Peripheral Artery Disease

Low-Flow Mediated Constriction is Endothelium-Dependent
Effects of Exercise Training After Radial Artery Catheterization

Ellen A. Dawson, PhD; Amr Alkarmi, MD; Dick H.J. Thijssen, PhD; Sudhir Rathore, MD; Diane E. Marsman, BSc; N. Timothy Cable, PhD; D. Jay Wright, MD; Daniel J. Green, PhD

Background—Radial artery catheterization is associated with endothelial denudation and impaired vasodilator function, while postcatheterization exercise training may enhance artery function. The impact of catheterization and subsequent exercise training on low-flow mediated vasoconstriction (L-FMC) has not previously been studied. The aim of this study was to examine whether radial artery L-FMC is impaired by catheterization and consequent endothelial denudation. A further aim was to examine the effect of local handgrip exercise training on radial artery L-FMC and flow-mediated dilation (FMD) after transradial catheterization.

Methods and Results—Thirty-two subjects undergoing transradial catheterization underwent assessment of L-FMC and FMD in the catheterized and contralateral radial artery before, and the day after, catheterization. A further 18 patients were recruited and randomly assigned to either a 6-week handgrip exercise training program (N=9) or a nonexercise control period (N=9). L-FMC was attenuated 1 day postcatheterization in the catheterized arm (−2.07±0.84 to 0.35±0.83), but unchanged in the noncatheterized arm (−0.93±0.86 to −0.90±0.92; P<0.05). In the training study, both FMD and L-FMC of the catheterized arm were preserved in the exercise group 7 weeks after catheterization (FMD-pre, 6.84±0.79; FMD-post, 6.85±1.16; L-FMC-pre, −2.14±1.42; L-FMC-post, −3.58±1.04%), but reduced in the control group (FMD-pre, 8.27±1.52; FMD-post, 4.66±0.70; P=0.06; L-FMC-pre, −3.26±1.19; L-FMC-post, −1.34±1.27%; P<0.05).

Conclusions—Catheterization, and associated endothelial denudation, decreases L-FMC in the radial artery, suggesting that it is endothelium-dependent. Moreover, we demonstrate for the first time that exercise training has beneficial impacts on radial artery vasodilator and constrictor function. (Circ Cardiovasc Interv. 2012;5:713-719.)

Key Words: low-flow mediated constriction • flow mediated dilation • catheterization • exercise training • endothelin-1

Low-flow mediated constriction (L-FMC) is a recently introduced method, proposed to assess conduit artery vasoconstrictor function.1–5 Previous studies have demonstrated that clinical groups that exhibit impaired flow-mediated dilatation (FMD) also present with a reduced radial artery vasoconstrictor L-FMC, although the 2 are not correlated in patients with cardiovascular disease.1,2 While FMD has been demonstrated to be endothelium- and shear stress-dependent, less is known about the mechanisms responsible for L-FMC.1 Coronary artery disease patients undergoing transradial catheterization for percutaneous coronary interventions (PCI) provide a useful in vivo model to study whether responses of the radial artery are endothelium-dependent. Due to the relatively small diameter of this artery, catheter sheath insertion is associated with endothelial denudation and impairment in endothelium-dependent FMD.6–8 Although previous studies have assumed that L-FMC of the radial artery is endothelium-mediated, none, to our knowledge, has examined whether radial artery L-FMC is directly affected by arterial catheterization.

Localized exercise training has been demonstrated to significantly improve vasodilator function,10 particularly in patients with impaired function a priori.11 Localized exercise training may therefore be beneficial for postcatheterization recovery of radial artery endothelial function. However, no previous studies have examined the impact of exercise training on vasoconstrictor or vasodilator function after catheterization.

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The aim of this study was therefore 2-fold: to examine the impact of catheterization on radial artery vasoconstrictor function (L-FMC) in the catheterized (Cath) and noncatheterized arms, and to examine the impact of localized handgrip exercise training on radial artery FMD and L-FMC after catheterization. We hypothesized that L-FMC would be...
Patients were given an instructive workshop to familiarize them with specific instructions about exercise for a similar time period. At least twice during the training period. The control group was given no specific instructions about exercise for a similar time period.

WHAT IS KNOWN

- Radial artery catheterization denudes the endothelium and acutely reduces artery flow-mediated dilator function.
- Localized exercise training improves artery dilator function.

WHAT THE STUDY ADDS

- Localized handgrip exercise training is beneficial in the noncatheterized, radial artery. In addition, we expected that L-FMC impairment as a result of catheterization would be ameliorated by exercise training.

Catheterization Procedure (Studies 1+2)

In preparation for the coronary angiography or angioplasty, the radial artery was positioned with the arm extended and the wrist in mild hyperextension. After disinfection of the puncture site, local anesthesia was achieved with 2% lignocaine. After the radial artery was punctured with a 21 gauge needle, a 0.118-inch platinum-tipped nitinol guidewire was introduced. Subsequently, the needle was withdrawn and a small skin incision was made. A 6F introducer sheath (external diameter 2.6 mm, Cook Medical, Bloomington, IN) with a dilator tip of 2.5 cm was inserted. A weight-adjusted dose of anticoagulant (heparin) was introduced into the central circulation after the insertion of the first catheter. All introducer sheaths were removed at the end of the intervention and hemostasis was achieved in the catheterization laboratory by a compression device. The patients were mobilized instantly and the compression device was removed after 2 to 4 hours.

Methods

Patients were recruited from 1 center, from a list of patients requiring transradial catheterization for coronary angiography or angioplasty. Patients who met the criteria and were willing to participate in this study gave written informed consent. We excluded patients with a history of coronary artery bypass surgery, previous ipsilateral transradial procedure, myocardial infarction in the previous 3 months, chronic obstructive lung disease, left ventricular ejection fraction <40%, valvular heart disease, and renal or hepatic dysfunction. Subjects in whom ultrasound images could not be adequately obtained during or after cuff deflation or who did not complete the study were also excluded. All subjects gave informed written consent. The Liverpool Local Regional Ethics Committee gave ethical approval for this study and it conformed to the standards set by the Declaration of Helsinki.

Study Design 1: Effect of Catheterization on Radial Artery L-FMC

Thirty-two subjects (clinical characteristics, Table 1) were included. Patients were tested on 2 occasions: the day of the transradial procedure (immediately before the catheterization [Pre]), the day after catheterization (Post). Bilateral radial artery assessments were made in the Cath and noncatheterized arm on each occasion.

Study Design 2: Effect of Postcatheterization Exercise Training on Radial Artery L-FMC

Eighteen subjects (different from study 1) were included (clinical characteristics, Table 1). Patients attended the laboratory twice: before the catheterization (Pre) and 7 weeks after the procedure (Post). The patients were assigned randomly to either an exercise group (N=9), consisting of 6 weeks local handgrip exercise training (postcatheterization) or a control group (N=9) who received no specific instruction about exercise for a similar time period. Radial artery assessments were made in the Cath arm and noncatheterized arm on each occasion.

Exercise Training

The exercise group undertook local handgrip exercise training of the Cath arm for 6 weeks starting 1 week after the catheterization. Patients were given an instructive workshop to familiarize them with the exercise. The training consisted of exercise with a handgrip dynamometer (Stoelting, Wood Dale, III), with a rhythmic sequence of 30 contractions per minute timed to a metronome, for 30 minutes in a seated position 3×1 week. They exercised at 40% of their maximal voluntary contraction, which was determined before the intervention. Patients performed this training at home. To ensure and monitor adherence, phone calls were carried out and hospital visits occurred at least twice during the training period. The control group was given no specific instructions about exercise for a similar time period.

Radial Artery Ultrasound Assessments

Subjects were instructed to abstain from caffeine, alcohol, and cigarettes for 12 hours before measurements and to fast for a minimum of 4 hours. All measurements were performed in a quiet, temperature-controlled room. Patients were requested to rest in the supine position for at least 20 minutes before examination. Radial artery diameter and blood velocity were recorded before, during, and after 5 minutes of forearm ischemia. Mean arterial pressure and heart rate were assessed at baseline using an automated sphygmomanometer (Dinamap; GE Pro 300V2) in the resting period before cuff inflation. Ultrasound images were obtained by a 12 MHz multi-frequency linear array probe attached to a high-resolution ultrasound machine (T3000, Terasma, MA) to simultaneously acquire artery diameter and Doppler derived blood velocity. The same region of the radial artery was used for assessment during repeat measurements, based on distance from anthropometric landmarks. A rapid inflation/deflation pneumatic cuff was placed around the wrist of the imaged arm. The radial artery was imaged proximally to the cuff to avoid the ischemic area. Baseline diameter and flow were measured in the final minute of the rest period. Subsequently, the cuff was inflated to >200 mm Hg for 5 minutes. Recordings were resumed for 30 seconds before cuff deflation to detect the L-FMC and for a further 3 minutes after release of the cuff for identification of the FMD. Post-test analysis was undertaken using custom designed edge detection and wall tracking software which significantly reduces investigator bias and improves reproducibility, compared with manual approaches.15

Low-Flow Mediated Vasconstriction

Diameter and flow were measured in the last 30 second of cuff occlusion. L-FMC is expressed as the percentage decrease in diameter of the radial artery during the last 30 second of cuff occlusion, compared with the resting diameter before cuff occlusion. For more detailed descriptions see previous studies.7 Separate regions of interest for analysis of artery diameter were used for L-FMC and FMD assessments to ensure adequate tracking of the artery wall during either the cuff inflation or the cuff deflation periods, respectively.

FMD, L-FMC+FMD

We also examined the FMD, which is expressed as the maximal increase in radial artery diameter after cuff release relative to baseline diameter.7 After assessment and analysis of the L-FMC and FMD data, L-FMC+FMD was calculated as the sum of L-FMC and FMD. We have previously reported the impact of radial catheterization on FMD in patients included in study 15,16 who are nonetheless included here to assess the impact of catheterization on L-FMC and combined L-FMC+FMD.
Statistics

Statistical analyses were performed using SPSS 17.0 (SPSS, Chicago, IL) software. Resting blood pressure and heart rate before and after catheterization were assessed using paired t tests. All other variables were assessed using a 2-way repeated measures GLM with time (pre versus postcatheterization) and arm (Cath versus noncatheterized arm) for study 1 and time (pre and 7-week post), and group (exercise versus control) for study 2. If significant differences were found, post hoc t tests were used and were not adjusted for multiple comparisons. The effect of cuff inflation on artery blood velocity and blood flow was determined using paired t tests. Results are expressed as mean±SE. P≤0.05 was considered significant.

Results

Study 1: Effect of Catheterization on Radial Artery L-FMC

Clinical characteristics for study 1 are described in Table 1. All patients were on a 3-hydroxy-3-methyl-glutaryl-CoA reductase inhibitor. Fifty percent were on a calcium channel blocker and 92% were on either or both angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers. All patients received weight-adjusted heparin and intraarterial nitrates during catheterization. Patients’ drug regimens remained the same throughout the study. All subjects had successful transradial PCIs with stenting. All patients achieved patent hemostasis.

Radial Artery Responses

There was no significant difference in mean arterial pressure (94±2 to 92±2 mm Hg) or heart rate (62±2 to 64±2 bpm) before versus postcatheterization. Baseline artery diameter was increased immediately postintervention in the Cath arm (P<0.01). Baseline velocity was not changed after the intervention in either arm (Table 2).

L-FMC and L-FMC+FMD

Cuff inflation induced a significant reduction in radial artery blood velocity and flow (Table 2). L-FMC was significantly attenuated in the Cath arm postintervention (2-way GLM interaction P=0.03; Figure 1). FMD was also reduced in the Cath arm, as previously reported6,7 (Table 2; GLM interaction P<0.01). When combining the results from both methods, we found a significant reduction in L-FMC+FMD in the Cath arm (Figure 2, 2-way GLM interaction P<0.01).

Study 2: Effect of Postcatheterization Exercise Training on Radial Artery L-FMC

Patient Characteristics

Clinical characteristics for study 2 are described in Table 1. All patients were on a 3-hydroxy-3-methyl-glutaryl-CoA reductase inhibitor. Subjects in the exercise group were on a calcium channel blocker (22%) and were on either or both angiotensin-converting enzyme inhibitors and angiotensin-II-receptor blockers (78%). In the control group, 22% were on calcium channel blockers and 45% were on either or both angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers. All patients received heparin and nitrates during catheterization. Patients’ drug regimens remained the same throughout the study. All subjects had successful transradial PCIs with stenting. All patients achieved patent hemostasis.

Handgrip Exercise Training

There was no significant difference in mean arterial pressure before and after the 6-week intervention in both groups (104±4 to 105±3 and 97±4 to 97±5 mm Hg in exercise and control groups, respectively). Likewise, there was no significant
change in heart rate after the intervention (exercise, 59±4 to 63±5; control, 62±3 to 63±4 bpm). Baseline artery diameter, velocity, and blood flow were not changed after the 6-week intervention in either group (Table 3).

**L-FMC and FMD**

Cuff inflation induced a significant reduction in radial artery blood velocity and flow both before and after the 6-week intervention in both groups (Table 3). L-FMC decreased in controls 7 weeks postcatheterization, while this decline was prevented in the exercise training group (2-way GLM interaction \( P<0.05 \); Figure 2). A trend was also evident in controls for reduction in FMD 7 weeks postcatheterization, while the FMD was preserved in the exercise group (2-way GLM interaction \( P=0.06 \); Table 3). When combining the results from both methods, we observed a significant reduction in combined L-FMC+FMD in controls which was prevented in the exercise group (Figure 2, 2-way GLM interaction \( P<0.01 \)).

**Discussion**

This study indicates that endothelial denudation, as a consequence of catheterization, results in abolition of L-FMC in the radial artery, suggesting that L-FMC is an endothelium-dependent phenomenon. We also demonstrate that radial artery function (measured as L-FMC+FMD) remains impaired by catheterization for at least 7 weeks. This study is also the first, to our knowledge, to demonstrate that exercise training aids in the recovery of vasodilator and vasoconstrictor function after catheterization. These observations are novel and contribute to our understanding of the impact of catheterization and exercise training on arterial function.

Catheterization has previously been shown to reduce endothelial-dependent vasodilator function (FMD).6–9 We support and extend these studies by demonstrating that L-FMC, a measure of vasoconstrictor function in radial arteries, is also impaired postcatheterization. This effect is unlikely to be related to systemic or neural changes, as the immediate attenuation in L-FMC was apparent in the Cath arm only. Our observation that L-FMC is endothelium-dependent complements recent findings which suggest that this phenomenon is partially mediated by a combination of EDHF and cyclooxygenase products.1 There is also evidence that endothelin-1 plays a role.1,13 While these substances are derived from the endothelium, our data provides the first evidence that endothelial denudation abolishes radial L-FMC, at least in patients with coronary artery disease. Furthermore, while we and others have previously demonstrated that catheter-induced reduction in FMD lasts for at least 9 weeks after sheath insertion,6,7,9 results of this study are the first to demonstrate that catheterization induces persistent impairment in the vasodilator and vasoconstrictor function of the radial artery.

Our study is also the first, to our knowledge, to examine the impact of exercise training on radial artery L-FMC. L-FMC and FMD in the exercise group were preserved in comparison with the control group, who exhibited persistent impairment in L-FMC after 7 weeks. This is in agreement with previous observations that exercise training attenuates the peripheral vasoactive effects of the endothelin-1 pathway14 and that

| Table 2. Radial Artery Characteristics Pre and Postcatheterization in the Catheterized and Noncatheterized Arms (Study 1) |
|----------------------------------|-----------------|-----------------|-----------------|
|                                  | Cath (n=32)     | NoCath (n=32)   | 2-Way GLM       |
|                                  | Pre      | Post      | Pre      | Post      | Time×Cath            |
| Rest                            |          |           |          |           |                      |
| Diameter, mm                   | 2.90±0.08 | 3.14±0.07* | 2.78±0.07† | 2.85±0.07† | \( P=0.05 \)         |
| Velocity, cm/s                 | 10.42±1.08 | 10.41±1.01 | 10.54±1.06 | 11.92±1.09 | \( P=0.13 \)         |
| Blood flow, mL/min             | 43.0±5.5  | 50.0±5.7  | 38.5±4.0  | 47.5±5.0  | \( P=0.64 \)         |
| L-FMC                           | -2.07±0.84 | 0.35±0.83  | -0.93±0.86 | -0.90±0.92 | \( P=0.03 \)         |
| Minimum diameter, mm           | 2.85±0.08 | 3.15±0.07* | 2.76±0.08  | 2.83±0.08† | \( P<0.01 \)         |
| Velocity, cm/s                 | 1.17±0.44‡ | 1.24±0.16‡ | 0.72±0.14‡ | 0.78±0.12‡ | \( P=0.98 \)         |
| Blood flow, mL/min             | 4.2±1.4†‡ | 6.0±0.8‡  | 2.5±0.42‡  | 3.4±0.6†‡ | \( P=0.61 \)         |
| FMD                             |          |           |          |           |                      |
| Baseline diameter, mm          | 2.77±0.08 | 3.06±0.08* | 2.67±0.08  | 2.69±0.08† | \( P=0.01 \)         |
| FMD%                            | 9.28±0.61 | 4.64±0.62* | 9.73±0.65  | 9.32±0.63† | \( P=0.03 \)         |
| Peak diameter, mm              | 3.02±0.08 | 3.20±0.07* | 2.92±0.08  | 2.93±0.08† | \( P=0.10 \)         |
| Shear rate, AUC, s⁻¹×10³        | 29.2±2.7  | 23.4±2.4  | 26.1±3.6  | 27.8±2.2  | \( P=0.10 \)         |
| Time to peak, s                 | 100±8     | 100±8     | 84±6      | 85±10     | \( P=0.10 \)         |

L-FMC indicates low-flow mediated vasoconstriction; FMD, flow-mediated vasodilation; Cath, catheterized arm; NoCath, noncatheterized arm; shear rate, AUC, shear rate area under the curve from cuff deflation to peak dilation; and time to peak, time from cuff deflation to automatically detected peak dilation.

Results presented as mean±SE.

*Post hoc t test significantly different from precatheterization.
†Post hoc t test significantly between catheterized and noncatheterized arm.
‡Significantly different from rest at \( P<0.05 \) (paired t test).
Exercise training enhances FMD. The mechanisms responsible for the impact of exercise on FMD in the present study may involve progenitor cell mobilization and early return to functional integrity of the endothelial layer. It is well established that shear stress is the principal stimulus to FMD, and impaired FMD in the presence of a similar postdeflation shear stimulus in this study indicates that extant cells are dysfunction or that cell damage or denudation has occurred. Alternatively, exercise training may protect against the putative effects of oxidation or inflammation in the artery wall and hence on endothelial function. The mechanisms responsible for the impact of exercise on FMD are currently unclear and future studies involving arterial cannulation and blockade might examine the relative impact of exercise training on the different vasoconstrictor and dilator pathways associated with FMD and L-FMC.

The most directly relevant implications of this study relate to the beneficial impact of exercise training on recovery of conduit artery function. In the case of the radial artery, this recovery may be relevant as the artery is sometimes harvested as a graft for coronary bypass. Rapid recovery in artery function is also likely to minimize complications of sheath insertion, such as spasm, thrombosis, reactive arterial wall thickening, and stenosis. This may also have implications for thenar muscles and hand function. Larger studies, with longer follow up, will be required to address these questions fully. In a broader sense, if the radial artery is accepted as a surrogate for similarly sized conduits such as the epicardial conduit arteries, our findings suggest that exercise, and associated localized phenomena such as increased flow and arterial shear stress, are beneficial in preserving vasoconstrictor and dilator function after the insult of catheter insertion.

The physiological understanding of L-FMC is in its infancy. There is some evidence that impaired vascular function in the radial artery is associated with diminished L-FMC responses, whereas brachial artery L-FMC may be increased in subjects with risk factors or coronary disease. Our findings are in broad agreement with previous studies of the radial artery, but contrast with those in the brachial artery, reinforcing a previous suggestion of arterial site specificity in vasoconstrictor function. Furthermore, the impact of coronary catheterization on systemic conduit artery function...
resonances may differ according to arterial site. Our patients, who underwent transradial PCI, did not exhibit impaired L-FMC of FMD in the uncatheterized radial artery, indicating that systemic impacts of coronary interventions were not apparent. In contrast, the study of Spiro et al\textsuperscript{11} suggested that PCI, though not angiography per se, increased L-FMC in the brachial artery.

This study had a number of limitations. We did not control for age, preexisting vascular disease, history of smoking, or drug treatment. This is somewhat mitigated by the repeated measures designs and the inclusion of either a within-subject control arm (study 1) or a dedicated control group (study 2). The study also possesses ecological relevance, as it was performed in a typical unselected group of patients requiring PCI. However, future studies should be carried out in other populations. Changes in artery diameter during L-FMC are small, but the use of the custom-developed automated edge-detection improves detection and is largely operator-independent.\textsuperscript{12} The sample size of our studies was relatively small, however our findings were statistically significant and, by definition, this indicates that the study was adequately statistically powered. Our technical approaches including the use of edge-detection software and within-subjects experimental designs, also empower our findings.

In conclusion, we found that catheterization resulted in a reduction in endothelium-mediated vasoconstriction and vasodilator function immediately after catheterization, which was maintained at least until 7 weeks after the procedure. These functional deficits after catheterization were prevented in the group that undertook localized exercise training. These studies provide evidence that L-FMC is endothelium-dependent and that exercise training is beneficial for conduit artery function and health after catheterization.

### Table 3. Radial Artery Characteristics Pre (0 wk) and 7 Weeks (7 wk) Postcatheterization in the Exercise and Control Group (Study 2)

<table>
<thead>
<tr>
<th></th>
<th>Exercise (n=9)</th>
<th>Control (n=9)</th>
<th>2-Way GLM</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre (0 wk)</td>
<td>Post (7 wk)</td>
<td>Time</td>
</tr>
<tr>
<td>Diameter, mm</td>
<td>2.85±0.10</td>
<td>2.81±0.15</td>
<td>2.61±0.18</td>
</tr>
<tr>
<td>Velocity, cm/s</td>
<td>12.65±2.88</td>
<td>10.10±2.03</td>
<td>9.73±2.25</td>
</tr>
<tr>
<td>Blood flow, mL/min</td>
<td>50.3±11.6</td>
<td>38.0±9.0</td>
<td>31.6±6.5</td>
</tr>
<tr>
<td>L-FMC%</td>
<td>−2.14±1.42</td>
<td>−3.58±1.04</td>
<td>−3.26±1.19</td>
</tr>
<tr>
<td>Minimum diameter, mm</td>
<td>2.79±0.13</td>
<td>2.71±0.15</td>
<td>2.53±0.18</td>
</tr>
<tr>
<td>Velocity, cm/s</td>
<td>0.89±0.26*</td>
<td>1.30±0.32*</td>
<td>0.80±0.14*</td>
</tr>
<tr>
<td>Blood flow, mL/min</td>
<td>3.0±0.8*</td>
<td>4.5±0.9*</td>
<td>2.6±0.5*</td>
</tr>
<tr>
<td>Baseline diameter, mm</td>
<td>2.79±0.04</td>
<td>2.82±0.04</td>
<td>2.64±0.05</td>
</tr>
<tr>
<td>FMD%</td>
<td>6.84±0.79</td>
<td>6.85±1.16</td>
<td>8.27±1.52</td>
</tr>
<tr>
<td>Peak diameter, mm</td>
<td>3.00±0.13</td>
<td>3.02±0.15</td>
<td>2.84±0.16</td>
</tr>
<tr>
<td>Shear rate\textsubscript{ave} s\textsuperscript{-1}×10\textsuperscript{3}</td>
<td>20.9±4.7</td>
<td>21.1±5.2</td>
<td>29.2±4.1</td>
</tr>
<tr>
<td>Time to peak, s</td>
<td>54±9</td>
<td>50±10</td>
<td>68±9</td>
</tr>
</tbody>
</table>

L-FMC indicates low-flow mediated vasoconstriction; FMD, flow-mediated dilation; shear rate\textsubscript{ave}, shear rate area under the curve from cuff deflation to peak dilation; and time to peak, time from cuff deflation to automatically detected peak dilation.

Results presented as mean±SE.

*Significantly different from rest at P<0.05 (paired t-test).

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### Disclosures
None.

### References


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