showed no significant atherosclerosis in the latter [4]. Special morphologic structures (elastin) between the intima and internal elastic lamina of the internal mammary artery, elasticity itself, intact vasoregulation, and physiologic adaptability may play a role in maintaining this unique condition 5–7. Cosgove and coworkers [8] reported that internal mammary artery bypass grafts cause less progression of atherosclerosis in bypassed coronary arteries than do saphenous vein grafts.

In vitro studies described endothelial function of the internal mammary artery in detail. Experimental and clinical data revealed, that the production of endothelium-derived nitric oxide in the internal mammary artery is significantly greater than that observed in saphenous vein [9–11]. Besides the mentioned vessel wall structure, the high concentration (55 to 81 μMol; data of this study) of continuously produced nitric oxide may play a role in resistence to atheroclerosis since, in case of intimal injury, this substance maintains an inhibition of local platelet aggregation and adhesion, while in the tunica media it blocks smooth muscle cell mitogenesis. Meanwhile, intravasally, endothelium-derived nitric oxide induces local and downstream vasodilatation. It is also known that, in the balance of endothelium-dependent vasoregulation of the internal mammary artery, there is a tendency toward vasodilatation (nitric oxide plus prostacyclin against endothelin plus thromboxane) [12–14].

In this study—utilizing a modified method for screening stable metabolite of endothelium-derived nitric oxide (described in detail in other work of ours)—we investigated whether the internal mammary artery bypass graft would increase nitric oxide concentration in the recipient coronary vessel [15]. We hypothesized, that an enhancement of stable metabolite concentration of nitric oxide could be measured in the venous drainage of the recipient coronary artery.

Patients and Methods

This study was conducted under approval of the Institutional Review Board of the National Medical Centre. Between January 2002 and January 2003, 50 patients underwent off-pump coronary revasclarization utilizing the left internal mammary artery, anastomosed to the left anterior descending branch. Additionally, vein grafts were also applied in patients with triple vessel disease (in 41 of

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Abbreviations and Acronyms

AIV = anterior interventicular vein
AIV1 = AIV blood sample taken prior to anastomosis completion
AIV2 = AIV blood sample taken after anastomosis completion
EDNO = endothelium derived nitric oxide
IMA = internal mammary artery
LAD = left anterior descending artery
LIMA = left internal mammary artery
μMOL = micromol
s.d. = standard deviation

50 cases). All patients gave their informed consent regarding blood tests and analysis in accordance with the Helsinki declaration.

Patient inclusion criteria included a usable internal mammary artery (free flow greater than 80 mL/min). Intact anatomy of the left subclavian and internal mammary artery was proved by angiography. Feasable sampling site for insertion a polyethylene canula into the anterior interventricular vein (AIV) was also a prerequisite. No drug containing nitrates was given to patients in the perioperative period. (Patients requiring nitrates for clinical reasons were excluded from the study.)

Preoperative demographics and relevant clinical data are summarized in Table 1.

Surgical Techniques

All patient underwent operation and through a standard median sternotomy under general anaesthesia. Normothermia was maintained with heating mattress and warmed (37°C) intravenous fluids. After harvesting the pedicled internal mammary artery, it was wrapped into a swab containing 80 mg papaverine diluted to 200 mL isotonic saline solution. The distal end of the IMA was not dissected until the anastomosis construction. Patients received a "half pump" dose of heparin (150 U/kg), followed by 2,500 U every 25 minutes to maintain activated clotting time greater than 300 seconds. Myocardial revascularization was carried out off pump using stabilizers for immobilization of the recipient coronary vessel. No conversion was necessary. Left internal mammary artery to left anterior descending branch anastomosis completion was carried out first, as a rule. Grafts per patient were 3.2, and arterial grafts per patient, 1.66.

Table 1. Preoperative Patient Demographics

Variable	Patient (n = 50), %
Mean age (years)	62.1 ± 2.7
Male sex	82
Ejection fraction <50%,	52
Previous AMI within 1 year	38
Repeat AMI within 90 days	14
Rest angina in preceding week	70

AMI = acute myocardial infarction.

After heparinization a polyethylene canula with a diameter of 1 mm was inserted into the anterior interventricular vein for passive sampling. The quantity taken was 4 mL (AIV1).

This was followed by taking a left internal mammary artery (LIMA) free flow sample at 75 mm Hg mean systemic pressure. As a third step, a sample was taken from the anterior interventricular vein, 5 minutes after the anastomosis completion (AIV2). Finally, a sample from the subclavian vein was collected before protamine administration, as a reference point. (In the first 9 patients, a steel needle was used for sampling from the anterior interventricular vein with active suction, which resulted in severe hemolysis, making these samples unsuitable for evaluation.)

All test tubes containing 4 mL sampled blood were stored in a tank with ice cubes (2°C to 4°C) and transported to the laboratory without delay, where all were deep frozen for later analysis. (Nitrite is stable in frozen blood samples for at least 1 year). Nitrite level determination was carried out utilizing the modified Takafumi Ohta method, details of which are given elsewhere [14]. Nitrate content of all samples was removed on Cadmium pearls. Sample analysis was carried out without the knowledge of its origin.

Statistical Analysis

Values are expressed as the mean ± SEM. Comparisons of the four kinds of samples were carried out by analysis of variance (ANOVA) and the Tukey method. A p value of less than 0.05 was considered as statistically significant.

Results

Nitrite concentration in the interventricular vein before LIMA-LAD anastomosis is 44.8 μmol (SD 4.9), which increased to 70.7 μmol (SD 8.1) after anastomosis completion ($p < 0.001$) The highest nitrite concentration was measured in the LIMA free flow, and the lowest in the subclavian vein. The differences between the groups are statistically significant (ANOVA F [3.160] = 215.2; $p < 0.001$; Fig 1). There is a positive correlation between nitrite concentration of the LIMA free flow sample and that of the AIV sample taken after anastomosis completion (AIV2; Fig 2).

Comment

The long-lasting patency rate of the internal mammary artery bypass graft with high flow capacity relates to well identified factors. One of these being the intact vasoregulation of humoral (adenosine, inosine) and vasomotor (central afferentation) components. The unique relation between the intima and the internal elastic lamina, which contains a high number of elastic fibers, as a special hystologic structure, also plays an important role in maintaining sufficient blood supply. Also, ideal geometry