INTIMAL HYPERPLASIA IN RESPONSE TO REDUCTION OF WALL SHEAR STRESS

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BLOOD FLOW AND WALL SHEAR STRESS are recognized as important hemodynamic factors that regulate arterial wall remodeling.1 Arteries enlarge in response to increased flow and wall shear stress with no intimal thickening.2 Low levels of shear stress have been implicated in the development of intimal thickness.3,4 The purpose of this study was to assess arterial wall morphologic changes after periods of both increased and decreased flow in the same artery and to determine whether intimal thickness developed during periods of reduced wall shear stress.
Hemodynamic and morphologic results in the left common carotid artery

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Blood flow (mL/min)</th>
<th>Arterial diameter (mm)</th>
<th>Wall shear stress (dynes/cm²)</th>
<th>Intimal thickening (mm²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>4</td>
<td>17.2 ± 1.0</td>
<td>2.2 ± 0.1</td>
<td>12.9 ± 3.2</td>
<td>0</td>
</tr>
<tr>
<td>4 wk AVF</td>
<td>6</td>
<td>332 ± 177*</td>
<td>4.1 ± 0.4*</td>
<td>33.2 ± 7.7*</td>
<td>0</td>
</tr>
<tr>
<td>3 wk rev</td>
<td>4</td>
<td>15.6 ± 1.9</td>
<td>3.4 ± 0.1*</td>
<td>2.9 ± 1.6*</td>
<td>0.6 ± 0.2*</td>
</tr>
<tr>
<td>6 wk rev</td>
<td>4</td>
<td>20.8 ± 5.7</td>
<td>3.2 ± 0.3*</td>
<td>4.2 ± 1.7*</td>
<td>0.4 ± 0.1*</td>
</tr>
<tr>
<td>26 wk rev</td>
<td>5</td>
<td>17.2 ± 1.9</td>
<td>3.5 ± 0.3*</td>
<td>2.8 ± 0.2*</td>
<td>0.8 ± 0.1*</td>
</tr>
</tbody>
</table>

* P < 0.05.

MATERIALS AND METHODS

For this study, we used an animal model of increased blood flow that could be easily reversed to normal flow. Six-millimeter side-to-side arteriovenous fistulas were created in 23 Japanese male rabbits (3.5–4.0 kg) between the left common carotid artery and the corresponding external jugular, using continuous 8.0 nylon. Previous research has indicated that arteriovenous fistulas result in measurable proximal arterial enlargement. After 4 weeks of increased flow, the fistulae were closed surgically by placement of a Sugita clip across the anastomosis to restore normal flow (Rev Group). Animals were sacrificed at 3, 6, and 26 weeks after fistula closure.

At all time points, in situ blood flow was measured using an electromagnetic flow probe, arterial diameter was measured from calibrated macroscopic photographs, and wall shear stress was calculated. After sacrifice, vessels were pressure perfusion–fixed with 3% glutaraldehyde to preserve in vivo geometry. Carotid arteries were harvested and prepared for light microscopy, scanning electron microscopy, and morphologic quantification with a Nikon Cosmozone-1 digitizing system. Each afferent artery was divided into equal zones for histologic analysis. Control animals underwent vessel mobilization, followed by fistula creation, and immediate ligature of the venous outflow to establish normal arterial flow.

RESULTS

Control carotid arteries had normal blood flow and wall shear stress for 10 weeks. There was no measurable intimal thickness. Four weeks after fistula creation, there was a 15-fold increase in blood flow in the afferent carotid artery and a 2-fold increase in arterial diameter. Wall shear stress was increased and there was no intimal thickening (Table). Histologic analysis revealed fragmentation of the internal elastic lamina and elastic fibers of the media with proliferation of the
adventitia. After fistula ligation, blood flow returned to normal levels, but arterial diameter remained 80% larger than control, and wall shear stress was significantly lower than control arteries. Despite normal blood flow, significant intimal thickening was present at 3 weeks (0.6 ± 0.2 mm²) and continued to thicken at 26 weeks (P < 0.05) in the zones proximal to the fistula. Histologic analysis revealed normal endothelial surface with smooth muscle cell proliferation in the intima parallel to the vessel axis.

CONCLUSIONS

These observations confirm that increased wall shear stress and blood flow result in arterial enlargement and arterial wall remodeling with no intimal thickening. Prolonged exposure to subnormal levels of shear after previous enlargement is associated with intimal proliferation and thickening as early as 3 weeks after fistula closure, with progressive thickening continuing in response to low shear. Development of intimal thickening may be an adaptive response to subnormal shear, in an attempt to reduce lumen diameter and normalize wall shear stress. Thus, levels of wall shear stress reduced below normal can stimulate intimal thickening and may play a role in pathologic intimal hyperplasia.

REFERENCES