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Adventitial dissection: a simple and effective way to reduce radial artery spasm in coronary bypass surgery

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Abstract

OBJECTIVES: Over the last two decades, the radial artery (RA) has become a routinely used conduit for coronary artery bypass graft surgery. One potential disadvantage of the radial artery is its higher susceptibility to vasospasm compared with other arterial grafts. We investigated whether adventitial dissection of the radial artery can reduce vasoconstriction and increase free blood flow.

METHODS: Following harvesting, the adventitia of the radial artery was dissected using coronary scissors. Surplus distal radial artery segments ($n = 35$) with and without adventitial dissection of patients undergoing coronary artery bypass surgery were collected and pairwise assessment of vasoreactivity to potassium chloride, U46619 and acetylcholine was performed in organ bath experiments. Free blood flow was measured before and after adventitial dissection.

RESULTS: Full curve and maximal vasoconstriction of the RA to potassium chloride ($P = 0.015$ and 0.001) and U46619 ($P = 0.048$ and 0.001) was significantly reduced after adventitial dissection compared with non-adventitial dissected radial arteries. Endothelium-dependent relaxation to acetylcholine of adventitial dissected radial arteries was significantly increased ($P = 0.006$) compared with non-adventitial dissected radial arteries. Maximal vasorelaxation to acetylcholine was significantly increased for adventitial dissected radial arteries compared with non-adventitial dissected radial arteries ($P = 0.018$). Free blood flow was significantly increased after adventitial dissection ($P = 0.037$).

CONCLUSIONS: The adventitial dissected radial artery is less susceptible to vasoconstriction and more prone to vasorelaxation *ex vivo* and shows an increased free blood flow. Therefore, we suggest adventitial dissection of the radial artery graft to reduce vasospasm for arterial revascularization in coronary artery bypass surgery.

Keywords: Coronary artery bypass graft arterial grafts • Vascular tone and reactivity • Coronary artery bypass graft new technology • Off-pump surgery

INTRODUCTION

After its introduction as a coronary artery bypass graft (CABG), the radial artery (RA) was soon abandoned due to its high incidence of occlusion [1–3]. Graft failure was most probably caused by spasm, which increased the likelihood of peri- and/or postoperative myocardial ischaemia [4, 5], and intimal hyperplasia, resulting from endothelial denudation due to mechanical dilatation and/or trauma from skeletonized harvesting [1, 6]. Over the last two decades, however, early and late patency of RA bypass grafts improved significantly thanks to improved harvesting techniques, routine perioperative use of vasodilators and postoperative treatment with calcium-channel blockers [6]. Prevention of graft spasm was proved to be beneficial in the acute period following CABG surgery [7], which led to an increased popularity of the RA as bypass graft. As a consequence, in many centres the RA replaced the saphenous vein in complementing the left internal mammary artery (IMA) [6–8]. Nevertheless, the RA is still more susceptible to spasm than the IMA or gastroepiploic artery [6, 9]. This fact has been considered a possible cause of the relatively high rate of early RA graft failure, observed in up to 5–10% [6, 7] of the cases. Perioperative use of vasodilating drugs may be insufficient to entirely prevent early postoperative spasm of the RA [4, 5, 10]. On the other hand, the method of RA harvesting and handling may play an even more important role in preventing spasm [5, 11].

In clinical practice, the RA is generally harvested, with or without pedicle, with an intact adventitia. A preserved adventitia (i) provides structural support to the vessel, which may limit flow-related vascular enlargement and (ii) participates in the modulation of vasomotor tone, which may promote spasm [12–14]. In the present study, we therefore investigated distal surplus segments of the RA harvested during CABG surgery. These segments were

tested in organ-bath experiments for the hypothesis that adventitial dissection may reduce the likelihood of vasospasm and determine an increase in free blood flow compared with RA segments with an intact adventitia.

MATERIALS AND METHODS

This prospective study was approved by the Medical Ethical Committee of the Medisch Spectrum Twente (METC: K11–02), Enschede, Netherlands. Surplus material of distal RA segments which would have otherwise been discarded was collected at the Departments of Cardiothoracic Surgery of the Medisch Spectrum Twente and University Medical Center Groningen. Written informed consent was obtained from patients prior to surgery. All patients underwent conventional Allen's test and modified Allen's test using pulse oximetry prior to surgery. An Allen's test of <5 s was considered negative. The RA was harvested from the non-dominant arm. Thirty-five consecutive patients undergoing CABG were included in the study, according to the standard practice of the two participating centres.

Surgical technique

Several methods to harvest the RA have been described [15, 16]. In our study, the RA was harvested together with surrounding tissue and veins with minimal manipulation using the open technique as described by Reyes *et al.* [17]. Adventitial dissection of the RA was performed after topical administration of 1.0 mg/ml (0.1% w/v) papaverine solution (pharmacy Catharina Hospital, Eindhoven, Netherlands) in physiological saline solution (Aguettant Versol, France). Papaverine was administered topically to avoid endothelial damage due to its acidity [10]. Adventitial dissection was carried out as longitudinal dissection of total adventitia and all bundles of circumferential collagen fibres over the entire length on the ventral side of the RA, using coronary scissors, as shown in Fig. 1. While performing adventitial dissection, the most distal 1.5 cm of RA graft was left non-dissected for comparison of the effect of adventitial dissection within each single patient. Surplus distal RA segments were kept in oxygenated 4°C Krebs–Henseleit buffer solution following retrieval and functional analysis was performed within 24 h of harvesting [9].

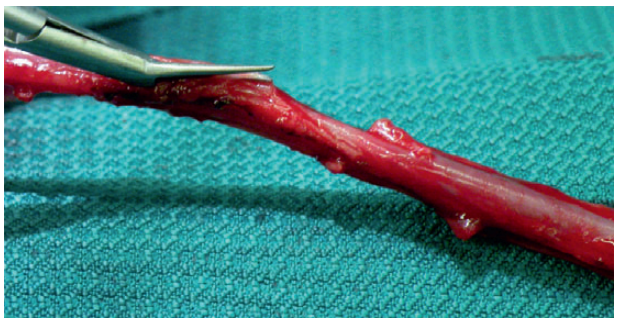

Figure 1: Adventitial dissection of RA. After heparinization and topical administration of 1.0 mg/ml papaverine solution in physiological saline solution, the surgeon opens the adventitia along the entire vessel length with coronary scissors. After completion of the last distal anastomosis, surplus distal segments of the RA were used for research purposes.

Morphology

Scanning electron microscopy (SEM) was performed on adventitial dissected ($n = 5$) and non-adventitial dissected RA segments ($n = 5$) which were fixed in 4% formaldehyde for 14 days and then dehydrated in increasing ethanol series and were critical point dried with liquid CO_2 (Balzers, Lichtenstein). The samples were sputtercoated (Cressington Scientific Instruments, UK) with a 60–90-nm thick film of gold and examined in a scanning electron microscope at an accelerating voltage of 2.5 keV (Philips XL30 ESEM-FEG, Netherlands).

Organ bath technique

For functional analysis, distal RA segments with and without adventitial dissection of each patient were carefully dissected from their surrounding fat tissue and divided into ring segments of 3 mm. Two wire stirrups were placed through each ring and attached to a transducer for isotonic displacement measurements, as previously described [9]. The rings were lowered into separate organ bath chambers filled with 15 ml Krebs–Henseleit buffer solution (pH 7.4, 37°C) continuously aerated with 95% O_2 and 5% CO_2 [9]. The set-up consisted of a myograph system, eight organ baths, a computer with the Contraction Measurement System software (v2005), an AD-converter and Neslab GP-100L incubator (Neslab Instruments, Inc., Portsmouth, NH, USA). RA segments were stretched to a preload of 50 mN to an estimated resting tension for equilibration for 90 min. Thereafter, ring segments were subjected to three consecutive stimulations with 60 mM potassium chloride (KCl; Merck, Germany).

To assess the effect of adventitial dissection on vasoconstriction, RA ring segments ($n = 16$ patients) were exposed to increasing concentrations of 10–60 mM KCl and 1.0 nM–1.0 μM U46619 (Merck, Germany), a stable analogue of the endoperoxide prostaglandin (PG) H_2 that mimics the effect of thromboxane, respectively Protocol A and B.

In Protocol C, dose dependent relaxation of RA ring segments ($n = 22$ patients) to 1.0 nM–100 μM acetylcholine (ACh; Sigma-Alderich, St. Louis, MO, USA) was performed after reaching a stable preconstriction plateau with U46619. The concentration U46619 used ranged from 10 to 30 nM and was chosen to induce a vasoconstriction level of 60–80% of the maximal vasoconstriction to 60 mM KCl. In Protocol D, the involvement of cyclo-oxygenase (COX) derived vasoactive PG was blocked by preincubation with 10 μM indomethacin (Sigma-Alderich, St. Louis, MO, USA) for 20 min and dose-dependent relaxation to 1.0 nM to 100 μM ACh was then repeated. 10 mM sodium nitroprusside (SNP; Sigma-Alderich, St. Louis, MO, USA) was finally added at the end of both Protocols C and D to induce direct smooth muscle cell relaxation.

Measurement of free blood flow

Intraoperative free blood flow was measured before performing the distal anastomosis, and after systemic heparinization, completion of IMA Y-graft RA anastomosis and after topical administration of 1.0 mg/ml papaverine solution in physiological saline solution ($n = 12$). The pedicled IMA was distally closed with an atraumatic bulldog clamp. Blood flow was measured as the amount of blood collected in a sterile bowl in 15 s at a systolic

blood pressure of 100 ± 5 mmHg and was measured before and after adventitial dissection by the surgeon and presented as ml/min. Blood was returned to the patient using a cell saver (Electa 225 ml bowl, Sorin Group, Arvada, CO, USA).

Statistical analysis

Statistical analysis was performed using IBM® SPSS® Statistics 20.0.0 (IBM Corp., Armonk, NY, USA). Of each patient one surplus distal RA segment was obtained with and without adventitial dissection, so each patient was its own control. Experiments in organ bath studies were performed *in duplo* and the mean value was used to represent the patients' average response with *n* the number of patients. Relaxation responses to ACh and SNP were expressed as a percentage of U46619-induced preconstriction. Vasoconstriction response to KCl and U46619 were expressed as absolute values in micrometers (μm). Full-concentration response curves to ACh, KCl and U46619 were analysed using repeated measures analysis of variance (ANOVA). Wilcoxon signed-ranks test was performed to assess the effect of adventitial dissection on preconstriction to U46619, maximal vasorelaxation to SNP and free blood flow. Comparison between adventitial dissected and non-adventitial dissected RA ring segments at each single concentration point in the dose response curves to ACh, KCl and U46619 was also evaluated using a Wilcoxon signed-ranks test. $P < 0.05$ was considered statistically significant. Data are presented as mean ± standard error of the mean unless stated otherwise.

RESULTS

Morphology

Non-adventitial dissected segments showed collagen fibrils of 50–200 μm (Fig. 2A). Adventitial dissected samples showed dissection of large collagen bundles with an intact dense connective tissue consisting of small, 5–10 μm, collagen fibrils (Fig. 2B). In both groups no media was exposed.

Vasoreactivity

Maximal vasoconstriction to 60 mM KCl ($P = 0.001$) and 1.0 μM U46619 ($P = 0.001$) was reduced for adventitial dissected RA segments compared with non-dissected segments. This also accounts for the full vasoconstriction curves to KCl ($P = 0.015$) and U46619 ($P = 0.048$), see Fig. 3. Furthermore, adventitial dissection significantly reduced absolute preconstriction to U46619 compared with non-adventitial dissected RA segments ($P = 0.009$), as shown in Fig. 4A, although in both groups the preconstriction was 60–80% of its maximal vasoconstriction to 60 mM KCl. Vasoconstriction was significantly reduced following COX-inhibition with indomethacin ($P < 0.001$, Fig. 4B).

Endothelium-dependent relaxation to ACh of RA rings with adventitial dissection was significantly increased ($P = 0.006$) compared with RA rings without adventitial dissection (Fig. 5A). Maximal vasorelaxation to ACh was 33.1 ± 4.6% for adventitial dissected RA compared with 20.9 ± 3.5% for non-adventitial dissected RA ($P = 0.018$). Maximal relaxation to SNP was not influenced by adventitial dissection ($P = 0.268$), Fig. 5B.

Free blood flow

Adventitial dissected RAs showed a significant increase ($P = 0.037$) in perioperative free blood flow of 154.3 ± 16.0 ml/min compared with 106.3 ± 13.8 ml/min of non-adventitial dissected RAs, as shown in Fig. 6.

DISCUSSION

The main findings of this present *ex vivo* study are that the adventitial dissected RA segments were significantly less susceptible to the vasoconstrictors potassium chloride and U46619 and more prone to endothelium-dependent relaxation induced by acetylcholine. No difference in direct smooth muscle cell relaxation to SNP was observed. Furthermore, free blood flow of the RA increased after adventitial dissection.

It is known that the adventitia is involved in the modulation of vasomotor tone [12–14, 18]. It can be assumed that the modulation of vasomotor tone may be reduced by adventitial dissection. Furthermore, changes in vasoreactivity could be attributed to a change in mechanical properties of the vessel by dissection of large collagen fibres. We hypothesize that adventitial dissection of the RA may reduce the mechanical barrier of adventitia and the vascular tone of its smooth muscle cells. Furthermore, the sensitivity of the RA to the vasoconstrictor U46619 was strongly attenuated following incubation with indomethacin, which is indicative

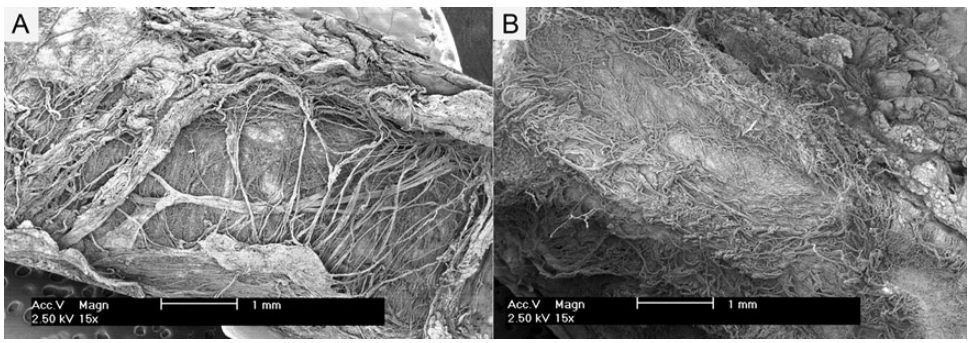

Figure 2: SEM images of RA. (**A**) Representative non-adventitial dissected segment shows collagen fibrils of 50 μm up to 200 μm. (**B**) Representative adventitial dissected sample shows dissection of large collagen bundles with an intact dense connective tissue consisting of small, 5–10 μm, collagen fibrils. In both groups no media is exposed, which indicates that only collagen fibrils of the adventitia are dissected during adventitial dissection.

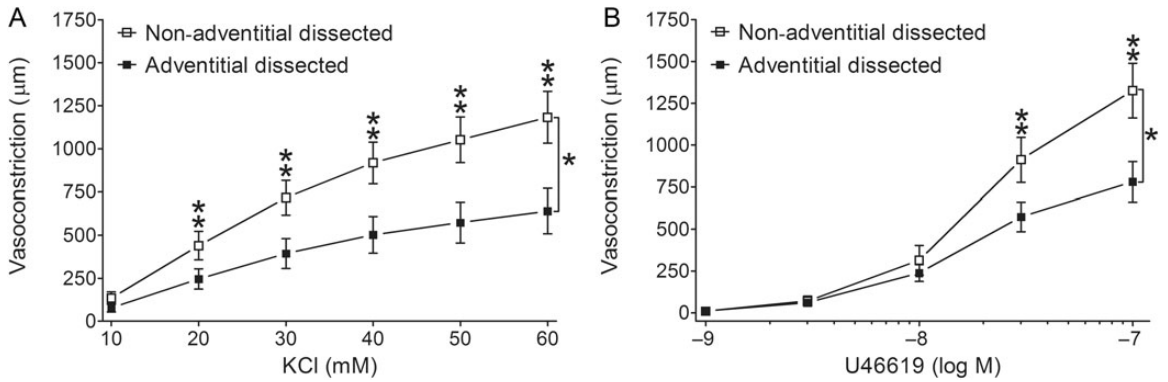

Figure 3: Vasoconstriction curves to (**A**) KCl and (**B**) U46619. Full curve vasoconstriction of adventitial dissected RA segments was significantly reduced compared with non-adventitial dissected RA segments for increasing concentrations of KCl and U46619. Maximal vasoconstriction to 60 mM KCl and 1.0 µM U46619 was significantly reduced for adventitial dissected RA (KCl: 640.1 ± 130.9 µm; U46619: 781.2 ± 120.8 µm) compared with non-dissected RA (KCl: 1182.8 ± 150.9 µm; U46619: 1326.3 ± 163.4 µm); *n* = 16; KCl = potassium chloride; N.B.: a Wilcoxon signed-ranks test was performed to compare the responses at each single concentration. A repeated measures ANOVA was performed to test the full-curve response. *=*P* < 0.05 and **=*P* < 0.01.

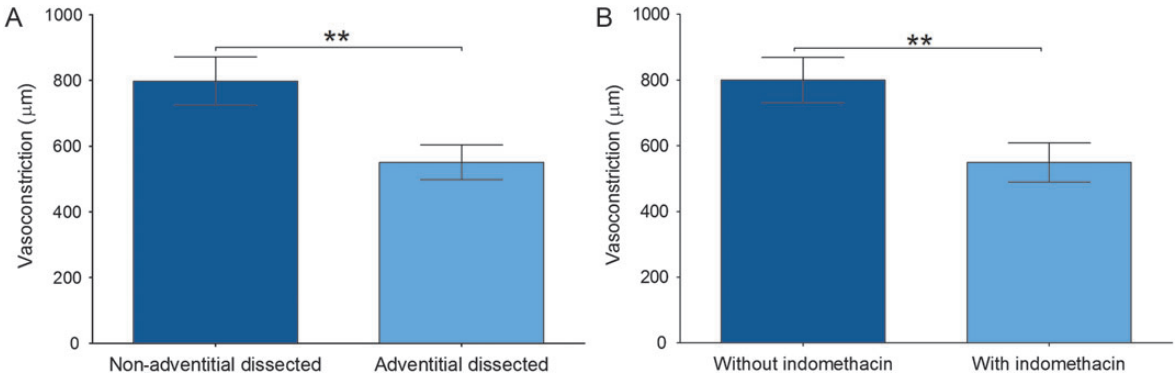

Figure 4: Preconstriction level to U46619. (**A**) Adventitial dissected RA ring segments show a significantly reduced preconstriction (551.0 ± 53.1 µm) compared with non-adventitial dissected RA segments (797.8 ± 74.0 µm). (**B**) Incubation with 10 µM indomethacin resulted in a significant decrease in preconstriction (799.7 ± 69.2 vs 549.1 ± 59.1 µm). Data were pooled irrespective of indomethacin (A) or adventitial dissection (B). *n* = 22; N.B.: a Wilcoxon signed-ranks test was performed to compare the responses. **P* < 0.01.

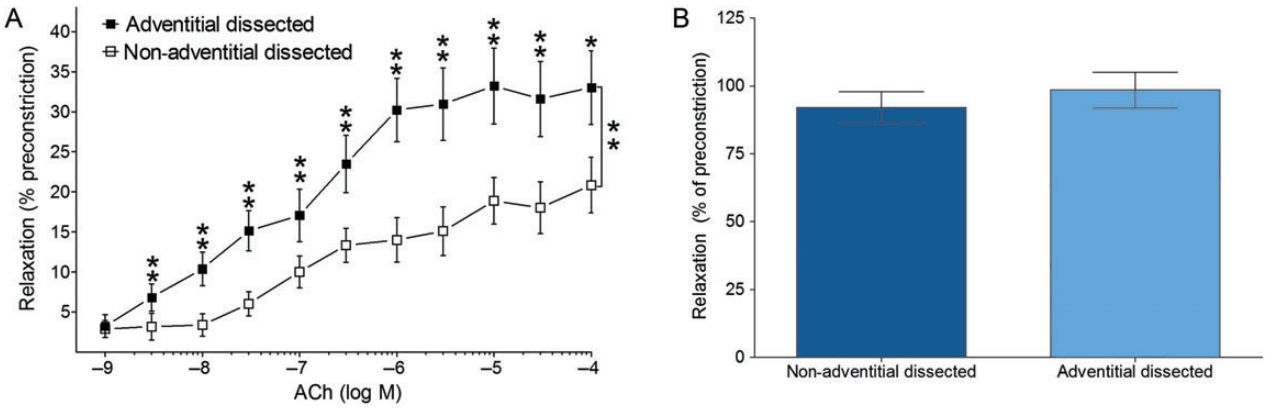

Figure 5: Vasorelaxation curve to increasing concentrations of ACh and endothelium-independent vasorelaxation to 10 mM SNP as a percentage of preconstriction to U46619. (**A**) Vasorelaxation to ACh significantly increased for adventitial dissected RA segments compared with non-adventitial dissected RA segments. (**B**) Vasorelaxation to SNP was not influenced by adventitial dissection (92.0 ± 5.7 vs 98.4 ± 6.6%; *P* = 0.268). Data were pooled irrespective of indomethacin. *n* = 22; Ach: acetylcholine; SNP: sodium nitroprusside; N.B.: a Wilcoxon signed-ranks test was performed to compare the responses at each single concentration. A repeated measures ANOVA was performed to test the full-curve response. **P* < 0.05 and ***P* < 0.01.

of the involvement of contractile PGs in generally enhancing vasoconstriction in the human RA. The results presented here are comparable with the results of Gonzalez *et al.* [18], who showed a decreased preconstriction and increased relaxation after enzymatic digestion of collagen fibres of the adventitia of rat carotid and iliac arteries, and the results of Mu *et al.* [19], who reported a decreased vasoconstriction following mechanical removal of the adventitia of rabbit carotid arteries.

ORIGINAL ARTICLE

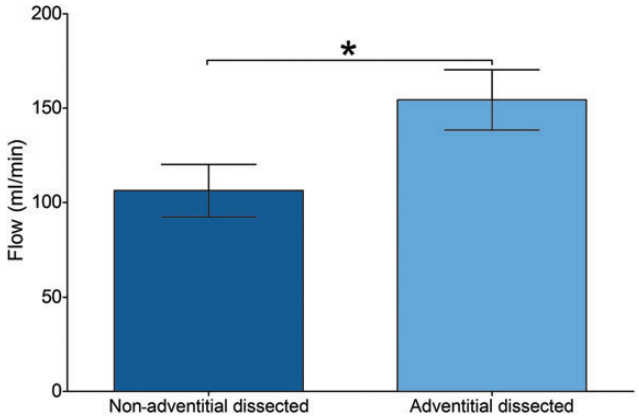

Figure 6: Adventitial dissected RAs showed an increase in perioperative free blood flow of 154.3 ± 16.0 ml/min ($P = 0.037$) compared with 106.3 ± 13.8 ml/min of non-adventitial dissected RAs. $n = 12$; N.B.: a Wilcoxon signed-ranks test was performed to compare the flow rates. *$P < 0.05$.

Vasorelaxation of the adventitial dissected RA segments increased for endothelium-dependent response to ACh and maximal relaxation to SNP was not influenced by adventitial dissection compared with non-dissected segments. The enhanced ACh-induced relaxation after adventitial dissection could be due to a diminished preconstriction since a less constricted vessel is more prone to vasorelaxation. However, as shown in Fig. 3, there is an absolute difference in vasoconstriction to KCl and U46619. Furthermore, all RA ring segments reached a stable preconstriction level to U46619 which was 60–80% of its maximal vasoconstriction to 60 mM KCl. Therefore, we hypothesize that the difference in preconstriction may be explained by a reduced capacity of the adventitial dissected RA to constrict. Moreover, the maximal non-endothelium-dependent vasorelaxation to SNP did not differ for adventitial dissected compared with non-adventitial dissected segments, suggesting that the difference in vasorelaxation may not merely be attributed to a reduced absolute preconstriction. The enhanced ACh-induced relaxation after adventitial dissection of the RA suggests a specific interaction between the endothelial mediators released and the active response of the adventitia. These findings indicate that adventitial dissected vessel may be less prone to contractile responses to endothelium-derived contracting factors. Besides these changes in vasoreactivity, an increase in free blood flow was observed after adventitial dissection. The increase in flow is of clinical relevance to improving the flow capacity of the grafts. Free blood flow of the graft was measured before performing the distal anastomosis. Once the RA is anastomosed to the target vessel, the blood flow characteristics change. The free blood flow provides an indication for the potential flow. The true postoperative patency of the adventitial dissected RA can be determined by angiographic follow-up. Adventitial dissection results in a visible increase in vessel diameter, so it is hypothesized that the increase in free blood flow is due to an increase in lumen diameter, comparable with the skeletonization technique as shown for the IMA [11, 20–23].

As far as the technique is concerned, adventitial dissection of RA during CABG surgery is relatively easy to perform and needs minimal tissue handling. Moreover, complete dissection of total adventitia and all bundles of circumferential collagen fibres of the RA is not time-consuming and accounts for just a few minutes. As shown in Fig. 2, large collagen fibres are dissected and the outermost layer is formed by a dense network of small collagen fibrils and no media is exposed. Our adventitial dissection technique differs from skeletonization in such a way that all collagen fibres of the adventitia are dissected, thereby reducing the mechanical barrier to promoting vasodilation. Damage to the arterial adventitia can provoke positive (adaptive) or negative (constrictive) vascular remodelling by the activation of fibroblast of the adventitia, which could lead to vessel stenosis [24]. On the other hand, in a previous study of a large cohort of patients we have already demonstrated that the use of RA with adventitial dissection as Y-graft to the LIMA is a safe treatment for patients undergoing off-pump coronary surgery at mid-term follow-up [25]. Based on these mid-term follow-up results, we hypothesized that adventitial dissection may positively influence RA graft function, which is in accordance with the results presented here.

Study limitations

Organ bath experiments with RAs were done with potassium chloride, U46619 and SNP, which are generally used in these kinds of experiments. However, in a clinical setting blood pressure is generally managed by using norepinephrine and nitroglycerin. Furthermore, we investigated the distal segment of the RA and it is known that the lamina media of the proximal segment is thicker than the distal segment. In our institutions, the proximal segment of the RA is anastomosed as Y-graft to the LIMA to enable full-arterial revascularization. After completion of the last distal anastomosis, surplus distal segments were obtained for research purposes. Angiographic patency studies of the RA for CABG are needed to confirm whether adventitial dissection maintains its clinical advantages at the long-term follow-up.

Conclusion

In conclusion, the results of this study show that the RA are less susceptible to vasoconstriction and more prone to vasorelaxation *ex vivo* after adventitial dissection and this results in an increase in free blood flow through the RA before anastomosis. These *ex vivo* results justify the policy of standard adventitial dissection of the RA as a valuable tool to reduce vasospasm. Therefore, we suggest adventitial dissection of the RA graft to reduce vasospasm for arterial revascularization in coronary artery bypass surgery.

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Conflict of interest: none declared.

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eComment. Is adventitial dissection enough as a simple and effective way to reduce radial artery spasm?

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We read with great interest the article by Sandker *et al.* on the effectiveness of reduced radial artery (RA) spasm in coronary bypass surgery by dissecting the adventitia [1]. The authors conclude that the RA is less susceptible to vasoconstriction and more prone to vasorelaxation *ex vivo* after adventitial dissection and results in an increase in free blood flow through the RA before anastomosis.

The tunica intima includes a single layer of endothelial cells lining the vessel lumen and the internal elastic lamina membrane. The tunica media comprises the muscular portion of the blood vessel, whereas the tunica adventitia includes the external elastic lamina, terminal nerve fibres, and surrounding connective tissue, which contains fibroblasts and tissue macrophages. A preserved adventitia provides structural support to the vessel, which may limit flow-related vascular enlargement and modulation of the vascular tone.

Endothelium factors: Receptor-mediated (acetylcholine-induced) and receptor-independent (calcium ionophore-induced) factors modulate endothelium relaxation. These responses could be prevented through mechanical removal of the endothelium, guanylyl cyclase inhibition, or NO (nitric oxide) scavenging with oxyhaemoglobin. Pearson and coworkers [2] confirmed these observations and demonstrated that internal mammary artery relaxation to acetylcholine was attenuated by the NO synthase inhibitor NG-monomethyl-L-arginine (L-NMMA).

Age, gender, hormone influence: Joannides *et al.* [3] reported the influence of gender difference on RA dimension in flow-dependent dilatation. Men have a higher diameter of the RA compared with women. Herman and coworkers [4] have shown a deleterious effect of physiological levels of androgen hormone in men and a decrease of androgen levels related to age as a benefit in coronary artery disease and endothelium function. Majmudar and colleagues [5] showed the effects of oestrogen in increasing NO release in the arterial vasculature and maintaining the vasculature tone. Oestrogen hormone in the premenopausal woman plays a positive role in the modulation of endothelium flow-mediated dilatation of the RA. Men who receive RA conduits should have better results when they are over 60 years of age because of diminishing androgen hormone and its deleterious effect on the arterial wall [4].

Complex gender-/age-/hormone-related specific considerations play an important role in endothelium-dependent relaxation. We suggest that the authors consider the age and gender of the patients in their analysis, in short- and long-term follow-up.

We are not sure whether adventitial dissection, rather than other modulating endothelium factors, influences vasculature tone.

Conflict of interest: none declared

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