Morphological and functional consequences of transradial coronary angiography on the radial artery: implications for its use as a bypass conduit†

Mario Gaudinoa,*, Alessandro Leonea, Andrea Lupascu, Amelia Toescb, Andrea Mazzaa, Francesca Romana Ponzianib, Roberto Floreb, Paolo Tondib and Massimo Massettia

a Department of Cardiovascular Science, Catholic University, Rome, Italy
b Department of Angiology, Catholic University, Rome, Italy
c Department of Human Anatomy, Catholic University, Rome, Italy

* Corresponding author. Divisione di Cardiochirurgia, Policlinico Universitario ‘A. Gemelli’, Largo A. Gemelli 8, 00168 Rome, Italy. Tel: +39-063-055535; fax: +39-063-055535; e-mail: mgaudino@tiscali.it (M. Gaudino).

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Abstract

OBJECTIVES: To assess the degree of damage to the radial artery (RA) in coronary artery bypass grafting (CABG) patients who underwent preoperative transradial coronary angiography (RA-CA).

METHODS: From May 2012 to October 2013, 50 consecutive CABG patients who underwent RA-CA were prospectively enrolled in the study. All patients underwent echo-Doppler evaluation of the RA of the catheterized arm; the contralateral RA was used as control. The distal segment of the RA was submitted to immunohistochemical assessment of endothelial integrity. Patients were divided in three groups according to the time interval from angiography to evaluation: ≤24 h, >24 h to <7 days and ≥7 days.

RESULTS: Baseline RA median diameters were 0.25 ± 0.04 cm in the cannulated arm and 0.22 ± 0.04 cm in the non-cannulated arm (P = 0.01). The flow-mediated dilatation (FMD) in the RA in the catheterized arm and in the control arm were 11.6 ± 7.9 and 14.2 ± 8.9 (P = 0.01), respectively. A statistically significant correlation was found between FMD of the catheterized RA and the time from RA-CA (Pearson’s r = 0.348). Linear regression analysis confirmed that the FMD of the catheterized RA was dependent on days elapsed from the procedure (P = 0.032; OR 1.11, CI 0.009–0.203). Immunohistochemical evaluation showed extensive endothelial lesion in all examined RAs, with a trend towards reduction of the damage with time. Endothelial function and integrity of the cannulated arm did not reach those of the control arm in any of the study patients.

CONCLUSIONS: RA-CA produces extensive damage to the RA. The lesions tend to heal with time but incomplete recovery of endothelial integrity and function is still present more than 30 days after the procedure. After RA-CA, the cannulated RA should not be used for CABG.

Keywords: Radial artery • Coronary angiography • CABG

INTRODUCTION

The radial artery (RA) is often selected as a conduit for coronary artery bypass grafting (CABG) operations [1]. However, cardiologists more and more often use radial access coronary angiography (RA-CA) for both diagnostic and intervention purposes [2] and the effect of sheath insertion and instrumentation on RA integrity and function (and thus on the possibility to use the RA for CABG) remains a matter of debate.

This study was designed to evaluate the magnitude and time course of the lesions induced by RA-CA on the RA and their potential implications with regard to the use of the artery as a coronary bypass conduit.

MATERIALS AND METHODS

Patient population

This study protocol was approved by the local Institutional Committee and each patient gave their individual consent.

From May 2012, all consecutive CABG patients who underwent RA-CA were prospectively studied. Until October 2013, 50 patients were enrolled. Five patients had to be excluded after enrolment for echographic evidence of RA occlusion (4 cases)
and RA arterio-venous fistula (1 case) at echo-Doppler evaluation; overall 45 patients were included. According to our institutional policy, the RA was always harvested from the non-dominant arm using the pedicled harvesting technique previously described [3].

The patients were divided into three groups according to the time interval between the angiography procedure and the echo-Doppler evaluation

• ≤24 h (10 patients)
• >24 h to <7 days (19 patients)
• ≥7 days (16 patients).

Coronary angiography

A dedicated arterial puncture kit (with plastic cannula and hydrophilic wire) and long (25 cm) hydrophilic sheath (Radifocus, Terumo, Japan) were used for RA catheterization. Diagnostic procedures were performed by a 5- or 6-F catheter sheath.

Echo-Doppler method

Patients underwent an ultrasound examination of the RA and brachial artery (BA) using a Philips IU22 ultrasound system with a 17-MHz linear array transducer. All studies were carried out between 8 and 10 am after an overnight fast. An electrocardiogram (ECG) was recorded and all images were stored digitally. Measurements were made in all cases by the same (for measurement of homogeneity) blinded experienced specialist in internal medicine. A randomizing programme determined which artery to start with in order to avoid systematic errors.

Both the right and the left RAs and BAs were examined and measurements were performed. Each of the RAs and BAs was examined at baseline, after flow-mediated vasodilatation (FMD) and after nitroglycerine-mediated dilatation (NMD) according to the recommendations of Corretti et al. [4]. Baseline recordings were performed after 10 min of supine rest. The RA was localized and marked, and the diameter was measured 3–5 cm proximal to the styloid process of the radial bone. After baseline measurements of the RA, a segment of the BA 1 ± 6 cm above the antecubital crease was located, marked and imaged in the longitudinal plane, ensuring that the lumen diameter was maximized and the gain optimized to provide clear arterial wall interfaces.

B-mode ultrasound images were continuously recorded and frozen images were obtained by gating from the R wave of the ECG.

After baseline measurements of the RA and the BA, a blood pressure cuff was inflated at the forearm to 250 mmHg for 5 min. Upon cuff release, the RA diameter was re-measured at 1 min after cuff deflation when the most marked response in RA diameter appeared; this period was used to represent FMD expressed as the percentage change in the RA after cuff deflation compared with at rest, representing the endothelial function of the artery.

After baseline measurements of the RA and the BA, a blood pressure cuff was inflated at the forearm to 250 mmHg for 5 min. Upon cuff release, the RA diameter was re-measured at 1 min after cuff deflation when the most marked response in RA diameter appeared; this period was used to represent FMD expressed as the percentage change in the RA after cuff deflation compared with at rest, representing the endothelial function of the artery.

The NMD was expressed as the percentage change in radial diameter of nitrate responsiveness after cuff deflation compared with at rest, representing the endothelial-independent function of the artery.

Histological method

Specimens were fixed in 4% paraformaldehyde at room temperature (RT) for 12–24 h, depending on thickness. They were then rinsed in phosphate-buffered saline (PBS) (pH 7.4), dehydrated in an ascending series of alcohols and embedded in paraffin via xylene. Five-micrometre serial transverse sections were then cut and processed for histochemical (Mallory’s trichrome method modified according to Azan, haematoxylin and eosin, Unna-Tanzer–Livini stain for elastic fibres) or immunohistochemical studies. For immunohistochemistry, endogenous peroxidase activity was quenched with 0.5% H2O2 in absolute methanol for 30 min at RT; slides were then permeabilized with 0.2% Triton X-100 in PBS (20 min at RT) and incubated with 3% normal goat serum in PBS (30 min at RT) to block non-specific bindings. Sections were then incubated overnight at 4°C with primary polyclonal antibody against factor VIII (YLEM, Milan, Italy, diluted 1:150), a specific marker of endothelial cells used to assess the integrity of the endothelial layer after surgical preparation [5]. Control sections were treated with normal rabbit immunoglobulins at the same concentration used for the primary antibody. The reaction was revealed by the standard avidin–biotin peroxidase complex procedure (Vectastain Elite ABC kit, Vector, Burlingame, CA, USA) using 3,3′-diaminobenzidine (Sigma, Milan, Italy) as chromogen. For quantitative analysis, endothelial cells positive for factor VIII antibody falling into 35 randomly selected 55 mm squares for each patient were counted using a computerized system. For this purpose, images from immunostained sections were examined under a Zeiss Axiophot (Carl Zeiss, Germany) light microscope and images were captured on an Axiophot microscope equipped with a digital camera (AxioCam MRC) and image analysis software (Axiovision) (Carl Zeiss).

Statistical analysis

Statistical analysis was performed using the Statistical Package for Social Science (SPSS), release 15.0, and MedCalc, release 13.1. Continuous variables were expressed as median and standard deviation; categorical variables were reported as frequencies and percentage.

The Wilcoxon test was used to compare arterial diameters before and after coronary angiography for each patient (test for paired samples) and to assess the difference in Factor VIII immunostaining according to the time interval between angiographic procedure and the echo-Doppler evaluation of the RA (test for independent samples). Finally, the correlation between continuous variables was investigated using Pearson’s coefficient and the presence of a causal relationship was then verified with linear regression. All of the tests for statistical significance were two-sided and a P value below 0.05 indicated a significant difference.

RESULTS

The main preoperative characteristics of patients are summarized in Table 1. Time from RA-CA to echo-Doppler evaluation was
The percentage of RA marked with anti-factor VIII antibody was 38 ± 11% in the ≤24 h group, 57 ± 13% in the <7 days group and 83 ± 9% in the ≥7 days group (P < 0.01).

**Echo-Doppler results**

Baseline RA median diameters were 0.25 ± 0.04 cm in the cannulated arm and 0.22 ± 0.04 cm in the control arm (P = 0.01). Baseline BA median diameters were 0.40 ± 0.07 cm in the cannulated arm and 0.38 ± 0.06 cm in the control arm (P = 0.284).

The FMD in the RA was 11.6 ± 7.9% in the catheterized arm versus 14.2 ± 8.9% in the control arm (P = 0.01), whereas the NMD was 20.2 ± 17.5% in the catheterized arm versus 24.7 ± 21.6 in the control arm (P = 0.19).

The FMD in the BA of the catheterized arm was 5.3 ± 4.5 versus 4.4 ± 3.7% in the control arm (P = 0.22); the NMD was 20.0 ± 11.8 in the BA of the catheterized arm versus 21.2 ± 13.1 in the control arm (P = 0.75).

A significant correlation was found between FMD of the catheterized RA and BA and days from RA-CA with a Pearson’s r of 0.348 and 0.361, respectively. Linear regression confirmed that the FMD of the catheterized RA and BA were linearly dependent on days elapsed from the procedure (P = 0.032; OR 1.11, CI 0.009–0.203 and P = 0.024; OR 1.07, CI 0.009–0.118, respectively, Table 2). Even after excluding the outliers from the analysis, this observation was confirmed (Pearson’s r of 0.381; linear regression: P = 0.024; OR 1.43, CI 0.051–0.671).

**Immunohistochemical evaluation**

Anti-factor VIII immunostaining revealed diffuse endothelial lesions in the group of patients in whom RA-CA was performed within 24 h from the RA harvesting, with progressive increase in the percentage of preserved endothelial layer in the <7 days and ≥7 days groups (Figs 2 and 3).

The percentage of RA marked with anti-factor VIII antibody was 38 ± 11% in the ≤24 h group, 57 ± 13% in the <7 days group and 83 ± 9% in the ≥7 days group (P < 0.01).

**DISCUSSION**

The RA is often selected as the second arterial conduit for CABG due to its excellent long-term angiographic and clinical outcome. In fact, the mid-term patency rate of the conduit is around 80–90% and it has been shown that the use of the RA instead of the SV as the second graft is associated with substantial clinical benefits and improved graft patency [6].

On the other hand, RA-CA has grown in popularity among cardiologists and has been advocated as the access route of choice for coronary angiography and intervention on the basis of the reduction in bleeding and vascular complications associated with its use [7–9].

However, RA-CA may damage the RA due to the insertion of a sheath and/or passage of catheters through a vessel that is much smaller than the femoral artery.

In previous reports, the incidence of RA occlusion after RA-CA has ranged from 2 to 30% (mainly on the basis of the dimension of the sheath size used) [10–13].

However, apart from occlusion, sheath insertion and instrumentation during RA-CA may lead to structural and functional damage to the RA endothelium, which may preclude its use as a bypass conduit.

Several studies using intravascular ultrasound, optical coherence tomography or histology demonstrated significant degrees of morphological alterations such as intimal lesion, reactive intimal hyperplasia, inflammation and even medial dissection after RA-CA [14–17].

The functional counterparts of these morphological observations were investigated mainly by using FMD and NMD (as in the present series) [18].

Burstein et al. found impaired FMD and NMD, which remained significantly reduced up to 9 weeks, following RA-CA [19] and Dawson et al. reported early impairment in FMD and NMD following RA-CA with complete recovery only after a period of 3 months from procedure [20].

In the only study that specifically evaluated the clinical, angiographic and pathological findings of RA grafting in patients with and without previous RA-CA, Kamiya et al. showed an alarming reduction in RA patency rates in the RA-CA group (RA-CA 77% vs control 98%) [21].
Table 2: Results of linear regression analysis

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<tr>
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<th>Median ± SD (%)</th>
<th>P-value</th>
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<tbody>
<tr>
<td>FMD BA (control arm)</td>
<td>4.49 ± 3.71</td>
<td>0.223</td>
</tr>
<tr>
<td>FMD BA (cannulated arm)</td>
<td>5.30 ± 4.50</td>
<td></td>
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<tr>
<td>FMD RA (control arm)</td>
<td>14.20 ± 8.90</td>
<td>0.035</td>
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<tr>
<td>FMD RA (cannulated arm)</td>
<td>11.65 ± 7.94</td>
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<tr>
<td>NMD BA (control arm)</td>
<td>21.22 ± 13.15</td>
<td>0.758</td>
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<tr>
<td>NMD BA (cannulated arm)</td>
<td>20.08 ± 11.83</td>
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<tr>
<td>NMD RA (control arm)</td>
<td>24.77 ± 21.65</td>
<td>0.192</td>
</tr>
<tr>
<td>NMD RA (cannulated arm)</td>
<td>20.27 ± 17.50</td>
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BA: brachial artery; RA: radial artery; FMD: flow-mediated vasodilatation; NMD: nitroglycerine-mediated dilatation.

Figure 2: Anti-factor VIII immunostaining of a normal radial artery (×80). The complete endothelial layer is evident.

Figure 3: Anti-factor VIII immunostaining of a radial artery 2 weeks after transradial catheterization (×80). Diffuse endothelial damage is evident.

Our data testify how RA-CA induces diffuse endothelial disruption that results in markedly reduced endothelial-mediated vasodilatation at least in the first 30 days after the procedure. Both the immunohistochemical staining and the echo-Doppler evaluation in fact found a significant degree of endothelial damage in RA-CA arteries. The endothelial lesion tends to heal with time, as demonstrated by the time dependency of both the reduction in FMD and the percentage of factor VIII positive cells on immunostaining. Of note, in none of the study patients, the histological integrity and function of the endothelium of the cannulated RA reached those of the contralateral control arm at any time point.

In addition, a 20% decrease in NMD was evident in the RA at the site used for RA-CA (Table 2); although not statistically significant, this finding probably reflects some structural impairment of the muscular layer also related to the procedure.

The excellent concordance between the functional and morphological data and between the results obtained using two completely different techniques are strong arguments in favour of the reliability of our observations.

In conclusion, this study shows how RA-CA produces extensive damage in the RA. The lesions tend to heal with time but incomplete recovery of endothelial integrity and function can be seen up to 30 days after the procedure. On the basis of these data, we suggest that the choice of the site of harvesting of the RA for CABG should be based on the site of performance of preoperative RA-CA, as opposed to the current routine, which is based on the non-dominance of the arm. After RA-CA, the cannulated RA should not be used for CABG.

Conflict of interest: none declared.

REFERENCES


