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

PhD Dissertation

Jenő Szolnoky MD

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Publications related to the dissertation:

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

5-HT: 5-hydroxytryptamine
AT: Allen test
Ach: acetylcholine
BK: bradykinin
CABG: coronary artery bypass graft surgery
CAD: coronary artery disease
GTN: glyceryl trinitrate
KCl: potassium chloride
KH: Krebs-Henseleit solution
LAD: left anterior descending coronary artery
LITA: left internal thoracic artery
MIDCAB: minimally invasive direct coronary artery bypass
mN: milliNewton
NA: noradrenaline
Na-citrate: sodium-citrate
OPCAB: off pump coronary bypass surgery
PSV: peak systolic velocity
RA: radial artery
RITA: right internal thoracic artery
SVG: saphenous vein graft
UA: ulnar artery
VADCABG: video assisted direct coronary bypass grafting

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References

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Appendix

1. INTRODUCTION

1.1. CORONARY ARTERY SURGERY

1.1.1. GENERAL

In 1950 Arthur Vineberg was the first who performed myocardial revascularization by rerouting internal mammary artery into heart muscle, allowing side branches to bleed into, and nourish, heart muscle (Vineberg and Miller, 1950). Still on the beating heart, Kolesov was the first to report left internal thoracic artery anastomosis to the left anterior descending coronary artery in 1964 (Olearchyk, 1988).
In 1968 Favolaro achieves restoration of coronary blood flow in 171 patients with saphenous vein grafts bypassing occlusions in several positions, sometimes with multiple grafts in the same patient (Westaby, 1997). Since those early years coronary artery bypass grafting (CABG) has become the gold standard treatment for coronary artery disease.

1.1.2. OFF PUMP CORONARY BYPASS SURGERY

From 1995 the medical products industry launches innovative products to enable coronary revascularization on a beating heart. In the last decade many centers started to use this less invasive operative technique and reported encouraging results. The use of off-pump coronary artery bypass surgery (OPCAB) for surgical candidates deemed to be at high risk has become increasingly popular as a result of clear evidence showing outcome and cost benefits (Hart et al., 2001; Kihara et al., 2001; Lancey et al., 2000; Lee et al., 2000; Patel et al., 2002; Petro et al., 2000; Puskas et al., 1999). High-risk patients, especialy the elderly and women, appear to benefit, with lower rates of mortality and other adverse events with OPCAB, compared with conventional on-pump coronary artery bypass surgery (Puskas et al., 2001; Al-Ruzzeh et al., 2001). In fact, the female sex has disappeared as a risk factor from studies of OPCAB, which demonstrate reduced mortality, respiratory complications and lengths of hospital stay for

women (Brown et al., 2002). It also appears that high-risk patients may have lower rates of adverse outcomes with the use of OPCAB.

1.1.3. ARTERIAL CONDUITS IN CORONARY BYPASS SURGERY

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 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. The excellent patency rates achieved with the left internal thoracic artery (LITA) are well described. Over the past decade, there has been considerable interest in whether the right internal thoracic artery (RITA) and the radial artery (RA) may provide results comparable to LITA conduit. The gastroepiploic artery (GEA) is still sporadically used.

1.2.USE OF THE RADIAL ARTERY IN CORONARY BYPASS SURGERY

1.2.1. PATENCY RATE OF THE RADIAL ARTERY

The radial artery (RA) in coronary bypass surgery was first used by Carpentier in 1973 (Carpentier et al., 1973). The early experiences were rankling regarding the patency rate (50-65%). The RA was prone to spasm and development of early intimal hyperplasia (Curtis et al., 1975). After several years Acar reinstated the use of RA as a bypass graft in coronary surgery (Acar et al., 1992) because of some encouraging long-term results. Since the revival of the RA the patency rates have improved considerably and many groups report excellent mid-and long-term results.

Graft patency is a fundamental predictor of long-term survival after coronary artery bypass surgery. Left and right internal thoracic artery (arterial) graft patency has been shown

to be superior to that of saphenous vein grafts. There are some randomised angiographic studies about RA graft patency comparing it to other grafts. The Radial Artery Patency and Clinical Outcome Study (RAPCO) (Hayward et al., 2010) involved two groups of patients. The first group received LITA as first, and RA or free RITA as second graft depending on the randomisation. Subsequent grafts were saphenous veins (SVG). In the second group the second graft was either RA or SVG. Five year results did not show superior patency rates comparing RA to SVG or RITA grafts. The study was underpowered, however.

The Radial Artery Patency Study (RAPS) (Desai et al., 2004) was a multicentre study involving 531 patients. Patients were randomized to two revascularization strategy: RA to left circumflex territory and SVG to right territory or vice versa. Demografic data did not differ between the two groups. In this study RA grafts had higher patency rates after one year. The Radial Artery Versus Saphenous Vein Patency Study (RVPS) compared RA to SVG in the left circumflex territory (Collins et al., 2008). 142 patients were randomized and 103 were available for angiographic control after five years. There were no demographic differences between the two groups. In this study the RA patency was clearly superior to SVG in the left circumflex system. Clinical outcomes regarding survival and freedom from cardiac events seems to be also favourable using RA grafts. A retrospective study of 925 patients with RA grafts and 925 propensity-matched controls with SVGs showed similar survival in both groups at six months. At six years survival was 92,1% vs. 86,8% ($p<0,03$). The survival benefit was even more evident in woman, diabetics, younger patients and triple-vessel patients. Use of SVG was an independent predictor of mortality, risk ratio 0,675 (Zacharias et al., 2004). Longer follow-up clearly demonstrates the benefit of total arterial revascularisation. At twelve years risk ratio was 0,60 in patients with total arterial revascularisation with ITA and RA compared to ITA and SVG (Zacharias et al., 2009). In a randomized study (Muneretto et al., 2004) event-free survival at 18 months was significantly better in patients with RA graft compared to SVG patients.

Patient characteristics and target vessel quality seriously effect RA patency. The patency rate is considerably poorer if the RA was anastomosed to a vessel with less than 70% stenosis. Patency rates comparable to LITA patency were achived when RA was anastomosed to a vessel with 80 to 85% stenosis. Target vessel territory did not affect the patency.

Peripheral vascular desease, however, a risk factor to RA graft failure and it is recommended not to use RA in patients with severe peripheral vascular disease (Deasi and Fremes, 2007). Diabetes is not a contraindication for use of RA grafts, moreover clinical series show that use of RA has protective effect on outcome in patients with diabetes (Singh et al., 2008).

A recent systematic review and meta-analysis was published (Athanasiou et al., 2011) concerning the patency rates of RA and SVG. In this meta-analysis early SVG patency was similar to RA patency, medium- and long-term patency however was found to be better for RA conduits. An interesting study concerning the clinical and angiographic results of the RA used as a coronary bypass graft over 20 years was also published (Achouh et al., 2012). Separating four groups at successive follow-up intervals, RA patency was: 86.2%, 81.9%, 81.4%, and 81.6% at 1.0, 5.4, 8.3, and 13.1 years, respectively. The results of the four available randomized studies are summerized on Table 1. 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.

Table1.

Author	Year	Trial	RA Patency %	SVG Patency %	Follow-up
Buxton	2003	RAPCO	95	94	5.0 years
Desai	2004	RAPS	91.8	86.4	10.9 months
Collins	2008	RSVP	93.8	86.4	67 months
Goldman	2011		89	89	1.0 year

Prospective randomized trials about the patency rate of RA vs. SVG

1.2.2 PATIENT SELECTION

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.

1.2.2.1 THE ALLEN TEST

The Allen test (AT) was first described by Edgar V. Allen as a diagnostic test for occlusive disease of the ulnar circulation in 1929. The principles of the test have not changed over the decades. Allen did not specified any cut-off point for the return of the pallor. Several different values have been suggested between 3 and 10 seconds. Asif and Sarka tested more than 600 patients using a 6 seconds cut-off point and three digit compression. In this series no vascular insufficiency of the hand was developed postoperatively in patients with harvested RA (Asif and Sarkar, 2007).

In our preoperative protocol we set the cut-off point to a very rigorous 5 seconds and used a three-digit compresson on RA.

Modified AT refers to an AT performed together with Doppler test on a hand artery. During the modified test the wrist should keep in neutral position to avoid hyperextension because of the possible occlusion of the ulnar artery. The compresson of the RA should be sufficient to keep the total occlusion of the RA while compression of UA is released. Furthermore the hand should be kept at the level of the heart to exclude any hydrostatic pressure changes.

1.2.2.2. ULTRASONOGRAPHY

Ultrasonography is an ideal non-invasive method for the evaluation of morphology and flow patterns of tha RA and UA. Linear transducer is generally used with a frequency range of 10-12 MHz. Ultrasonography is an essential part of preoperative selection of the patients planned for RA harvesting. Despite negative AT there is a considerable amount of patients who should be contraindicated for RA harvesting due to ultrasonography findings.

Ultrasonographic contraindications for RA harvesting were outlined by Pola (Pola et al., 1996) and Rodriguez (Rodriguez et al., 2001). Based on their research Pola and his group estabilished guidelines for Doppler flow measurements that should be performed before accepting for RA harvesting. Accordingly, during compresson of RA the peak systolic velocity (PSV) in UA should increase at least 20%. According to the authors the main contraindication for RA harvesting is inadequate increase of ulnar flow. Rodriguez and his group suggested morphological criteria also: vessel size at least 2 millimeters, diffuse

calcification or anatomic variations such as RA agenesis or UA hypoplasia. In this series 187 patients were screened, 12.7% were contraindicated due to morphological findings. Calcified RA were found in 8.7%, congenital anomalies 2.3%, small vessel in 1.5 %.

1.2.2.3. OTHER METHODS

Plethysmography and scintigraphy are less routinly performed for preoperative screening for RA harvesting. The idea of pulse oximetry of thumb or index finger during AT has been put forward by many surgeons. Interventional cardiologists have done large series to verify the method for transradial PCI, but there have been no systematic studies in the surgical setting.

1.2.2.4. PATIENT SELECTION AT OUR DEPARTMENT

To avoid postoperative forearm and hand ischaemia and to achive optimal RA graft function we introduced a very rigorous preoperative screening criteria regarding physical and ultrasonographic examinations. In Figure 1. we demonstrate a RA suitable for coronary bypass graft with normal morphology and flow pattern.

Exclusion criteria for RA harvesting were as follows:

- AT with three digit compression longer than 5 seconds
- Diameter of RA <2 millimeters
- Diameter of UA <2 millimeters
- Calcification or intima-media thickness of RA
- Anatomical variation (tortuosity, ulnar hypoplasia)
- Modified AT with PSV increase at least 20%

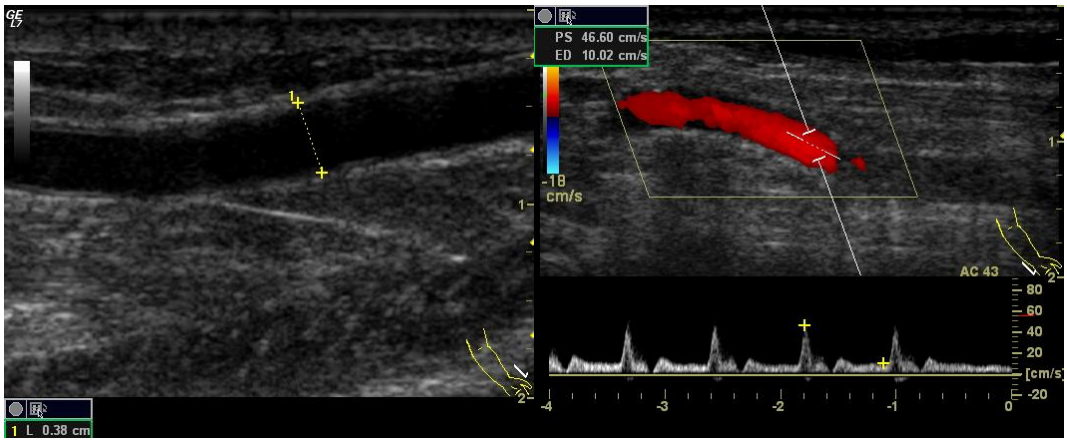

Figure 1. Normal morphology and flow pattern of the radial artery.

According to our criteria nearly 10% of preoperatively screened patients were contraindicated for RA harvesting due to ultrasonographic findings.

1.2.3. PATIENT FOLLOW-UP AFTER RADIAL ARTERY REMOVAL

Removal of the radial artery will definitively cause circulatory changes in the forearm. A number of studies have been published concerning the consequences of radial artery removal in coronary bypass patients. There is a strong evidence that this procedure is associated with significant increase in ulnar artey flow velocity after surgery. In a series of 34 asymptomatic patients the ulnar artery peak systolic velocity was greater in the operated arm compared with the control arm five years after radial artery harvesting (Serricchio et al., 1999). 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 ulnar artery of the operated versus control arm (Gaudino et al., 2006). In a recent larger series of investigation, however, this effect was not evident (Royse et al., 2008).

At our department we routinly perform a 3-6 months follow-up after RA harvesting included physical examination and complex ultrasonographic measurements regarding UA diameter, PSV in UA and UA flow patterns.

1.2.4. HARVESTING OF THE RADIAL ARTERY

1.2.4.1. NEUROVASCULAR ANATOMY OF THE HAND AND FOREARM

Figure 2. Intraoperative surgical anatomy of radial artery

Intraoperative picture demonstrates the surgical anatomy of the RA in Figure 2. The hand and forearm are mainly supported by two arteries, the RA and the ulnar artery (UA). The UA has major contribution to the circulation of the forearm. On the proximal half of its course the RA passes under the edge of brachioradialis muscle and is covered with connective tissue. Along its course it sends small perforating branches to the interosseus muscle and to the lateral aspect of the forearm. There are an average of 4.2 branches in the proximal half of the RA and an average of 9.6 branches in the distal half (Reyes et al., 1995). The superficial palmar artery is the second major branch of the RA and it branches from the main trunk at the level of the wrist crease. In contrast to the UA there are no major vessels arising from the RA between the cubital fossa and wrist that would contribute to the circulatory support of the forearm. The main arteries providing blood supply for the hand are the UA and RA. Anastomotic connections between the RA and UA are provided by two arterial arches.

According to their location they are referred to as deep palmar arch (DPA) and the superficial palmar arch (SPA). The DPA is complete in most individuals. The classic configuration of DPA could be found on 90-100% of subjects. The SPA is much more prone to variation. The prevalence of classic complete SPA varies between 10-56% in diferent studies (Bilge et al., 2006). The circulatory system of the forearm is complex and there is considerable variations from individual to individual in the type and number of the anastomotic connections between the RA and UA. The innervation of the forearm is provided by the ulnar nerve, median nerve and radial nerve. Sensory innervation of the radial and volar aspect of the forearm is provided by the lateral antebrachial cutaneous nerve, a branch of the musculocutaneous nerve. It runs along the edge of the brachioradialis muscle in the fascial sheath. The superficial radial nerve supports the sensory innervation of the radial aspect of the thumb and dorsum of the hand. It runs in close proximity to the RA.

1.2.4.2. SURGICAL TECHNIQUE

A lazy S-shape incision is made a two fingerbreadths from the wrist and elbow crease. The fascia is divided between the brachioradialis and flexor carpi radialis muscles. Special attention is made in order to avoid dividing the lateral antebrachial cutaneous nerve (usually can be kept to the lateral side of the fascial division). Retraction of the brachioradialis and flexor carpi radialis muscles reveals the radial artery. The RA is dissected as a pedicle graft including its two surrounding veins and some fat tissue. We believe that skeletonizing of the RA is a dangeorus technique. In our opinion the lenght of the pedicled RA is almost always enough to reach the target coronary artery (the posterior descending artery or the obtuse marginal branch). The surgical „no touch technique” is our another tool to reduce the risk of perioperative RA spasm. Arterial and venous branches are carefully divided. When dissection of the RA is completed, vascular clamps are applied at the proximal and distal ends. The RA and surrounding veins are divided and a 4-0 Prolene suture is sewn around the proximal and distal stumps of the RA. Wound closure is performed in two layers after adequate hemostasis is achieved. There is a greater risk of compartment syndrome in the harvest of the RA then in the harvest of the greater saphenous vein. A hemovac drain is placed prior to wound closure. The deep fascia is not closed. Running stitches are then used to close the subcuticular layer

and the skin. There are some surgical possibilities beyond the conventional method. Randomized study was published to compare Harmonic scalpel and conventional surgical methods (Oz et al., 2007). Two hundred patients were divided into two equal groups. In the conventional group electrocautery and haemostatic clips were used and in the Harmonic group the ultrasonic scalpel was used. Harvesting time was shorter in the Harmonic group (23.7 vs. 33.4 min), spasm rate was lower (2 vs. 8%) and the need for postoperative analgesia was also lower (5 vs. 17%). The occurance of neurological complications was similar in both groups. Minimally invasive surgical techniques have been applied also for radial artery harvest (Galajda and Péterffy, 2001). Randomised study was published concerning the functional and histological quality of the endoscopically harvested radial artery graft (Shapira et al., 2006). In this small study (18 patients in each groups), harvesting method did not have any affect on the functional or histological quality of the graft.

1.2.5. OFF PUMP CORONARY ARTERY BYPASS SURGERY WITH THE RADIAL ARTERY

After its atraumatic removal the RA is placed in a storage solution for 20-60 minutes to maintain the integrity and function of the artery known to frequently develop spasm in the intra/perioperative period. The RA is used either an aortocoronary or composite T graft fashion, depending on the patient's coronary anatomy or surgeon's preference. The operation is performed on the beating heart using special pericardial retraction sutures and stabilizers. During the construction of the proximal and distal anastomosis carefully handling RA is essential to avoid endothelial damage and subsequent spasm.

1.3. VASOREACTIVITY OF CONDUIT BYPASS GRAFTS

1.3.1 INODILATOR DRUGS

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 (Curtis et al., 1975; Sarabu et al., 1987). 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 (Acar et al., 1992, Borger et al., 1998), papaverine (Acar et al., 1992), milrinone (Tatoulis et al., 1998), nitroglycerin (Zabeeda et al., 2001), nicorandil (Sadaba et al., 2000) and alpha–receptor blockers (Taggart et al., 2000; Mussa et al., 2003). Nitroglycerin and diltiazem are the preferred drugs for relieving or preventing graft spasm (Shapira et al., 1999; Tabel et al., 2004). 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 (Katai et al., 2004). 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 (Haikala et al., 1995; Udvary et al., 1995; Hőhn et al., 2004). The inodilator also dilates conduit type of coronary arteries (Gruhn et al., 1998; Pataricza et al., 2003). Although, the preoperative administration of levosimendan improved the cardiac hemodynamic conditions in patients undergoing OPCAB surgery (Barisin et al., 2004), a direct effect of the drug on human bypass graft arteries has not been demonstrated yet.

1.3.2. STORAGE SOLUTION OF THE RADIAL ARTERY BYPASS GRAFTS

Over the different inodilator drugs, the storage solution of the RA grafts could have a resonable 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. The most convenient storage solution – in addition to its non-thrombotic property- would be expected to be inert and even to minimize the occurence of vasospasm. This can be achieved by preserving the vascular endothelial function and/or preventing the enhanced contractile capacity of the arterial smooth muscle. Although graft segments stored

in heparinized whole blood had greater endothelium-dependent relaxation to acetylcholine (Chong et al., 2001), blood-stored radial artery grafts revealed markedly increased smooth muscle contractions (Tatoulis et al., 1999). Papaverine, a widely used smooth muscle relaxant in storage solutions, impairs endothelial function (He, 1998).

The colloidal Biseko® solution is a cold sterilized liquid in which coagulation factors and bacterial toxins are absent or minimal. The immunglobulin concentrations and activities are equivalent to those in normal serum. Biseko® solution in patients with autoimmun diseases decreases the risk of infections and adverse drug reactions in comparison to fresh frozen plasma (Keller et al., 2000). In addition, a preliminary observation has suggested that this colloidal solution might protect vascular tissues by decreasing the permeability of the endothelium (unpublished observation).

2. 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®, 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.

3. USE OF LEFT INTERNAL THORACIC ARTERY IN SPECIAL SITUATIONS

3.1. 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. In a large retrospective study, investigating over 30,000 patients having undergone coronary artery bypass grafting after transmural myocardial infarction, perioperative mortality was described to be highest (14.2%) when coronary artery bypass grafting was performed within the first 6 hours after the ischemic event. When coronary artery bypass grafting was delayed for 4 to 7 days, perioperative mortality was reduced to 3.8% and could further be reduced when the delay was 8 to 14 days (2.9%) (Lee et al., 2003). On the other hand, if the patient is at acute risk and the myocardium can be salvaged, quick reperfusion of the infarcted vessel is warranted. When reperfusion of an occluded coronary artery occurred at 40 minutes, transmyocardial necrosis was reported to be 38 ± 4%. When reperfusion occurred at 6 hours, transmyocardial necrosis was reported to be 71 ± 7% (Reimer et al., 1970).

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 I, II, and aVL. He was now registered for emergency coronary artery bypass grafting. He was immediately transferred to the cardiac surgical center under continuous perfusion with heparin, nitroglycerin, oral clopidogrel, and diazepam, and with buprenorphine for pain relief. The electrocardiogram showed ST-segment elevation in leads I, II, avL and in the precordial leads V1–V4. He was directly transferred to the operating room 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 (Quickflow, Medtronic, MN) 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. Graft flow was determined using transit time flow measurement (Fig.3.). 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 2.

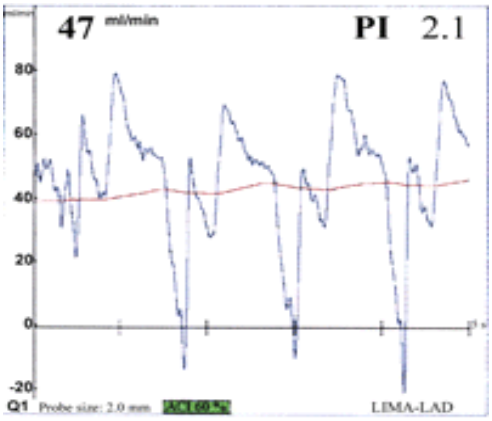

Figure 3. Transit time flow determination of left internal thoracic artery graft to the left anterior descending artery. Original intraoperative record.

The ST-segment elevation myocardial infarction is induced by complete occlusion of an epicardial coronary artery. After 3 to 6 hours of ischemia the possibility of salvaging the myocardial tissue from eventual transmural infarction dramatically decreases, depending on factors such as collateral blood flow. However even late reperfusion after more than 12 hours subsequent to an ischemic event was reported to be of benefit for patients with acute myocardial infarction treated with balloon angioplasty or stent implantation (Kastrati et al., 2004). When coronary artery bypass grafting is performed in cases of acute myocardial

infarction, aortocoronary shunting can immediately restitute 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. 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. 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.

3.2. 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 (Nataf et al., 2000; Calafiore and Angelini, 1996; Nishida et al., 2010). 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 achive 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. Before chest closure intercostal ropivacaine blockade was applied to reduce the early postoperative pain. 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 (Fig.4.) and a new significant stenosis of the right coronary artery.

Figure 4. Patent LITA-LAD anastomosis five years after successful VADCABG operation

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

4.1. ETHICS

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.

4.2. VASOREACTIVITY OF HUMAN ARTERIAL CONDUITS *IN VITRO*. EFFECT OF LEVOSIMENDAN.

4.2.1. CHARACTERISTICS OF PATIENTS

Sixteen patients undergoing elective coronary bypass surgery (CABG) were involved in this study. LITA was obtained from eight patients (age: 65.7±2.9 yrs), proximal and distal parts of RA were obtained also from eight patients (age: 65.4±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.

4.2.2. 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, USA). 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^{-1}): NaCl 120, KCl 4.2, $CaCl_2$ 1.5, $NaHCO_3$ 20, $MgCl_2$ 1.2, KH_2PO_4 1.1, glucose 11 and EGTA 0.27 μmol L^{-1}. In the laboratory, the arteries were dissected free from the surrounding connective tissue, and cut into rings of 3 mm long.

4.2.3. 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_2 and 5% CO_2 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 Elektronic, Type F30, Germany) to measure changes in isometric tension as previously described by Pataricza and colleagues (Pataricza et al., 2003). In each isolated type of grafts we optimazed 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^{-1} serotonin. 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.

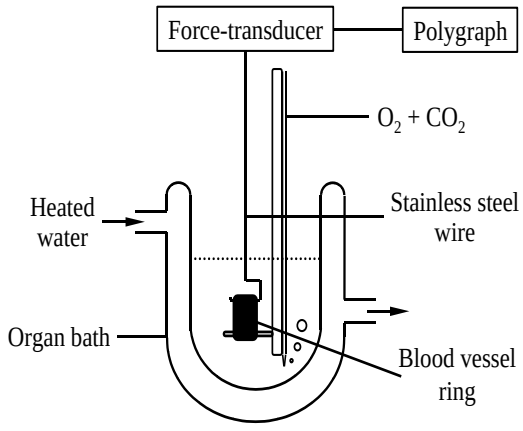

Figure 5. Measurement of isometric tension of radial artery rings using an organ chamber and a force-displacement transducer

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^{-1} serotonin. When the contraction reached a stable plateau levosimendan was administered cumulatively (0.009-1.14 μmol L^{-1}) into the organ baths.

4.2.4. DATA ANALYSIS

Contractions induced by 0.002-9.3 μmol L^{-1} 5-HT were expressed in mN. Relaxations induced by levosimendan was expressed as % of serotonin-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_{max} (a) and 50% effective concentration (b=EC_{50}) values were calculated. EC_{50} values were converted to pD_2 and expressed in –log mol L^{-1} concentrations.

4.3. INVESTIGATION OF THE EFFECT OF COLLOIDAL BISEKO ® 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®, 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.

4.3.1. CHARACTERISTICS OF PATIENTS

26 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. The clinical characteristics of the patients are summarized in Table 2.

Table 2. Characteristics of patients

Characteristics	Group I Radial artery incubated in crystalloid solutions*	Group II Radial artery incubated in colloidal solutions**
Number of patients	12	14
Sex	9 males, 3 females	11 males, 3 females
Age (year)	59.0 ± 2.4	60.1 ± 2.2
Diseases		
Hypertension	12 (100.0 %)	14 (100.0 %)
Hypercholesterolemia	11 (91.7 %)	13 (92.8 %)
Diabetes mellitus	2 (16.7 %)	2 (14.3%)
Drugs		
Beta blockers	11 (91.7 %)	13 (92.8 %)
ACE° inhibitors	10 (83.3 %)	13 (92.8 %)
Calcium antagonists	1 (8.3 %)	0 (0.0 %)
Antihyperlipidemics	11 (91.7 %)	13 (92.8 %)

% represents the percent occurence of the diseases or treatments within the group

* = either 0.9 % NaCl or Bretschneider solution

**= either 5 % human albumin or Biseko® solution

° = ACE: angiotensin converting enzyme

4.3.2. 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^{-1}) was given in intravenous infusion to prevent early vasospasm. Ont the basis of the results of our previous investigation, 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® solutions (Group II patients) for 45 minutes.

4.3.3. ISOMETRIC TENSION MEASUREMENT AND PROTOCOL OF INVESTIGATION

Two rings from the proximal part of RA grafts were mounted in parallel on stainless-steal 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_2 and 5 % CO_2 at pH 7.4. One of the hooks was anchored and the other one was connected to a force-displacement transducer (Hugo Sachs Elektronic, Type F30, Germany) 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^{-1} KCl. After washing the arterial rings contractions were repeated with 0.3 μmol L^{-1} 5-HT. Endothelium dependent relaxations were induced by acetylcholine (10 μmol L^{-1}) and bradykinin (1 μmol L^{-1}). Endothelium independent relaxations were produced by glyceryl trinitrate (10 μmol L^{-1}).

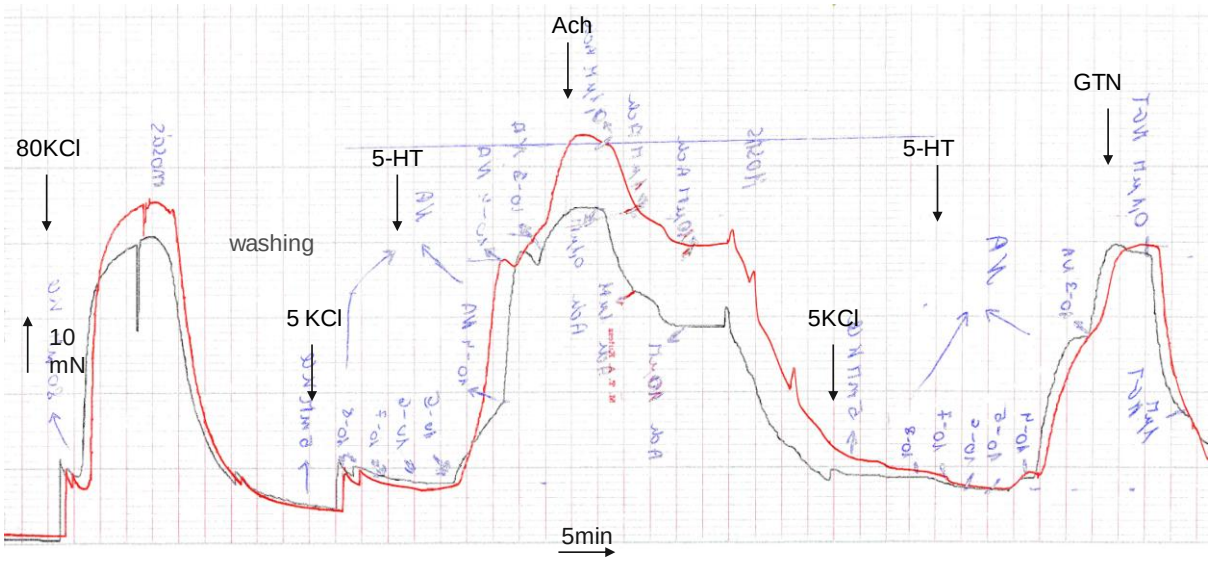

Figure 6. Original polygraph recording. Red line represents the control and the black line shows the effect of Biseko® solution. Precontracion was achived with 80 mmol L^{-1} potassium chloride (80 KCl). After washing contractions were repeated with the combination of 5 mmol L^{-1} KCl (5 KCl) and 0.31 µmol L^{-1} 5-HT. Endothelium dependent relaxations were induced by acetylcholine (Ach, 10 µmol L^{-1}). Endothelium independent relaxations were produced by glyceryl trinitrate (GTN, 10 µmol L^{-1}).

4.3.4. DATA ANALYSIS

Contractions and relaxations were expressed in milliNewton (mN). Data are presented as mean ± standard deviation (mean ± 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 then 0.05 were considered as significant.

4.4. DRUGS AND SOLUTIONS

Levosimendan (Orion-Pharma, Espoo, Finland) was dissolved in 70% ethanol and further diluted in Krebs-Henseleit solution. 5-hydroxytryptamine (5-HT: serotonin creatinine sulfate complex), noradrenaline (norepinephrine hydrochloride), acetylcholine (acetylcholine chloride), bradykinin (bradykinin acetate) and papaverine (papaverine hydrochloride) were obtained from Sigma-Aldrich (St Louis, MO, USA). Glyceryl trinitrate was purchased from Pohl Boskamp (Hohenlockstedt, Germany). The solutions used and their compositions: 5 % human albumin (50 g L^{-1} human albumin, 4 mmol L^{-1} caprylate, 4 mmol L^{-1} acetyltryptophan, 145 mmol L^{-1} sodium, 2 mmol L^{-1} potassium) and Biseko® solution (50 g L^{-1} human serum protein (31 g L^{-1} albumin, 10 g L^{-1} human immunoglobulin), 154.85 mmol L^{-1} sodium, 4.09 mmol L^{-1} potassium, 1.99 mmol L^{-1} calcium, 0.82 mmol L^{-1} magnesium, 100.56 mmol L^{-1} chloride) were obtained from Biotest (Hungaria Kft., Törökbálint, Hungary); Bretschneider solution (15 mmol L^{-1} NaCl, 10 mmol L^{-1} KCl, 4 mmol L^{-1} $MgCl_2$, 180 mmol L^{-1} histidine, 2 mmol L^{-1} tryptophane, 30 mmol L^{-1} mannitol, 1 mmol L^{-1} potassium dihydrogen oxoglutarate) and Krebs-Henseleit solution (120 mmol L^{-1} NaCl, 4.2 mmol L^{-1} KCl, 1.5 mmol L^{-1} $CaCl_2$, 20 mmol L^{-1} $NaHCO_3$, 1.2 mmol L^{-1} $MgCl_2$, 1.1 mmol L^{-1} KH_2PO_4, 11 mmol L^{-1} glucose and 0.27 μmol L^{-1} EGTA) and 0.9 % NaCl were purchased from Reanal (Budapest, Hungary).

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

4.5.1. 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 periferial arterial desease. Medical treatment included statins, aspirin, nitrates, ACE-inhibitors, calcium channel blockers, beta blockers, diuretics and antidiabetic drugs.

4.5.2. 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.

5. RESULTS

5.1 VASOREACTIVITY OF HUMAN ARTERIAL CONDUITS *IN VITRO*. EFFECT OF LEVOSIMENDAN.

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

5-HT (0.002-9.3 μmol L^{-1}) enhanced the tone of the LITA and that of the proximal and distal parts of RA concentration dependently (Fig.7). 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 at and above 0.31 μmol L^{-1} of 5-HT (at 0.31 μmol L^{-1} 5-HT: proximal RA=13.0±4.9 mN vs LITA 3.6±1.6 mN, n= 8 and 8, $p<0.05$). The distal RA also developed higher active tension than LITA but the difference in effect was not statistically significant. The developed maximum tension (E_{max}) calculated by fitting a logistic curve showed similar results (E_{max}: LITA= 11.0±1.9 mN, proximal RA= 27.0±4.5 mN and distal RA=18.5±6.8 mN, $p<0.01$ LITA vs proximal RA). The sensitivity of the grafts to the contractile agent, expressed as pD_2 values, did not differ significantly in the case of the three conduit blood vessels (pD_2 values: LITA= -6.04±0.51 log mol L^{-1}, proximal RA= -6.52±0.40 log mol L^{-1}, distal RA= -6.57±0.25 - log mol L^{-1}).

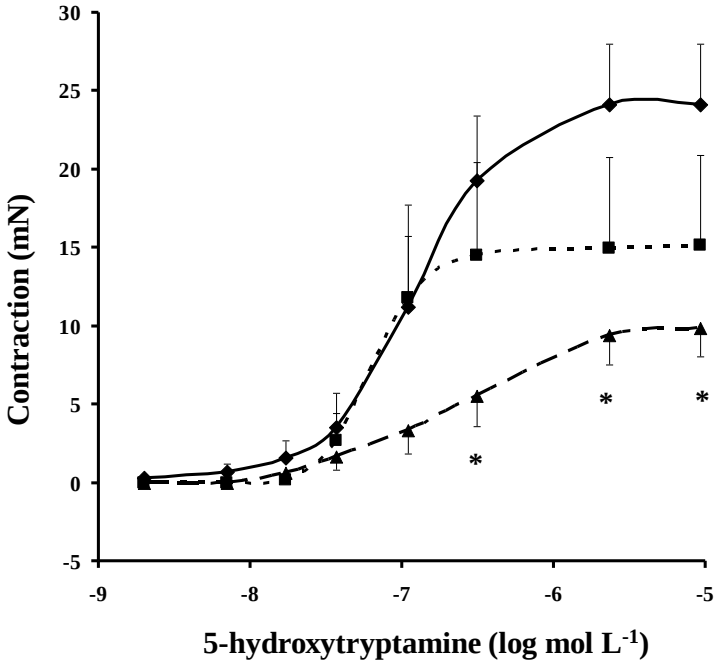

Figure 7. Effect of 5-HT (0.002-9.3 μmol L^{-1}) on the tone of the proximal and distal parts of the radial artery (RA) as well as on that of the left thoracic artery (LITA). Values are expressed as means ± standard error of the mean (♦ = proximal segment of RA, n = 8; ■ = distal segment of RA, n = 8; ▲ = segment of LITA, n = 8). Asterisk denotes significant differences (P<0.01) between the corresponding values of the proximal part of RA and LITA.

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

Fig. 8 demonstrates that levosimendan concentration dependently (0.009-1.14 μmol 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 (E_{max}: LITA= 100.3±16.2% of 5-HT-induced maximum tension, proximal RA= 86.9±8.6%). Levosimendan partially relaxed the distal RA= 59.4±17.5%, p<0.05 vs LITA.

The sensitivity of LITA as well as the proximal and distal RA samples to the vasodilating effect of the drug were calculated to possess comparable pD_2 values (LITA: -6.52±0.44 log mol L^{-1}, proximal RA: -6.60±0.49 log mol L^{-1}, distal RA: -6.85±0.45 log mol L^{-1}).

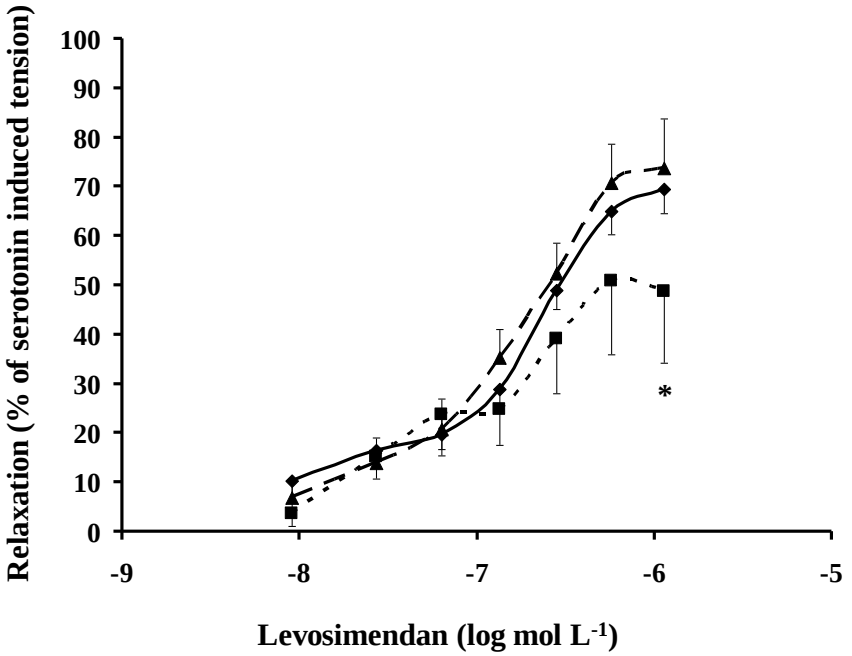

Figure 8. Vasorelaxing effect of levosimendan (0.009-1.14 μmol L^{-1}) in the proximal and distal radial arteries (RA) as well as in the left thoracic artery (LITA). The rings were contracted with 5-HT, added cumulatively (0.002-9.3 μmol L^{-1}). The relaxation of the tissue by levosimendan was expressed as a percentage of the contraction induced by 5-HT. Values are expressed as means ± standard error of the mean (♦ = proximal segment of RA, n = 8; ■ = distal segment of RA, n = 8; ▲ = segment of LITA, n = 8). Asterisk denotes significant difference ($P<0.05$) between the corresponding values of the distal part of RA and LITA.

5.2 INVESTIGATION OF THE EFFECT OF COLLOIDAL BISEKO ® AS STORAGE SOLUTION ON THE CONTRACTILE AND RELAXING CAPACITIES OF ISOLATED RADIAL ARTERY GRAFTS

5.2.1 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 μmol L^{-1}) are depicted in Figure 9. It can be seen that, following incubation of the radial artery segments in crystalline solutions, no considerable difference was found in their reactivity in 0.9 % NaCl (35.9 ± 11.9 mN, n=12) and in Bretschneider (26.7 ± 8.3 mN, n=12) solutions. Incubation of the radial arteries in the colloidal Biseco® solution revealed significantly smaller contractions to 5-HT than those obtained after incubation of the graft samples in 5% albumin (Biseco®= 12.6 ± 4.4 mN vs 5% albumin= 37.9 ± 13.9 mN, n=14 and 14, p‹ 0.05) or in 0.9% NaCl (35.9±11.9, $p<0.05$ compared to the values in Biseco® solution).

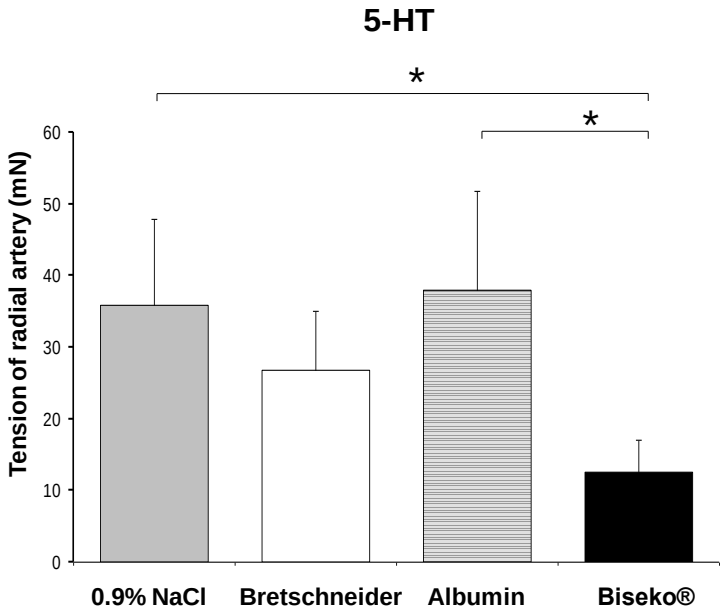

Figure 9. Isometric contractions of human isolated radial artery grafts preincubated in crystalline or colloidal solutions. Radial artery samples were submerged into crystalline (0.9% NaCl or Bretschneider) and colloidal (5% albumin or Biseko®) solutions for 45 min before the measurement of isometric tension of the grafts *in vitro*. Contractions were induced with 5-HT (0.31 μmol L^{-1}). Values are shown as mean ± standard deviation obtained from 12 (crystalline, group I) or 14 (colloidal, group II) individuals. *$p < 0.05$.

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

Endothelium-dependent vasorelaxants, acetylcholine (Ach, 10 μmol L^{-1}) or bradykinin (BK, 1 μmol L^{-1}) were administered in 0.31 μmol L^{-1} 5-HT-precontracted radial artery rings (Figure 10). 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. BK did not relax the radial artery in Bretschneider solution (compared to hypothetical zero values (n=12), not significant with Mann-Whitney non-parametric test).

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

Figure 10. (right side) demonstrates that the endothelium independent vasorelaxant, glyceryl trinitrate (GTN, 10 μmol L^{-1}) exerted similar relaxations against 5-HT-induced contractions in crystalloid and colloidal solutions.

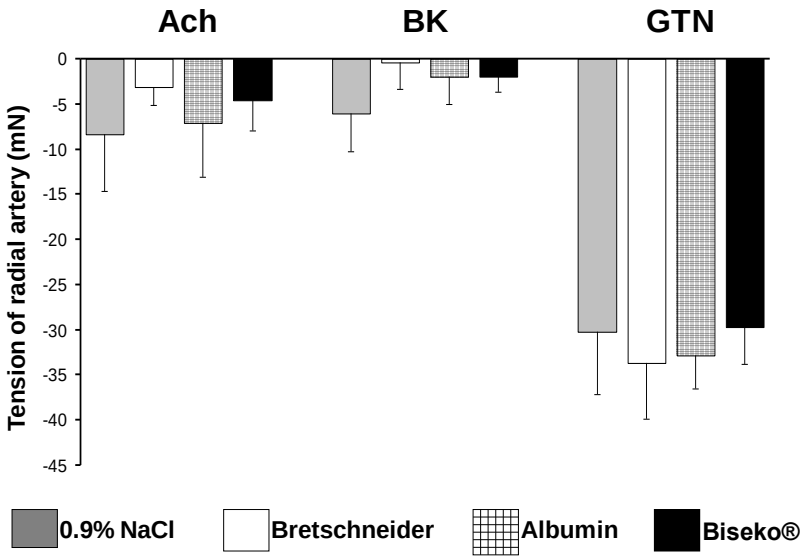

Figure 10. Endothelium-dependent and independent vasodilations of human isolated radial artery grafts preincubated in crystalline or colloidal solutions. Radial artery samples were submerged into crystalline (0.9% NaCl or Bretschneider) and colloidal (5% albumin or Biseko®) solutions for 45 min before the measurement of isometric tension of the grafts *in vitro*. Endothelium-dependent vasorelaxants, acetylcholine (Ach, 10 μmol L^{-1}) or bradykinin (BK, 1 μmol L^{-1}) as well as the endothelium-independent dilator, glyceril trinitrate (GTN, 10 μmol L^{-1}), were applied to 5-HT (0.31 μmol L^{-1}) precontracted arterial rings. Values are shown as mean ± standard deviation obtained from 12 (crystalline, group I) or 14 (colloidal, group II) individuals.

5.3 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 results are demonstrated in figure 11. The pre-and postoperative diameter of the UA did not show significant change: 2.56 mm, 2.84 mm, respectively. All of the patients were free of any sign of forearm ischaemia and any relevant neurological or functional disturbances.

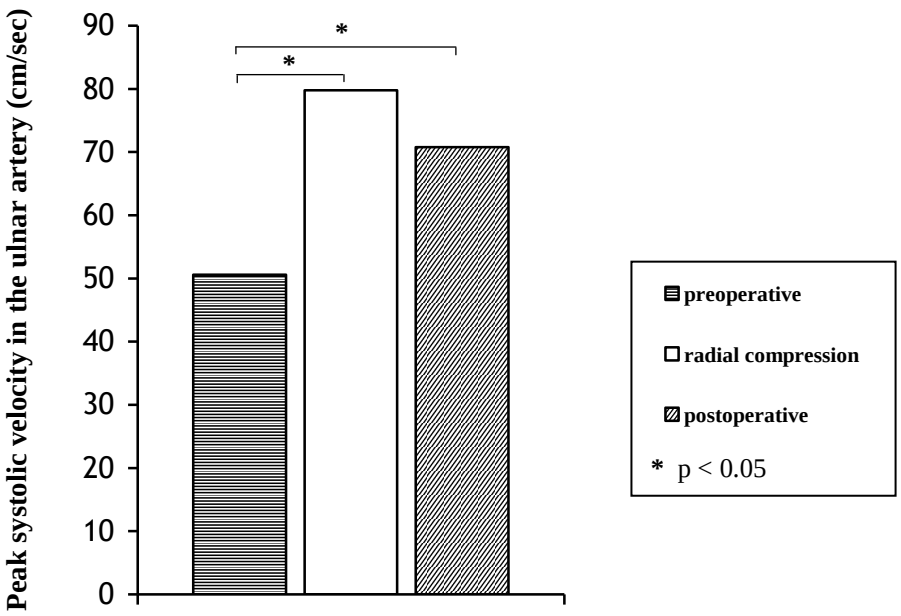

Figure 11. Peak systolic velocity changes in the ulnar artery. 3-6 months after RA removal the flow of the UA is significantly higher (* $p < 0.05$) but does not reach the preoperative value measured during RA compression.

6. 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 restitute 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 approches: 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 (Nobuaki et al., 2001), in 2004 we published the first 5 VADCABG cases in Hungary. The LITA preparation was performed using the endoscopic Ultracision harmonic scalpel to achive 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 (Pataricza et al., 2003; Hőhn et al., 2004). 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 (Sperti et al., 1999). 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 (Chester et al., 1998) 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 resonable effect on the vasoreactivity of the RA bypass conduits. We demonstrated the beneficial effect of the colloidal Biseko® solution on the vasoconstrictive capacity of RA grafts. RA segments incubated in the colloidal Biseko® solution produced diminished contractions to 5-hydroxytryptamine as compared to the colloidal albumin or physiologic saline solutions. The maximum vasocontrictive 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® 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 (Nielsen, 2005; Chuang and Otagin, 2007) being absent or minimal in Biseko® solution. Some coagulation factors such as thrombin and tissue factor were found to cause direct vasoconstriction and protein C enhanced the α-adrenergic receptor mediated contractile responses of arteries (Salloum et al., 2005; Wiel et al., 2006). A bacterial toxin, e.g. Escherichia coli hemolysin, is able to release thromboxane, a potent vasoconstrictor of the radial artery with damaged endothelium (Seeger, et al., 1989; Arshad et al., 2006). 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 (Tatoulis et al., 1999). 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 int he organ chamber. At least, these results exclude a considerable non-specific effect of N-acetyl-L-tryptophan and caprylate, stabilizers of pharmaceutical-grade albumins, on the tone of the radial arteries (Olsen et al., 2004). We assume that the decreased endothelial permeability -evoked by the colloidal Biseko® 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® 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® solution useful for decreasing the risk of intra/perioperative spasm of radial artery.

Removal of the radial artery will definitley 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 then

preoperative, 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 (Gaudino et al., 2006). In a recent, larger series this effect was not observed (Royse et al., 2008). 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.

7. SUMMARY

Use of arterial conduits in coronary bypass surgery is an independent factor of improved long-term survival. 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 achive 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 month after the operation.

We have also demonstrated the vasodilating efficiency of the inodilator, 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® solution on the vasoconstrictive capacity of RA grafts. RA segments incubated in the colloidal Biseko® 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® 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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APPENDIX