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The Shelhigh No-React® bovine internal mammary artery: a questionable alternative conduit in coronary bypass surgery?☆

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Abstract

Background: Increasing age and comorbidities among patients undergoing coronary artery bypass surgery (CABG) stimulates the exhaustive research for alternative grafts. No-React® treatment should render the tissue resistant against degeneration and reduce early inflammatory response. The aim of the present study was an invasive assessment of the patency of No-React® bovine internal mammary artery (NRIMA grafts) used as bypass conduit in CABG surgery. **Patients and methods:** Nineteen NRIMA grafts were used in 17 patients (2.9%) out of a total of 572 patients undergoing CABG surgery within a 12-month period. All intraoperative data were assessed and in-hospital outcome was analysed. Follow-up examination was performed 7.0 ± 4.0 months after initial surgery, including clinical status and coronary angiography to assess patency of the NRIMA grafts. **Results:** Average perioperative flow of all NRIMA grafts was 71 ± 60 ml/min. One patient died in hospital due to a multi-organ failure. Four patients refused invasive assessment. Follow-up was complete in 12 patients with overall 13 NRIMA grafts. Nine NRIMA grafts (69.2%) were used for the right coronary system, two NRIMA grafts (15.4%) on the LAD and two on the circumflex artery. Graft patency was 23.1% and was independent of the intraoperative flow measurement. **Conclusions:** NRIMA grafts show a very low patency and cannot be recommended as coronary bypass graft conduits. Patency was independent of the perioperative flow, assessed by Doppler ultrasound. Because of this unsatisfying observation, this type of graft should be utilised as a last resource conduit and used only to revascularise less important target vessels, such as the end branches of the right coronary artery.

Keywords: CABG; Graft; Shelhigh; Outcome; Patency; Alternative

1. Introduction

Patients undergoing coronary artery bypass surgery (CABG) currently present with an increasing age and risk-profile. In older patients quality of saphenous vein grafts may be impaired. Therefore, alternative bypass conduits are always welcome. Arterial grafts (such as bilateral internal thoracic artery and radial artery) represent the best option, however harvesting is more demanding and the availability is limited. Previous attempts with xenografts and synthetic conduits in CABG surgery were not successful. No-React treatment is a proprietary technique established by Shelhigh, Inc., Union, NJ, USA: there is increasing evidence of its ability to resist in vivo and in vitro calcification. However, these findings are discussed controversially [1–3].

No-React bovine internal mammary artery (NRIMA) conduit for CABG surgery has been available for restricted clinical use in Europe. Only a few clinical experiences have been published in the literature so far [4]. The manufacturer underlines that the indication and the use of this product are the responsibilities of the treating physician and that patency of NRIMA as coronary graft is around 60–80% and therefore less favourable than the patency observed with the same conduit in peripheral vascular disease. Shelhigh recommends the use of anticoagulation, antiaggregants or a combination of the two, for the first 3 months following surgery and salicylic acid once daily as life-long prophylaxis. The aim of the present study was the invasive assessment of patency of No-React® bovine internal mammary artery (NRIMA grafts) following CABG surgery.

2. Patients and methods

Five hundred and seventy two patients underwent CABG surgery during a 12-month period at our institution. In 17 patients (2.9%) an NRIMA graft was implanted due to unavailable autologous graft material. All in-hospital data of these patients were analysed, especially the surgical

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report looking at the target vessel, which received the NRIMA as bypass graft, its diameter and the flow measured in the graft at the end of surgery. Transit-time flow was measured with the Medi-Stim Butterfly Flowmeter (Medi-Stim AS, Oslo, Norway). An invasive follow-up was performed in all patients 7.0 ± 4.0 months after surgery. One patient died in hospital due to a multi-organ failure, 4 patients refused an invasive follow-up and 12 patients (70.6%) underwent coronary angiography. Patient characteristics are summarized in Table 1. All patients received oral anticoagulants for at least 3 months following surgery combined with salicylic acid and 100 mg salicylic acid thereafter according to the instructions of the manufacturer.

3. Results

The mean age of the 17 patients was 73.0 ± 4.4 years and 41.8% were male gender. Patients presented with the usual cardiovascular risk factors encountered in CABG surgery population (arterial hypertension 88.2%, diabetes mellitus 29.4%, history of smoking 41.2% and cholesterol 52.9%). Average EuroScore was 7.0 ± 3.4. Average number of distal anastomoses was 3.4 ± 0.9. Internal thoracic artery was used in 16 patients, in 12 of them bilateral. The reasons for using NRIMA grafts were related to the poor quality of the saphenous vein in 16 patients (94.1%) and in 8 patients (47.1%) harvesting of the radial artery was not possible due to a pathological Allen's test. In 17 patients, a total of 19 NRIMA grafts were implanted. Eleven grafts (57.3%) were used for the right coronary artery (RCA) out of which five (26.3%) were anastomosed to the end branches of the right coronary system, four grafts (21.1%) were used for the left anterior descending artery (LAD) or its side branches and the remaining four grafts (21.1%) were anastomosed to the circumflex artery (RCX). In four patients (21.1%) the NRIMA was used as a sequential bypass. Average distal diameter of the NRIMA was 3.0 ± 1.3 mm. The intraoperative flow, assessed by Doppler ultrasound, was 71.0 ± 59.5 ml/min. The flow was 100.0 ± 90.1 ml/min for the RCA, 40.0 ± 15.8 ml/min for the end branches of the RCA, 87.0 ± 40.4 ml/min for the LAD and 55.0 ± 20.8 ml/min for the RCX. There was no difference looking at the quality and the diameter of the target vessel at the site of the distal anastomoses. Good quality of the target vessel was reported in nearly 50% of the sites of the distal anastomoses in all three vessels and the diameter of the LAD was slightly higher, compared to the diameter reported for RCX and RCA. There were no significant differences between quality and diameter in vessels grafted with NRIMA or with the internal thoracic artery, respectively, saphenous vein grafts.

Twelve patients accepted an invasive assessment with coronary angiography after a mean follow-up period of 7 ± 4 months: a total of 13 NRIMA grafts were assessed (Table 2). Four grafts (30.8%) on the RCA, five (38.5%) on the end branches of the RCA, two (15.4%) were anastomosed to the LAD and two on the RCX. Three out of 13 NRIMA grafts were patent (23.1%): one NRIMA graft anastomosed to the LAD and two grafts anastomosed to the end branches of the RCA. Eight patients (66.7%) were asymptomatic at the time of follow-up. The remaining four patients suffered from unspecific symptoms. Patency of the internal thoracic artery was 100% (nine left internal thoracic artery and six right thoracic artery) and patency of saphenous vein graft was 94% (15 out of 16 vein grafts were patented).

4. Discussion

Alternative conduits in CABG surgery may be welcome. An off-shelf graft of good quality would allow reducing the incidence of postoperative problems at the site of harvesting and facilitating surgical procedure. However, previous attempts with xenografts and synthetic conduits in CABG surgery were not successful and autografts are not routinely available. The No-React bovine internal mammary artery is described by the company as a valuable alternative with an acceptable patency rate in the animal model. Preliminary clinical results revealed a patency rate of 57% at a follow-up

Table 1
Patients' characteristics (n = 17)

Number of patients	17	100.0%
Mean age (years)	73.0 ± 4.4	
Male gender	7	41.2%
Height (cm)	166.0 ± 7.2	
Weight (kg)	76.0 ± 16.1	
Risk factors		
Arterial hypertension	15	88.2%
Diabetes	5	29.4%
Cholesterol	5	52.9%
History of smoking	7	41.2%
EuroScore	7.0 ± 3.4	
Intraoperative data		
Combined surgery	10	58.8%
±AVR	9	
±AVR and Asc Aorta	1	
ECC-time (min)	104.3 ± 43.3	
ACC-time (min)	65.2 ± 30.0	
Postoperative data		
Myocardial infarction	1	5.9%
Atrial fibrillation	2	11.8%
Length of stay (days)	14.3 ± 14.8	

Results displayed as absolute values or average value ± first standard deviation. AVR = aortic valve replacement; AVR and Asc Aorta = aortic valve replacement and ascending aorta replacement; ECC-time = extracorporeal circulation time; ACC-time 0 aortic dross-clamping time.

Table 2
Follow-up data

Number of patients	17	100.0%
Follow-up mortality	1	5.9%
Refused PCI	4	23.5%
Follow-up completed	12	70.6%
Average follow-up (m)	7.0 ± 4.0	
Number of NRIMA	13	100.0%
RCA end branches	4	
RCA end branches	5	
LAD	2	
Circumflex artery	2	
Patency at follow-up		
Overall	3	23.1%
LAD	1	
RCA end branches	2	

of 2.5 years. However, these results have been obtained in a small collective of six patients revascularised with seven NRIMA grafts [4].

In our experience alternative grafts are usually required in less than 3% of the patients undergoing CABG surgery. The widespread use of the radial artery as arterial graft in our institution helps to solve these problems when the quality of saphenous vein was not sufficient enough. In our collective the NRIMA was anastomosed to the RCA in the majority of the patients. Average intraoperative flow (71.0 ± 59.5 ml/min) was slightly higher from the average flow usually measured in conventional grafts [5]. However, graft patency was independent of the intraoperative flow measurement. Two out of three grafts (23.1%) anastomosed to the end branches of the right coronary system were patent follow-up but had a significantly lower intraoperative flow that observed in the overall collective (40 ± 16 ml/min in comparison to the average flow of 71.0 ± 59.5 ml/min in the total collective). This observation is not congruent with the findings described in the literature for autologous grafts where patency is superior in high-flow grafts [6]. One explanation for the finding that low-flow NRIMA grafts have a better mid-term patency than high-flow grafts may be the observation described from Ostapczuk et al. [7] in the calf model, where a chronic rejection of the NRIMA was observed.

In other Shelhigh No-React treated implants, for instance the porcine pulmonic valve conduit, Schreiber et al. [8] found that these valves are largely resistant to calcification. However, pseudointimal peel formation was found in all explanted valves, which finally led to multilevel conduit stenoses [8]. Poor experiences have also been described by another group using a porcine internal mammary artery in a calf model. In an observation period of 103 days one calf died due to an acute thrombosis of the graft and in the remaining four calves the porcine internal mammary artery was occluded due to multiple calcifications and a severe chronic rejection (host–graft immunological response) [7]. An in vivo evaluation of the No-React bovine internal mammary artery in a sheep-model revealed a progressive increase of calcification within 3–6 months with minimal inflammatory changes and preservation of the inner surface and ultrastructure [9].

Further advances in tissue engineering will hopefully provide us with a valuable bypass conduit alternative in cardiac surgery in the near future. There are some promising reports about endothelial cell-seeded bovine internal mammary artery which could be an alternative in the future [10].

NRIMA grafts have a very low patency and cannot be recommended as bypass conduit for coronary surgery. Mid-term patency is unpredictable and independent from the intraoperative flow. As a last resource bypass conduit, this graft may be used only for less important target vessels, such as the end branches of the right coronary artery.

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Appendix A. Conference discussion

Dr M. Grimm (*Vienna, Austria*): May I ask you two questions? The one is I do fully agree with you that this is not a graft we should use. Anyhow, you recommend this for the small vessels as an alternative graft, which I think the smaller the vessel, the higher the risk this graft will occlude.

The second question: When using it, do you think you can overcome it by very aggressive antiplatelet therapy?

Dr Englberger: According to the first question, there is in our small patient cohort also a bit of a bias compared to the native grafts. We tried to avoid placing this alternative graft in really main vessels. However, we had to do it in two LAD grafts, and one was occluded afterwards.

To your second question: we did an oral anticoagulation for 3 months in these patients. This is the recommendation which is given by the company followed then by regular antiplatelet therapy with aspirin. I cannot say if more aggressive antiplatelet therapy, maybe a combination of aspirin and clopidogrel, will overcome this problem.