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First Report of No-React Bovine Internal Mammary Artery Performance and Patency

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ABSTRACT

Background: No-React treatment is known to render tissues resistant to calcific degeneration and to reduce early inflammatory response. No-React bovine internal mammary artery (NR-IMA) is available for restricted use in Europe. In this first study, our aim was to use magnetic resonance imaging (MRI) to investigate the clinical performance and patency rates of this conduit.

Methods: Seven patients received 8 grafts with NR-IMA. Approval from the Medical Devices Agency of the United Kingdom was obtained for use of this material. One patient needed salvage coronary artery bypass grafting (CABG). Graft patency was investigated with cardiac MRI. One patient was excluded from the MRI study because of the presence of intracerebral metal clips. The mean follow-up period was 2.5 years with a range of 1 to 4.5 years.

Results: There was no mortality in this group. After treatment 6 patients were asymptomatic, and 1 patient had class II anginal symptoms. Four (57%) of the 7 NR-IMA grafts remained patent. The longest patency was 4.5 years in a patient who underwent salvage CABG. Other associated grafts in this cohort of patients were 5 left internal mammary arteries (all patent), 1 radial artery graft (patent), and 7 saphenous vein grafts (4 [57%] of 7 patent). There were no occluded NR-IMA grafts in a patient with patent vein grafts.

Conclusion: We concluded that at 2.5 year follow-up, NR-IMA had a patency rate of 57% (4 of 7 cases). This rate matched the vein graft patency rate in this cohort of patients. With the longest patency of 4.5 years, use of NR-IMA seems to hold promise for the future.

INTRODUCTION

Since the advent of coronary artery bypass surgery, surgeons have felt the need for an off-the-shelf conduit. Current practice is standardized to a combination of arterial and venous grafts. Any future developments in new conduit technology have to at least match the results of current practice. Previous attempts with xenografts and synthetic conduits proved unsuccessful. No-React treatment is an established technique, and there is growing evidence of its ability to resist in vitro and in vivo calcification. Experience with No-React-treated pericardium, valves, and conduits is accumulating. Marked attenuation of the inflammatory process and calcification in No-React-treated aortic valve cusps was reported by Abolhoda et al [1996a]. Those investigators also reported similar results with No-React-treated pericardium [Abolhoda 1996b]. Similar experience with No-React-treated pulmonic valve conduits in pediatric practice was reported by Marianeschi et al [2001].

No-React bovine internal mammary artery (NR-IMA) (Shelhigh, Inc., Union, NJ, USA) conduit for coronary artery bypass grafting (CABG) has been available for restricted clinical use in Europe. (The NR-IMA recently has been renamed the Shelhigh internal mammary artery [SIMA]). There have been scattered reports of its use, most being notifications of personal experiences by a few cardiac surgeons. There have been no data on the extent of the use, clinical performance, and patency of this conduit. Our aim was to study the clinical performance and patency rates of NR-IMA.

MATERIAL AND METHODS

In our experience over the last 5 years, 8 NR-IMAs were used in 7 patients. Use of the material was approved by the Medical Devices Agency of the United Kingdom after applications were made explaining the clinical justification of its use in each patient. This study was conducted after approval of the local ethics committee. We retrospectively reviewed the patients' records to study the clinical situation of each patient. Operative notes were reviewed for details about the NR-IMA target vessel. Clinical status and cardiac symptoms at the time of last clinical review were recorded. All the patients received standard antiplatelet therapy with aspirin. Use of anticoagulation with warfarin was left to the discretion of individual surgeons. Of the 7 patients, 6 underwent cardiac magnetic resonance imaging (MRI). The studies were performed with a cardiac-optimized 1.5 Tesla imager (Sonata; Siemens, Malvern, PA, USA). All images were obtained with

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breath hold and were cardiac gated. Parallel black blood (turbo spin echo) images were obtained axially through the ascending aorta to identify and localize the grafts. Oblique images were then obtained along the long axis of the grafts. Selected non-contrast-enhanced three-dimensional fast imaging with steady precession angiographic images was then performed along the grafts. One patient could not undergo imaging because of the presence of an intracranial metal clip applied for subarachnoid hemorrhage. Clinical and operative details on all the patients in this study are as follows.

Patient 1

A 70-year-old woman presented with unstable angina and underwent urgent CABG after elective preoperative insertion of an intraaortic balloon pump (IABP). The estimated ejection fraction was 30%. The patient had bilateral varicose veins, and availability of adequate conduit was a concern. At surgery the patient received the following grafts: left internal mammary artery (LIMA) to left anterior descending (LAD) artery, right internal mammary artery to distal right coronary artery (RCA), and radial artery (RA) to obtuse marginal (OM) artery. The patient recovered well from this initial procedure only to have her condition deteriorate suddenly with pulmonary edema on the second postoperative day. The diagnosis was severe mitral valve regurgitation resulting from rupture of a papillary muscle. Aggressive resuscitation was started, and emergency surgery was performed. At surgery, the RA conduit to the OM artery was found to be blocked. Mitral valve repair was performed, and NR-IMA was used to regraft the OM. The patient made an excellent recovery from her second surgery, and after 4.5 years of follow-up remained well and asymptomatic. She received anticoagulation with warfarin for 3 months to avoid early NR-IMA graft occlusion.

Patient 2

A 68-year-old obese woman underwent urgent CABG for unstable angina. She had grossly edematous legs and poor-quality leg veins. She had bilateral positive Allen test results, which made both RAs unusable. At surgery she received the following grafts: LIMA to LAD and saphenous vein grafts (SVGs) to RCA and OM. NR-IMA was used to graft the first diagonal artery. The patient made a good recovery and received anticoagulation with warfarin for 3 months. At review 2 years and 4 months after surgery, the patient was asymptomatic but continued to recover from venous ulceration of the leg, which resulted in delayed wound healing.

Patient 3

A 70-year-old woman presented with unstable angina and received the diagnosis of 99% left main stem stenosis. She had an episode of ventricular fibrillation arrest after which an IABP was inserted. At emergency surgery, she received the following grafts: SVG to first and second OM arteries and LIMA to the first diagonal artery. The LAD was found ungraftable because of small caliber and diffuse disease. NR-IMA was used to graft the proximal RCA. After 2 years and 2 months of follow-up, the patient was asymptomatic. She received anticoagulation with warfarin for 3 months.

Patient 4

A 71-year-old woman presented with class III angina and bilateral varicose veins. Because of a history suggestive of Raynaud disease, both RAs were unusable. A short segment of usable vein was harvested from the upper thigh. At surgery, the patient received the following grafts: LIMA to first diagonal artery and NR-IMA to first OM artery. After distal anastomosis of the posterior descending artery (PDA), the SVG fell short of adequate length to reach the proximal aorta. A composite graft was constructed with proximal anastomosis of a suitable length of NR-IMA to the SVG, facilitating its proximal anastomosis to the ascending aorta. The LAD was found to be small, diffusely diseased, and ungraftable. The patient did not receive anticoagulation with warfarin. After 2 years and 3 months of follow-up, the patient was found to have residual angina adequately controlled with antianginal medication.

Patient 5

A 69-year-old obese man presented with class III angina. He had bilateral varicose veins. One length of suitable vein was harvested from the thigh and used to graft the first diagonal artery. LIMA was used to LAD and RA to the first OM. Proximal RCA was grafted with NR-IMA. The patient did not receive anticoagulation with warfarin. After 2 years and 6 months of follow-up, the patient was found to be asymptomatic.

Patient 6

An 82-year-old man presented with advanced mitral valve disease along with 2-vessel coronary artery disease. He had bilateral varicose veins and was of very thin build. He underwent mitral valve replacement and CABG with NR-IMA to the PDA and first OM. Because of the risk of devascularization of the chest wall, LIMA was not used. The patient received anticoagulation with warfarin for 3 months.

Patient 7

A 71-year-old woman underwent CABG for coronary artery disease. In the past she had undergone stripping of both long saphenous veins because of varicosities. Two years prior to CABG she experienced subarachnoid hemorrhage and was treated with clipping of the intracerebral aneurysm. She underwent CABG with LIMA to LAD, RA to RCA, and NR-IMA to first OM. At review 4 years and 4 months after surgery, she was asymptomatic. Because of the presence of intracerebral metal clips, she could not undergo MRI.

RESULTS

In this small cohort of patients, there were 5 women and 2 men with a mean age of 71.5 years (range, 68-82 years). Mean duration of follow-up was 29 months with an SD of 13 months (range, 12-54 months). Among the 6 patients who underwent MRI, there were a total of 20 grafts for study, of which 7 were NR-IMA grafts. Other grafts in the study were 5 LIMAs, 1 RA, and 7 SVGs. Four (57%) of the 7 NR-IMA grafts were found to be patent. All the arterial grafts were patent, and of the 7 vein grafts, 4 (57%) were patent. In this

Summary of the Relevant Data on the No-React Internal Mammary Artery (NR-IMA) Target Vessel and Patency*

Patient No.	Age, y	NR-IMA Target Vessel	Target Vessel Size, mm	Target Vessel Runoff	Follow-up, y	Patency
1	70 (salvage CABG)	OM	1.5	Good	4.5	Patent
2	68	DG	1.25	Moderate	2.4	Occluded
3	70	RCA	2	Moderate	2.2	Patent
4	71	DG	1.5	Poor	2.3	Occluded
5	69	RCA	2	Good	2.6	Patent
6	82	PDA	2	Moderate	1	Patent
		OM	2	Poor	1	Occluded

*CABG indicates coronary artery bypass grating; OM, obtuse marginal artery; DG, diagonal artery; RCA, right coronary artery; PDA, posterior descending artery.

study, NR-IMA graft performed as well as SVGs did. The longest patency was 4.5 years in a patient who underwent salvage myocardial revascularization in the postoperative period. Patency of the NR-IMA grafts in relation to the other associated grafts in each patient was of observational interest. There were no occluded NR-IMA grafts in a patient in whom all vein grafts were patent. In 1 patient, NR-IMA remained patent in the presence of an occluded vein graft. NR-IMA graft patency data along with relevant patient data are summarized in the Table. MRI views of patent NR-IMA grafts are shown in Figures 1 and 2.

DISCUSSION

Our understanding of the mechanisms that contribute to allograft and xenograft degeneration in the body is steadily improving. Bioprosthetic tissue valves and conduits have variable and unpredictable durability. Connective tissue in native valves and blood vessels is in a metabolic and biological continuum in the body and undergoes constant remodeling and regenerative changes in its structural proteins. Unfortunately, all currently available bioprosthetic material is devoid of such metabolic integration. Foreign-body reactions and immunological cellular responses are observed in these tissues soon after they are implanted [O'Brien 1984]. Macrophage and lymphocyte infiltration results in ultrastructural changes in the connective tissue matrix. This process renders the tissues prone to platelet aggregation and further cellular infiltration. This cascade of inflammatory changes paves the way for long-term degenerative calcification, which results in failure of the prosthesis. Free glutaraldehyde and aldehyde molecules can leak from the tissue and evoke a strong foreign-body reaction that initiates the chain of degenerative events. No-React treatment is a heparin-based proprietary detoxification process that further stabilizes tissue cross-linking and prevents the release of aldehyde and glutaraldehyde molecules [Gabbay 1994]. Abolhoda et al [1996b] reported a significant reduction in calcification and inflammatory changes in No-React-treated bovine pericardium compared with glutaraldehyde-treated pericardium after subcutaneous implantation in rats. They also reported similar results in aortic valve cusps [1996a]. Histological studies on explanted No-React-treated porcine pulmonic valve conduit in pediatric practice showed almost absent calcification and well-preserved cellular and connective tissue architecture, which denoted its biocompatibility [Marianeschi 2001]. No

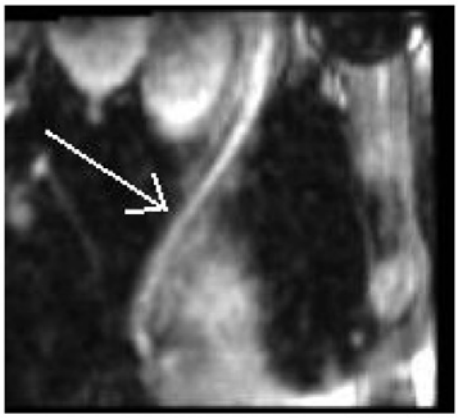

Figure 1. Magnetic resonance image. Three-dimensional true fast imaging with steady precession angiographic image shows full length of a graft (arrow).

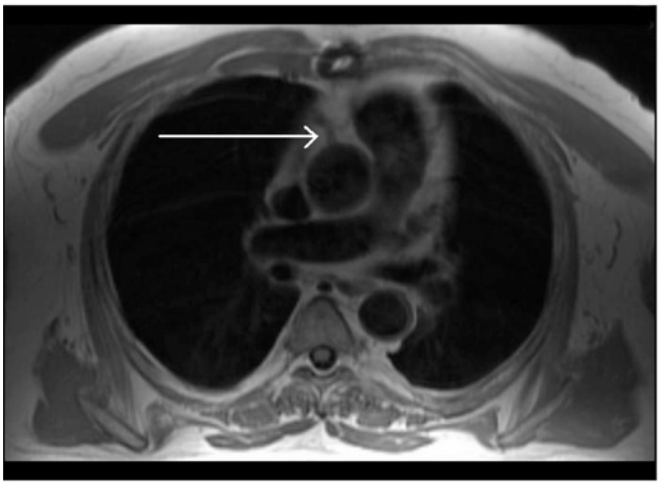

Figure 2. Magnetic resonance image. Axial black blood image through ascending aorta shows graft origin (arrow).

direct histological data are available on explanted NR-IMA conduits. However, it is logical to reflect on the biological behavior of the NR-IMA in light of the accumulating evidence from other areas of surgical practice.

SVGs undergo a form of accelerated atherosclerosis as the main mechanism of failure. It has been suggested that when it is exposed to arterial pressure, vascular endothelium initiates a cellular and subcellular chain of events leading to the classic atherosclerotic changes of smooth-muscle proliferation and intraluminal cholesterol deposition [Davies 1995]. NR-IMA is devoid of living cellular and subcellular components to participate in the atherosclerotic process. This proposed immunity from atherosclerosis along with increased biocompatibility and resistance to calcification could confer superior long-term patency to NR-IMA. However, much wider use and further studies are necessary for exploration of the possibility that this conduit is a suitable substitute for SVG. We hope this study will establish NR-IMA as the conduit of choice for salvage myocardial revascularization. Further to this, surgeons may be encouraged to use NR-IMA in patients who do not have a suitable conduit for complete revascularization. This practice will pave the way for further use of this conduit and in time will offer a chance to reinvestigate patency with adequate numbers of grafts.

In our limited study the patency of NR-IMA was similar to that of vein grafts. There was no occluded NR-IMA in the presence of all patent vein grafts in any of the patients in the study. This finding seems to suggest that NR-IMA has the potential for performing at least as well as a vein graft. The presence of an NR-IMA patent 4.5 years after insertion holds promise for the future possibilities of this conduit.

Absence of living endothelium on an NR-IMA may render slightly higher thrombogenicity. This possibility is an argument for short-term postoperative anticoagulation. Two patients in this series did not receive anticoagulation. In 1 of these patients the graft remained patent, but in the other it was occluded.

Limitations of the Study

The small numbers in this study were the main limitation. However, this study remains the only one of its kind as of this writing. Use of cardiac MRI to assess graft patency also may be considered a limitation. Galjee et al [1996] reported 98% sensitivity and 88% specificity for MRI compared with standard coronary angiography in evaluation of coronary bypass graft patency. Applying this information to our data gave an estimate of 0.82% false-positive results and 0.04% false-negative results. This justified use of MRI as a method of investigation. It was considered ethically unsound to subject asymptomatic patients to the risks of invasive coronary angiography, no matter how small the risks were.

Conclusion

We concluded that NR-IMA is a safe conduit. Patency at a mean of 2.5 years of follow-up was 57%, equal to the patency of the vein grafts in this small cohort of patients. The longest patency was 4.5 years, which offers hope for the potential of this conduit. Further use is advocated to establish the full scope of the NR-IMA conduit.

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