

**Use of arterial grafts in beating heart surgery; vasorelaxing effects of the colloidal Biseko solution and the inodilator drug, levosimendan, in isolated radial artery**

**Summary of PhD thesis**

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### **Publications related to the dissertation:**

- I. **Szolnoky J**, Ambrus N, Szabó-Biczók A, Bogáts G, Papp J.Gy, Varró A, Pataricza J.  
Biseko® colloidal solution diminishes the vasoreactivity of human isolated radial arteries.  
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- II. **Szolnoky J**, Ambrus N, Szabó-Biczók A, Bogáts G, Papp J.Gy, Varró A, Pataricza J.  
Kolloid és krisztalloid oldatok hatása humán arteria radialis bypass graftok tónusán in vitro.  
Cardiol Hung. 2009;39:42-46. IF = 0
- III. Pataricza J, **Szolnoky J**, Krassói I, Hegedus Z, Kun A, Varró A, Papp JG. Vasorelaxing effect of levosimendan against 5-hydroxytryptamine-induced contractions in isolated human conduit bypass grafts. J Pharm Pharmacol. 2006;58:1107-1112. IF = 1.533
- IV. Massoudy P, Thielmann M, Szabo A, Aleksic I, Kottenberg-Assenmacher E, **Szolnoky J**, Jakob H. Aortocoronary shunting during off-pump coronary artery bypass surgery as acute reperfusion strategy in ST-elevation myocardial infarction. Ann Thorac Surg. 2006; 82:1521-1523. IF = 2.342
- V. **Szolnoky J**, Babik B, Hegedús Z, Bitay M, Deák Z, Bogáts G. Minimálisan invazív koszorúérműtét videotorakoszkópos arteria mammaria interna preparálással. Cardiol Hung. 2004;34:169-172. IF = 0

### **Other publications related to the subject:**

- I. Ruzsa Z, **Szolnoky J**. Radial Artery Cannulation. A systemic review. Journal of Anesthesia & Clinical Research- in press (2012 August) IF = 0.48
- II. Ambrus N, **Szolnoky J**, Pollesello P, Kun A, Varró A, Papp JG, Pataricza J. Prolonged antispasmodic effect in isolated radial artery graft and pronounced platelet inhibition induced by the inodilator drug, levosimendan. Basic Clin Pharmacol Toxicol. 2012;110:269-274. IF=2.371

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I. Ambrus N, **Szolnoky J**, Szabó-Biczók A, Bogáts G, Papp JGy, Varró A, Pataricza J.

Tároló oldatok hatása az arteria radialis funkciójának megőrzésében in vitro. *Cardiol Hung.* 2009;39:S.A.64.

II. Ambrus N, **Szolnoky J**, Krassói I, Pataricza J. Perioperative preservation of graft function during CABG surgery with colloidal 'Biseko' in vitro.

Endothelium: The Determinant of Cardiovascular Health and Disease, International Workshop of The Physiological Society, Krakow, Poland. Abstract book 2007;26.

III. **Szolnoky J**, Pataricza J, Ambrus N, Krassói I, Szabó BA, Bogáts G.

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V. **Szolnoky J**, Séllei Á, Földeák D, Morvay Z, Szabó BA, Bogáts G.

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## INTRODUCTION

In the current „stent era” it had been hoped that drug-eluting stents would address some of the limitations of percutaneous coronary intervention with bare metal stents. However, a number of publications have questioned both the clinical results and cost-effectiveness of drug-eluting stents in the management of three vessel coronary artery disease. This has resulted in renewed interest in the midterm and long-term results that may be achievable with coronary artery bypass graft surgery (CABG). The ultimate goal of this operation is to achieve complete revascularization of the patient with conduits that will remain patent for the duration of the patient’s lifetime. Graft patency is a fundamental predictor of long-term survival after coronary artery bypass surgery. Left and right internal thoracic artery (LITA, RITA) graft patency has been shown to be superior to that of saphenous vein grafts (SVG). There are four randomised angiographic studies about radial artery (RA) graft patency comparing it to other grafts. Several non-randomised studies report also better medium- and long-term patency of RA then SVG conduits. These findings support the use of RA as bypass conduit due to its long-lasting clinical benefit and remarkably stable patency for up to 20 years.

The RA has a major function in the circulation of the hand and forearm. Ischaemic complications related to the harvest of RA are rare but have serious consequences for the patient. The consequences of an RA coronary bypass graft failure are even more serious than ischaemic complications of the hand. Proper selection of patients and careful preoperative planning are the goal to avoid these problems. To prevent postoperative forearm and hand ischaemia and to achieve optimal RA graft function we introduced a very rigorous preoperative screening criteria regarding physical and ultrasonographic examinations at our department. Removal of the radial artery will definitively cause circulatory changes in the forearm. To follow up these changes we routinely perform a 3-6 months control after RA harvesting included physical examination and complex ultrasonographic measurements regarding ulnar artery (UA) diameter, peak systolic velocity (PSV) in UA and UA flow patterns.

A major problem with the extensive use of arterial conduits (especially the RA) is spasm leading to acute ischemia which may contribute to graft failure. Recent improvements of mid-term and late patency rates of ITA and RA may be usually attributed to the less traumatic harvesting technique and to the use of vasodilators in the peri-and postoperative periods. Vasodilator therapy includes drugs with different mechanisms of action including calcium channel blockers, papaverine, milrinone, nitroglycerin, nicorandil and adrenergic receptor blockers. However, most of these drugs are devoid of inotropic action or even may deteriorate

cardiac contractility such as the calcium antagonists, decrease or increase heart rates, effects that may be harmful in the peri-CABG setting. The inotropic dopamine caused variable effect in ITAs and contracts RAs. Therefore, it is reasonable to assume that an inodilator drug can be superior over the currently used vasorelaxing drugs for relieving graft spasm, especially in patients with left ventricular dysfunction. Levosimendan is a novel inodilator drug that, in addition to its inotropic action, decreases the cardiac preload of the heart by relaxing capacitive veins. The inodilator also dilates conduit type of coronary arteries. Although, the preoperative administration of levosimendan improved the cardiac hemodynamic conditions in patients undergoing off-pump coronary artery bypass (OPCAB) surgery, a direct effect of the drug on human bypass graft arteries has not been demonstrated yet.

Over the different inodilator drugs, the storage solution of the RA grafts could have a reasonable effect on the vasoreactivity of the RA bypass conduits. These solutions are used to maintain the integrity and function of the radial artery known to frequently develop spasm in the intra/perioperative period of CABG. None of the currently used solutions provides an ideal graft function. Although graft segments stored in heparinized whole blood had greater endothelium-dependent relaxation to acetylcholine, blood-stored radial artery grafts revealed markedly increased smooth muscle contractions. Papaverine, a widely used smooth muscle relaxant in storage solutions, impairs endothelial function.

The colloidal Biseko<sup>®</sup> solution is a cold sterilized liquid in which coagulation factors and bacterial toxins are absent or minimal. The immunoglobulin concentrations and activities are equivalent to those in normal serum. A preliminary observation has suggested that this colloidal solution might protect vascular tissues by decreasing the permeability of the endothelium (unpublished observation).

## **AIMS**

Our studies were focused on the following:

Clinical operative studies were conducted to:

1. Demonstrate the safe use of arterial bypass grafts in special clinical situations: off pump bypass surgery in myocardial infarction (Clinical study I.) and minimally invasive coronary artery bypass grafting (Clinical study II.)

*In vitro* and *in vivo* investigations on the vasoreactivities of bypass grafts were performed to:

2. Demonstrate the vasodilating capacity of levosimendan in arterial conduit bypass grafts precontracted with 5-hydroxytryptamine. Isometric tension of isolated LITA and RA were studied.
3. Explore the possible differences in the contractile and/or relaxing capacities of the proximal and distal parts of RA.
4. Compare the effect of the colloidal Biseko<sup>®</sup>, as a storage solution, to 5% albumin as a control colloidal solution as well as to two crystalloid, physiological saline (0.9 % NaCl) and the cardioplegic Bretschneider solutions, on the contractile and relaxing capacities of isolated human RA grafts.
5. Follow up the changes in the forearm circulation 3-6 months after RA removal.

## **USE OF LEFT INTERNAL THORACIC ARTERY IN SPECIAL SITUATIONS**

### **CLINICAL STUDY I. OFF PUMP BYPASS SURGERY WITH THE LITA IN ST-ELEVATION MYOCARDIAL INFARCTION - CASE REPORT**

Coronary artery bypass grafting in acute myocardial infarction is known to be performed at a considerably increased perioperative risk. Mortality depends on the timing after transmural infarction. We report a 43-year-old man with a history of arterial hypertension and hyperlipidemia presented with an acute anterior myocardial infarction. He had suffered an acute anterior myocardial infarction 4 months earlier. A high-grade proximal stenosis of the left anterior descending (LAD) artery had been detected in coronary angiography and was treated with implantation of a bare metal stent. Then he underwent routine follow-up coronary angiography 4 months later. Because of an in-stent re-stenosis in the proximal LAD, a drug-eluting stent was implanted. Within 1 hour the patient complained about acute chest pain and

electrocardiographic signs of anterior myocardial infarction with ST-segment elevation in leads I, II, and aVL. He was now registered for emergency coronary artery bypass grafting. He was directly transferred to the operating room under continuous perfusion with heparin, nitroglycerin, oral clopidogrel and diazepam, and arrived within 3 hours after the onset of chest pain. A prophylactic intraaortic balloon pump was installed. The chest was opened and the LAD artery was exposed. Considerable hypokinesia of the anterior wall of the heart was visible. The LAD was stabilized in the mid-vessel region. There was almost no antegrade flow after opening of the vessel. Vessel lumen was 1.5 mm. An aortocoronary shunt was implanted in the LAD. Almost instantly a slow but steady decline of ST-segment elevation could be observed and there was improvement of the hypokinesia of the anterior wall. Following the left internal thoracic artery was harvested and thereafter anastomosed to the LAD without removing the shunt until the last stitch had been made. Surgery was uneventful and the patient was transferred to the intensive care unit with mild catecholamine support and with the aortic balloon pump. He was extubated 8 hours later, free from catecholamine support; the balloon pump was weaned and was removed on postoperative day. When coronary artery bypass grafting is performed in cases of acute myocardial infarction, aortocoronary shunting can immediately reconstitute coronary blood flow in an epicardial vessel, thus reperfusing ischemic tissue and salvaging the myocardium from transmural necrosis. This direct surgical technique seems to be of particular relevance in off-pump coronary artery bypass grafting where extracorporeal circulation and global cardiac ischemia are eliminated. Using this method the surgeon has appropriate time to prepare the LITA, rather than a saphenous vein graft. Less traumatic harvesting techniques and the use of vasodilators in the peri- and postoperative periods appear to be the key factors to use the LITA in beating heart surgery followed by acute ST-elevation myocardial infarction.

## CLINICAL STUDY II. MINIMALLY INVASIVE CORONARY ARTERY BYPASS SURGERY ON THE BEATING HEART USING THORACOSCOPICALLY HARVESTED LITA

In the recent years, the field of minimally invasive cardiac surgery has grown rapidly beginning with the minimally invasive direct coronary artery bypass (MIDCAB) operation and evolving toward totally endoscopic coronary artery bypass grafting. For MIDCAB, a small left anterior thoracotomy (LAST) or a lower split sternotomy (LSS) have been proposed to harvest the left internal thoracic artery. However, complete graft harvesting of the LITA is

difficult under direct vision in these circumstances and may necessitate costal resection and important chest wall retraction. Additionally, it carries the potential risk of kinking or coronary steal syndrome. Thoracoscopic harvesting of the LITA (video assisted direct coronary bypass grafting: VADCABG) avoids these hazards. It permits complete dissection from the subclavian artery to the sixth inter-costal space (ICS) with section of all collateral branches issuing from the LITA without any traumatic retraction.

In our initial series between September 2001 and July 2002 we reported the first 5 VADCABG cases in Hungary. All the patients suffered from isolated LAD stenosis not suitable for percutaneous coronary intervention (chronic occlusion, multiple stent implantation in history). The average EOROSCORE was 3.25, the mean age of the patients was 58.5 (53-67) years. The patients were positioned in the supine position. After general anesthesia, a double-lumen endotracheal tube was placed. Three 1-2 cm incisions were made in the third, fourth and sixth intercostal spaces, through which the endoscopic instruments were inserted sequentially under direct videoscopic guidance. The LITA preparation was performed using the Ultracision endoscopic harmonic scalpel to achieve atraumatic vessel dissection. During the preparation a low dose of intravenous nifedipin was given to avoid graft spasm. After administration of heparin a small (6-8 cm) left anterior thoracotomy was made in the fifth intercostal space. After opening the pericardium the LITA-LAD anastomosis was sutured manually with 7-0 Prolene on the beating heart using a special stabilizer. The patients were extubated in the operating room or in the first postoperative hour. The mean intensive care unit time and hospital stay length were 11 hours and 5-7 days, respectively. There were no postoperative complications, the patients remained asymptomatic and had negative stress test 12 month after the operation. One patient needed recatheterization five years after surgery because of positive stress test. The angiography confirmed a patent LITA-LAD anastomosis and a new significant stenosis of the right coronary artery.



## **MATERIALS AND METHODS FOR INVESTIGATING THE VASOREACTIVITY OF CONDUIT GRAFTS *IN VITRO***

This investigation received the approval of the local institutional review board (Human Investigation Review Board, University of Szeged, Hungary No. 164/2002 and No. 161/2004). Each patient gave informed consent to accept the aim and protocol of investigation.

### **I. VASOREACTIVITY OF HUMAN ARTERIAL CONDUITS *IN VITRO*. EFFECT OF LEVOSIMENDAN**

#### **CHARACTERISTICS OF PATIENTS**

Sixteen patients undergoing elective (CABG) were involved in this study. LITA was obtained from eight patients (age:  $65.7 \pm 2.9$  yrs), proximal and distal parts of RA were obtained also from eight patients (age:  $65.4 \pm 3.2$  yrs). Only 1-1 female patient was included in the two groups; three suffered from diabetes in each group. Conservative treatment included statins, aspirin, nitrates, ACE-inhibitors, calcium channel blockers, beta blockers, diuretics and antidiabetic drugs.

#### **HARVESTING TECHNIQUE OF BYPASS CONDUITS**

We obtained 0.5 –0.6 mm long segments of LITA as well as that of the RA. Arterial samples were prepared atraumatically with Ultracision Harmonic Scalpel (Ethicon Endo-Surgery, U.S.A.). This technique allows cutting, coagulation and dissection of tissue at lower temperature than in the case of electrosurgical method, thus minimizing thermal damage of the tissue. Once harvesting of the arterial samples was started, low-dose nifedipine (0.2-0.4 mg/hour) was given in intravenous infusion to prevent early vasospasm. LITA or RA were then carefully dissected with its accompanying veins. Arterial tissues were then placed into icecold Krebs-Henseleit (KH) solution and were immediately transported to the laboratory. The composition of the KH was the following (in mmol L<sup>-1</sup>): NaCl 120, KCl 4.2, CaCl<sub>2</sub> 1.5, NaHCO<sub>3</sub> 20, MgCl<sub>2</sub> 1.2, KH<sub>2</sub>PO<sub>4</sub> 1.1, glucose 11 and EGTA 0.27 μmol L<sup>-1</sup>. In the laboratory, the arteries were dissected free from the surrounding connective tissue, and cut into rings of 3 mm long.

## MEASUREMENT OF ISOMETRIC TENSION

Ring segments of LITA as well as the proximal and distal ones of RA were mounted on stainless steel hooks and placed into water-thermostated (at 37°C) organ chambers containing 2 mL of KH solution. The solution was continuously bubbled with a gas mixture of 95% O<sub>2</sub> and 5% CO<sub>2</sub> at pH 7.4. One of the hooks was anchored inside the organ chamber and the other one was connected to a force-displacement transducer (Hugo Sachs Elektronik, Type F30, Germany) to measure changes in isometric tension. In each isolated type of grafts we optimized the resting (basal) tension during a preliminary series of experiments. The tension to which the vessels were subjected was increased manually in increments of 5 mN over 30 min to achieve maximum active tension for the minimum resting tension using 10 µmol L<sup>-1</sup> serotonin (5-HT). The optimum values were found to be 20 milliNewton (mN) for all the three grafts. In this series of experiments the rings were stretched up to 20 mN and equilibrated for 60 min. During this period tension was continuously readjusted to the above value of stretch and the medium was changed in every 15 minutes. RA ring segments cut from the proximal and distal part of the same artery were mounted parallel in separate organ chambers –LITA samples from different individuals were studied independently- and equilibrated for 60 min. Following the equilibration period the rings were contracted with 0.002-9.3 µmol L<sup>-1</sup> 5-HT. When the contraction reached a stable plateau levosimendan was administered cumulatively (0.009-1.14 µmol L<sup>-1</sup>) into the organ baths.

## DATA ANALYSIS

Contractions induced by 0.002-9.3 µmol L<sup>-1</sup> serotonin were expressed in mN. Relaxations induced by levosimendan was expressed as % of 5-HT-induced steady-state contraction amplitude. The equation of  $a*x/(x+b)$  was fitted to the individual dose-response curves for levosimendan and efficacy/E<sub>max</sub> (*a*) and 50% effective concentration (*b*=EC<sub>50</sub>) values were calculated. EC<sub>50</sub> values were converted to pD<sub>2</sub> and expressed in -log mol L<sup>-1</sup> concentrations.

## II. INVESTIGATION OF THE EFFECT OF COLLOIDAL BISEKO<sup>®</sup> AS STORAGE SOLUTION ON THE CONTRACTILE AND RELAXING CAPACITIES OF ISOLATED RADIAL ARTERY GRAFTS

In this study, we compared the effect of the colloidal Biseko<sup>®</sup>, as a storage solution, to 5% albumin as a control colloidal solution as well as to two crystalloid, physiological saline

(0.9 % NaCl) and the cardioplegic Bretschneider solutions, on the contractile and relaxing capacities of isolated human RA grafts.

## CHARACTERISTICS OF PATIENTS

Twenty-six patients were divided into Group I -in that radial arteries were incubated in crystalline solutions- and Group II – in that radial arteries were incubated in colloidal solutions. All of the patients suffered from hypertension, 92% from hypercholesterinaemia and near 15% of diabetes. Conservative treatment included statins, aspirin, nitrates, ACE-inhibitors, calcium channel blockers, beta blockers, diuretics and antidiabetic drugs.

## PREPARATION OF RADIAL ARTERY SEGMENTS FOR IN VITRO TESTING

Arterial samples were prepared atraumatically with the Ultracision Harmonic Scalpel (Ethicon Endo-Surgery, USA). Once harvesting of the arterial tissue samples had been started, low dose nifedipine (0.2-0.4 mg h<sup>-1</sup>) was given in intravenous infusion to prevent early vasospasm. We prepared a 5-6 mm long segment of the radial artery (RA) at the origin of the brachial artery (proximal part). The RA was then carefully dissected and cleaned from the surrounding connective tissue. The segment of the artery was cut into two 2.5-3-mm long rings and submerged to 0.9 % NaCl and Bretschneider solutions (Group I patients) or 5 % human albumin and Biseko<sup>®</sup> solutions (Group II patients) for 45 minutes.

## ISOMETRIC TENSION MEASUREMENT AND PROTOCOL OF INVESTIGATION

Two rings of RA grafts were mounted in parallel on stainless-steel hooks and placed into organ chambers containing 2 ml Krebs-Henseleit solution maintained at 37°C. The solution was continuously aerated with a gas mixture of 95 % O<sub>2</sub> and 5 % CO<sub>2</sub> at pH 7.4. One of the hooks was anchored and the other one was connected to a force-displacement transducer to measure changes in isometric tension. Vessel rings were subjected to 20 mN tension and equilibrated for 45 minutes. During this period the tension was continuously readjusted to the above value of stretch and the medium was changed in every 15 minutes. Following the equilibration period the rings were precontracted with 80 mmol L<sup>-1</sup> KCl. After washing the arterial rings contractions were repeated with 0.3 μmol L<sup>-1</sup> 5-HT. Endothelium dependent

relaxations were induced by acetylcholine ( $10 \mu\text{mol L}^{-1}$ ) and bradykinin ( $1 \mu\text{mol L}^{-1}$ ). Endothelium independent relaxations were produced by glyceryl trinitrate ( $10 \mu\text{mol L}^{-1}$ ).

## DATA ANALYSIS

Contractions and relaxations were expressed in milliNewton (mN). Data are presented as mean  $\pm$  standard deviation (mean  $\pm$  sd). For comparisons of the data one-way analysis of variance followed by Newman-Keuls multiple range test was used. In the case of bradykinin relaxations were also analysed with the non-parametric Mann-Whitney test. Statistical significance between two groups was tested with Student's t-test and p values less than 0.05 were considered as significant.

### III. CHANGES IN THE FOREARM CIRCULATION 3-6 MONTH AFTER RADIAL ARTERY REMOVAL *IN VIVO*

#### CHARACTERISTICS OF PATIENTS

172 patients undergoing elective CABG between 2003 and 2006 were examined 3-6 months after RA removal in this series. There were 143 male and 29 female patients (age: 60.5 yrs). 31.9% suffered from diabetes, 32% from obesity (using the body mass index) and 7.5% from peripheral arterial disease. Medical treatment included statins, aspirin, nitrates, ACE-inhibitors, calcium channel blockers, beta blockers, diuretics and antidiabetic drugs.

#### PROTOCOL OF THE EXAMINATION AND DATA ANALYSIS

With physical examination we determined the neurofunctional integrity of the operated forearm, testing the sensoral and motoral status. The patients' forearm circulation was examined by Duplex ultrasound. Atherosclerotic status, diameter, and flow parameters of the UA were detected. For comparisons of the data one-way analysis of variance followed by Newman-Keuls multiple range test was used.

## RESULTS

### CONTRACTILE EFFECT OF 5-HYDROXYTRYPTAMINE ON THE PROXIMAL AND DISTAL RADIAL ARTERIES AS WELL AS ON THE LITA

5-HT ( $0.002-9.3 \mu\text{mol L}^{-1}$ ) enhanced the tone of the LITA and that of the proximal and distal parts of RA concentration dependently. The contractile effect of 5-HT was more pronounced in the radial arteries than in the thoracic artery. The proximal RA responded with significantly larger contraction than LITA. The distal RA also developed higher active tension than LITA but the difference in effect was not statistically significant.

### VASORELAXATION BY LEVOSIMENDAN IN PROXIMAL AND DISTAL RADIAL ARTERIES AS WELL AS IN LITA

Levosimendan concentration dependently ( $0.009-1.14 \mu\text{mol L}^{-1}$ ) relaxed the three conduit bypass grafts precontracted with 5-HT. Relaxations of the three grafts were evident at even submicromolar concentrations of the inodilator drug. The maximal relaxing responses to the inodilator were similar in the case of LITA and proximal RA and the calculated efficacy values also showed no statistically significant differences between the two grafts. Levosimendan partially relaxed the distal RA=  $59.4 \pm 17.5\%$ ,  $p < 0.05$  vs LITA.

### CONTRACTILE TENSIONS INDUCED BY 5-HYDROXYTRYPTAMINE AFTER INCUBATION OF THE GRAFTS IN CRYSTALLINE AND COLLOIDAL SOLUTIONS

Contractions of the radial arteries induced by 5-HT ( $0.31 \mu\text{mol L}^{-1}$ ) were investigated. Following incubation of the radial artery segments in crystalline solutions, no considerable difference was found in their reactivity in 0.9 % NaCl and in Bretschneider solutions. Incubation of the radial arteries in the colloidal Biseco<sup>®</sup> solution revealed significantly smaller contractions to 5-HT than those obtained after incubation of the graft samples in 5% albumin.

## ENDOTHELIUM-DEPENDENT RELAXATIONS AFTER INCUBATION OF THE GRAFTS IN CRYSTALLINE AND COLLOIDAL SOLUTIONS

Endothelium-dependent vasorelaxants, acetylcholine ( $10 \mu\text{mol L}^{-1}$ ) or bradykinin ( $1 \mu\text{mol L}^{-1}$ ) were administered in  $0.31 \mu\text{mol L}^{-1}$  5-HT-precontracted radial artery. No significant differences in relaxations were obtained among the two crystalloid and the two colloidal solutions. In all the four groups, small endothelium-dependent relaxations and large individual variabilities could be detected.

## ENDOTHELIUM INDEPENDENT RELAXATIONS AFTER INCUBATION OF THE GRAFTS IN CRYSTALLINE AND COLLOIDAL SOLUTIONS

The endothelium independent vasorelaxant, glyceryl trinitrate ( $10 \mu\text{mol L}^{-1}$ ) exerted similar relaxations against 5-HT-induced contractions in crystalloid and colloidal solutions.

## CHANGES IN THE FOREARM CIRCULATION 3-6 MONTH AFTER RADIAL ARTERY REMOVAL

The mean preoperative diameter of the RA and UA was 2.68 mm and 2.56 mm, respectively. During radial compression, the peak systolic velocity of the UA increased from 50.6 cm/s to 79.8 cm/s. At the 3-6 month follow-up, the flow of the UA proved to be significantly higher (70.8cm/s), but did not reach figures measured during preoperative RA compression. The pre- and postoperative diameter of the UA did not show significant change. All of the patients were free of any sign of forearm ischaemia and any relevant neurological or functional disturbances.

## DISCUSSION

Extensive use of arterial grafts in beating heart surgery became our surgical tool in the past decade. When coronary artery bypass grafting is performed in emergency cases of acute myocardial infarction, using the LITA is still in question. In our case report we demonstrated that in special clinical situation applying the off pump technique and using the aortocoronary shunting can immediately reconstitute the coronary blood flow reperfusing the ischemic tissue and salvaging the myocardium from transmural necrosis. The anastomosis can be completed with the aortocoronary shunt in place, thus eliminating any further period of local or global ischemia. Using this method the surgeon has appropriate time to prepare the LITA, rather than a saphenous vein graft, which is the key factor of long term graft patency. Less traumatic harvesting techniques and the use of vasodilators in the peri-and postoperative periods are very important supportive elements to use the LITA in beating heart surgery followed by acute ST-elevation myocardial infarction.

Several less invasive techniques are introduced in the clinical praxis to harvest the LITA for MIDCAB operation. In our department we started to use two different approaches: lower split sternotomy (LSS) and video assisted direct coronary bypass grafting (VADCABG). Using the LSS method, complete graft harvesting of the LITA is difficult under direct vision in these circumstances. Thoracoscopic harvesting of the LITA permits its complete dissection from the subclavian artery to the sixth inter-costal space (ICS) with section of all collateral branches issuing from the LITA without any traumatic retraction. After reporting the first series of angiographically assessed thoracoscopically harvested LITA in 2001, in 2004 we published the first 5 VADCABG cases in Hungary. The LITA preparation was performed using the endoscopic Ultracision harmonic scalpel to achieve atraumatic vessel dissection. After a small (6-8 cm) lateral thoracotomy the LITA-LAD anastomosis was sutured manually with 7-0 Prolene on the beating heart using a special stabilizer. There were no postoperative complications, the patients remained asymptomatic and had negative stress test 12 month after the operation. Thoracoscopic technique for LITA harvesting is more time consuming, surgeon dependent and requires extended instrumentarium in the operating room. We believe, however, that applying this method several complications regarding the appropriate length of LITA graft are avoidable.

A major problem with the extensive use of the RA is its tendency to spasm. Recent improvements of midterm and late patency rates of ITA and RA may be attributed to the use of special vasodilators in the peri-and postoperative periods. The novel inodilator,

levosimendan, dilates human saphenous vein and also conduit blood vessels by activating ATP-sensitive and other types of hyperpolarizing potassium channels. In our study we demonstrated the vasodilating efficiency of Levosimendan in the two main conduit arteries, LITA and RA. In isolated organ baths, the inodilator drug relaxed the 5-HT-evoked active contractions of both LITA and RA. Levosimendan completely or almost completely relaxed the LITA and proximal RA, respectively. Distal RA revealed 50-60 % maximum relaxation to the inodilator drug. Active contraction induced by 5-HT is considered to be an important pathological mechanism for inducing arterial spasm and may cause perioperative and late failure of bypass conduits. The response of LITA to the constrictor effect of serotonin was less than that of the proximal part of the RA whereas the distal RA developed tension in magnitude between LITA and the proximal segment of RA. In an early study there was no difference in the response to noradrenaline and adrenaline between proximal and distal RA. We observed however a remarkable difference in the contractile and relaxing capacities of the proximal and distal part of the RA. These findings may play important role in further surgical application of RA conduits.

Over the different inodilator drugs, some storage solutions could have a reasonable effect on the vasoreactivity of the RA bypass conduits. We demonstrated the beneficial effect of the colloidal Biseko<sup>®</sup> solution on the vasoconstrictive capacity of RA grafts. RA segments incubated in the colloidal Biseko<sup>®</sup> solution produced diminished contractions to 5-HT as compared to the colloidal albumin or physiologic saline solutions. The maximum vasoconstrictive and vasodilating capacities of the isolated radial artery -measured with potassium chloride and papaverine, respectively- did not differ in the four storage solutions. Vasodilating functions of the arteries obtained with the endothelial stimulators, acetylcholine and bradykinin, as well as with the direct relaxant of the smooth muscle, glyceryl trinitrate, also revealed no significant differences. These results support the intact contractile machinery of the isolated RA grafts during our investigational period.

The exact mechanism by which Biseko<sup>®</sup> solution caused antispasmodic effect remains to be speculative. Lack of purity of standard colloidal solutions may offer some explanations. Although pure colloids are hypocoagulable by their own, the standard colloidal albumins are usually contaminated with coagulants and also with bacterial toxins, viruses and prions being absent or minimal in Biseko<sup>®</sup> solution. Some coagulation factors such as thrombin and tissue factor were found to cause direct vasoconstriction and protein C enhanced the  $\alpha$ -adrenergic receptor mediated contractile responses of arteries. A bacterial toxin, e.g. Escherichia coli hemolysin, is able to release thromboxane, a potent vasoconstrictor of the radial artery with



damaged endothelium. The ultimate presence of one or more of these contractile factors may render the standard albumin preparations unsuitable for the storage of radial artery before CABG surgery. Because the whole blood also contains some of the above-mentioned mediators, this partly explains why blood-stored radial artery grafts revealed augmented smooth muscle tensions. In our study, however, arterial responses did not differ from saline-stored ones, possibly because these control solutions contain vasodilatory contaminants, too. Simply, the variable phosphate anion content of water can produce insoluble calcium complex that decreases the contractility of the blood vessel in the organ chamber. We assume that the decreased endothelial permeability -evoked by the colloidal Biseko<sup>®</sup> solution- is partly responsible for the diminished transport of the hydrophylic contractile amines through the endothelial pores to the underlying smooth muscle cells. Our results suggest that storage of radial artery in Biseko<sup>®</sup> colloidal solution before the implantation during CABG decreases the sensitivity of the graft to vasoconstriction. The superiority over human serum albumin, physiologic saline and Bretschneider solutions may make Biseko<sup>®</sup> solution useful for decreasing the risk of intra/perioperative spasm of radial artery.

Removal of the radial artery will definitely cause circulatory changes in the forearm. There is a strong evidence that this procedure is associated with significant increase in UA flow velocity after surgery. In our study we could confirm these findings: at the 3-6 month follow-up of our patient population the flow of the UA proved to be significantly higher than before surgery, but did not reach the values measured during preoperative RA compression. The pre- and postoperative diameter of the UA did not show significant change. All of the patients were free of any sign of forearm ischaemia and any relevant neurological or functional disturbances. Long-term follow up data suggest that the intima-media thickness of the ulnar artery is significantly higher on the operated side, and this difference reached statistical significance at 10 years follow-up. There is also significantly higher prevalence of atherosclerotic plaques in the UA of the operated versus control arm. In a recent, larger series this effect was not observed. In our study we did not find any structural deterioration of the UA at the short-term follow-up. We are continuing our patient's follow-up to reveal any late disturbances in the forearm circulation after RA removal.

## SUMMARY

We demonstrated the safe use of LITA in emergency case of acute myocardial infarction, applying the off pump technique with aortocoronary shunting. Using this method the surgeon has appropriate time to prepare the LITA rather than a saphenous vein graft. We reported the first VADCABG series in Hungary. The LITA preparation was performed using the endoscopic Ultracision harmonic scalpel to achieve atraumatic vessel dissection. After a small lateral thoracotomy the LITA-LAD anastomosis was sutured manually on the beating heart using a special stabilizer. There were no postoperative complications, the patients remained asymptomatic and had negative stress test 12 months after the operation.

We have also demonstrated the vasodilating efficiency of levosimendan in the two main conduit arteries, LITA and RA *in vitro*. Levosimendan completely or almost completely relaxed the LITA and proximal RA, respectively. Distal RA revealed 50-60 % maximum relaxation to the inodilator drug. The response of LITA to the constrictor effect of 5-HT was less than that of the proximal part of the RA whereas the distal RA developed tension in magnitude between LITA and the proximal segment of RA. These observations prove the viability of the proximal part of RA and point to the necessity of an antispasmodic medication of this part of RA before surgical implantation.

We demonstrated the positive effect of the colloidal Biseko<sup>®</sup> solution on the vasoconstrictive capacity of RA grafts. RA segments incubated in the colloidal Biseko<sup>®</sup> solution produced diminished contractions to 5-HT as compared to the colloidal albumin or physiologic saline solutions. Our results suggest that storage of radial artery in Biseko<sup>®</sup> colloidal solution before the implantation during CABG decreases the sensitivity of the graft to vasoconstriction.

We could confirm the previously reported changes in the forearm circulation after RA removal. At the 3-6 month follow-up the flow of the UA proved to be higher than before surgery, but did not reach the values measured during preoperative RA compression. All of our patients were free of any sign of forearm ischaemia and any relevant neurological or functional disturbances.

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