Structural properties of rat mesenteric small arteries after 4-wk exposure to elevated or reduced blood flow

FABRICE POURAGEAUD AND JO G. R. DE MEY
Department of Pharmacology and Cardiovascular Research Institute Maastricht, Universiteit Maastricht, 6200 MD Maastricht, The Netherlands

Pourageaud, Fabrice, and Jo G. R. De Mey. Structural properties of rat mesenteric small arteries after 4-wk exposure to elevated or reduced blood flow. Am. J. Physiol. 273 (Heart Circ. Physiol. 42): H1699–H1706, 1997.—We determined the structure of mesenteric small arteries after chronic elevation and chronic reduction of blood flow. In 6-wk-old rats, we ligated second-order side branches of every other first-order side branch of the superior mesenteric artery. This persistently reduced blood flow (~90%) in the vessels feeding into the ligated trees and elevated blood flow (~80%) in the nonligated mesenteric artery side branches. Four weeks after surgery, vessels that had been exposed to high blood flow (HF) or low blood flow (LF) and vessels from sham-operated rats (Sham) were isolated and mounted in a pressure myograph system. At an intraluminal pressure of 100 mmHg, the internal diameter at rest was larger in HF (533 ± 23 μm) and smaller in LF (262 ± 14 μm) than in Sham vessels (427 ± 15 μm). Also, wall and media cross-sectional areas were larger in HF and smaller in LF than in Sham vessels (media: 22 ± 1, 11 ± 2, and 16 ± 1 × 10^3 μm^2, respectively), but circumferential wall stress did not differ among groups. DNA content was significantly increased in HF vessels (+100%) and was not modified in LF vessels. Maximal vasoconstrictions elicited by high potassium or norepinephrine were slightly increased in HF vessels but were reduced by 50% in LF vessels. Thus chronic changes in blood flow give rise to structural changes that normalize circumferential wall stress. Elevated blood flow resulted in outward hypertrophic remodeling involving hyperplasia. Reduced blood flow resulted in inward hypertrophic remodeling accompanied by hyporeactivity of the arterial smooth muscle.

CIRCUMFERENTIAL WALL STRESS and wall shear stress are considered to be important driving forces during development of the arterial wall (10, 27). They also modulate arterial wall structure in the adult. Elevation of transmural pressure, as in chronic hypertension, leads in many cases to an increase in arterial wall mass (8). The consequence of this hypertrophy on lumen diameter depends on the anatomic location of the vessel and on the etiology of the hypertention (5, 12). That different processes influence arterial wall mass and arterial lumen diameter may help in understanding the inward or outward nature of arterial remodeling (22). With respect to the regulation of arterial structural lumen diameter, several studies (14, 36) have shown that chronic elevation of blood flow leads to a widening of large arteries. Less is known about the effects of chronic blood flow reduction. They have been investigated in large arteries without changes of transmural pressure (3, 17) and also in poststenotic arteries that experience reductions in both flow and transmural pressure (7). Nonetheless, few studies have investigated the long-term effects of blood flow alterations on the structure of small resistance-sized muscular arteries (33, 34). These may be of particular interest from both the pathophysiological and mechanistic point of view. Small collateral vessels can play an important role in tissue perfusion after large artery occlusion (4, 26). Unlike large arteries, the density of smooth muscle cells is particularly high in small muscular arteries. This component of the arterial wall may be more susceptible to structural modulation than the extracellular matrix components such as collagen and elastin.

In the present study, we evaluated structural changes in rat mesenteric small arteries exposed for 4 wk to either an increase or decrease in blood flow. To this end we 1) ligated the connections to the arterial anastomoses for every other first-order side branch of the superior mesenteric artery that run parallel to the gut; 2) determined the acute (30 min) and chronic (4 wk) effects of these ligations on the blood flow through the trunks of the ligated and intermittent trees; 3) isolated first-order vessels that had been exposed to elevated or reduced flow for 4 wk; and 4) analyzed structural, mechanical, and contractile properties by organ chamber and histological techniques. For comparison, we also investigated vessels from 6-wk-old rats and 10-wk-old sham-operated (Sham) rats, representing the control conditions at initiation and termination, respectively, of the experimental intervention.

MATERIAL AND METHODS

Experimental groups. Six-week-old Wistar-Kyoto rats (Central Animal Facilities, Universiteit Maastricht, The Netherlands) that weighed 136 ± 8 g were randomly divided into three groups of seven animals each. In the first group, surgery was performed to modify blood flow in the mesenteric arteries (Fig. 1). In the second group, a similar surgical intervention was performed but without flow modification (Sham). The experimental and Sham groups were used 4 wk later. The third group, which was not subjected to surgery, was used for in vitro experimentation at 6 wk of age. The experimental protocols were approved by the Ethical Committee for Animal Welfare of the Universiteit Maastricht.

Blood flow measurements and arterial ligations. The animals were anesthetized with pentobarbital sodium (60 mg/kg ip), and a medial laparotomy was performed. Body temperature was maintained at 37.5°C by a thermostatically controlled heating platform. A section of the ileum was extracted and spread over a gauze swab that had been dampened with a sterile physiological salt solution (PSS). A segment of the first-order mesenteric artery side branch was gently freed of fat and connective tissue under a dissection microscope. With the use of a micromanipulator, a transit-time ultrasonic flow probe (0.5-mm V-series, Transonic Systems, Ithaca, NY) was placed around the artery (Fig. 1). Flow was determined with a...
All preparations were mounted in an arteriograph system (Living System Instrumentation, Burlington, VT), in which wall thickness and internal diameter could be continuously monitored while intraluminal pressure and flow were controlled (11). Segments were cannulated at both ends with a glass micropipette (internal diameter at tip 200 µm), tied to the pipettes with 11-0 surgical suture, and filled with filtered 1% albumin-PSS. The vessels were kept in a bath (7 ml) filled with warmed (37°C) and oxygenated (5% CO₂ in O₂) PSS. In the absence of flow, the pressure was increased to 50 mmHg. The pressure-servo system that controlled the intraluminal pressure was placed in the manual mode (i.e., without automatic control of pressure) to check for leaks in the cannulated preparation. Leaks were detected by a drop in pressure. In the absence of leaks, the pressure-servo system was set back to the automatic mode. The distance between the pipettes was set during pressurization at 150 mmHg and was adjusted by positioning the movable cannula to prevent warping, axial compression, or stretch of the vessel. Thereafter, the preparation was pressurized at 100 mmHg in the absence of flow and was allowed to equilibrate for 1 h.

The arteriograph system was placed on the stage of an inverted microscope (Nikon TMS) equipped with a black-and-white video camera (Stemmer). An electronic system (Living System Instrumentation) analyzed the signal obtained from the video image and continuously determined the internal diameter and wall thickness of the vessels. These parameters were recorded together with the intraluminal pressure with a chart recorder.

Experimental protocols. After the equilibration period, constrictions were studied by recording the decrease in the internal diameter in response to a high K⁺ solution (125 mM). After the preparations were washed with PSS until complete relaxation, a concentration-response curve was constructed by the cumulative addition of norepinephrine (NE; 0.01–10 µM) in the presence of cocaine (1 µM). Then the preparation was washed until a complete dilation was observed.

Spontaneous tone was assessed by recording the difference in internal diameter before and after the addition of sodium nitroprusside (100 µM) to the bath solution. Thereafter, the bath solution was replaced by Ca²⁺-free PSS + 0.3 mM EGTA, and stepwise increases in intraluminal pressure from 10 to 160 mmHg were applied, with an incremental pressure of 10 mmHg. Internal diameter and wall thickness of the preparation were measured at each pressure step. The intraluminal pressure was maintained for 1 min at each step.

Calculation of parameters. From parameters measured with the arteriograph system, other vascular parameters were calculated (11). Wall cross-sectional area (CSA) was defined as CSA = π(D² – D₀²)/4, where D₀ is the external diameter (in mm) and D is the internal diameter (in mm). Wall tension was calculated as T = PD₂/2, where T is tension (in N/m) and P is intraluminal pressure (in N/m²). Circumferential wall stress (WS) was calculated with the formula WS = T/h, where h is wall thickness (in m). Wall shear rate (WSR) was calculated with the formula WSR = 4Q/r², where Q is blood flow (in ml/s) and r is the vessel radius (in cm).

Histology and morphometry. After contractile reactivity was recorded, the preparations were removed from the arteriograph and fixed without intraluminal pressure and longitudinal stretch. They were placed overnight in phosphate-buffered formaldehyde (4%), stored in ethanol, and embedded in paraffin.

Cross sections (4 µm) were stained with Lawson's solution (Boom, Meppel, The Netherlands) to visualize internal and...
external elastic laminae. Video images were generated from the cross section with a Zeiss axioline (Zeiss) and a standard charge-coupled device camera (Sony). Internal and external media circumscriptions, demarcated by the internal and external elastic laminae and external circumference adventitia, were measured (Sigma Scan, Jandel Scientific, Corte Madera, CA). From these values, media and adventitia cross-sectional areas, internal radius, and media thickness were calculated for each section (2).

Additional cross sections were stained with eosin and hematoxylin, and the number of nuclear profiles in the medial and adventitial parts of the sections were counted separately at ×400 magnification by two independent investigators.

Biochemical analysis. The DNA content of first-order mesenteric side branches was determined with the fluorometric assay of Labarca and Paigen (16) with calf thymus DNA as internal standard. The method exploits the enhancement by DNA of the fluorescence of bisbenzimidazole (Hoechst 33258). The quantity of DNA (in ng) determined in the preparations was divided by the length of the vessel segments (in mm).

Solutions and drugs. The composition of the PSS was (in mM): 119 NaCl, 4.7 KCl, 2.5 CaCl2, 2.5 MgSO4, 25 NaHCO3, 1.2 KH2PO4, and 5.5 glucose. In the high K+ solution, all NaCl was replaced by an equimolar amount of KCl. In Ca2+-free PSS, CaCl2 was omitted from the normal PSS and 0.3 mM EGTA was added. The drugs used were pentobarbital sodium (Sanofi, Bordeaux, France), Hoechst 33258 (Biochem, Bruges, Belgium), and norepinephrine, cocaine, sodium nitroprusside, EGTA, calf thymus DNA, and bovine serum albumin (Sigma Chemical; St. Louis, MO). All drugs were dissolved in distilled water.

Data analysis. In all experiments, n equals the number of rats. Results are shown as means ± SE. Statistical significance of differences was evaluated with two-way analysis of variance followed by post hoc comparisons with Fisher’s least significant difference test. A P value of < 0.05 was considered significant.

RESULTS

Blood flow. In anesthetized 6-wk-old rats, blood flow in first-order mesenteric artery branches was on the order of 0.3 ml/min and did not differ among experimental groups (Table 1). After ligation of the connections to the mesenteric arterial anastomosis, a drastic reduction in blood flow (close to 90%) was observed in the upstream arteries. In the feeding vessel of the nonligated arterial trees, a marked increase in blood flow (close to 80%) was recorded (Table 1). Four weeks later, all rats were still alive, and flow changes were still present in the obstructed arteries and the unobstructed parallel vessels (Table 1). These vessels will be referred to as LF and HF arteries, respectively. The late changes in blood flow were comparable to those noted immediately after the ligation (Table 1). In Sham control rats, blood flow values had not changed during the 4-wk period.

Table 1. Effect of outflow obstruction of every other mesenteric artery side branch on blood flow

<table>
<thead>
<tr>
<th></th>
<th>Sham</th>
<th>HF</th>
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<tbody>
<tr>
<td>n</td>
<td>6</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Before ligations</td>
<td>0.30 ± 0.03</td>
<td>0.29 ± 0.03</td>
<td>0.27 ± 0.02</td>
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<tr>
<td>After ligations</td>
<td>0.51 ± 0.06*</td>
<td>0.03 ± 0.01*</td>
<td>0.03 ± 0.01*</td>
</tr>
<tr>
<td>4 wk after operation</td>
<td>0.26 ± 0.02</td>
<td>0.61 ± 0.08</td>
<td>0.05 ± 0.01*</td>
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</table>

Values are means ± SE in ml/min; n, no. of rats. Blood flow in 1st-order mesenteric artery side branches was measured under anesthesia by ultrasonic flow probe before, 30 min after and 4 wk after obstruction of outflow of every other branch as described in MATERIAL AND METHODS. LF, obstructed vessels (low flow); HF, intermittent nonligated vessels (high flow); Sham, vessels from sham-operated control rats. *Significance difference from Sham, P < 0.001.

Mean intra-aortic blood pressure, measured in awake conditions at the end of the experimental period, did not differ significantly between experimental (125 ± 4 mmHg; n = 7) and Sham animals (120 ± 2 mmHg; n = 7). Also, body weight did not differ among groups (268 ± 10 vs. 255 ± 11 g for experimental and Sham groups, respectively).

Vessel structure. Figure 2 illustrates that overall vessel wall structure was well preserved after 4 wk of modified blood flow. For instance, in neither HF nor LF vessels was disruption of the internal elastic lamina or a neointimal layer observed. Table 2 summarizes quantitative changes in vessel wall structure. No statistically significant differences were observed between 6-wk-old rats and 10-wk-old Sham control rats. In HF compared with Sham vessels, lumen diameter and media cross-sectional area were significantly increased. In LF compared with either Sham or HF vessels, lumen, diameter, media, and adventitia cross-sectional areas, and media thickness were significantly reduced.

Total DNA content did not differ significantly between the mesenteric arteries of 6-wk-old rats and those of Sham rats (Fig. 3). In HF vessels, the DNA content was approximately twice as large as in Sham vessels (Fig. 3). The DNA content was, however, not modified in vessels that had been chronically exposed to reduced blood flow (Fig. 3). The number of nuclear profiles in both the medial and adventitial parts of the 4-µm-thick cross sections was significantly larger in HF than in Sham vessels (Table 2). In LF vessels, on the other hand, the
number of nuclear profiles was not modified in the media and significantly increased in the adventitia compared with Sham vessels (Table 2). Nuclear density, assessed as the number of nuclear profiles per unit surface area, was significantly elevated in the media and adventitia of LF compared with Sham vessels.

Pressure-diameter relationship. Figure 4 depicts the relationship between internal diameter and intraluminal pressure observed in isolated cannulated arteries incubated in Ca<sup>2+</sup>-free solution. Between 10 and 160 mmHg, the internal diameter did not differ between mesenteric arteries of 6-wk-old rats and those of Sham rats. Over this range of pressures, the diameters were significantly greater in HF and significantly smaller in LF than in Sham vessels.

Circumferential wall stress calculated at an in vitro intraluminal pressure of 100 mmHg did not differ significantly among HF (122 ± 8 N/m<sup>2</sup>), LF (110 ± 5 N/m<sup>2</sup>), and Sham vessels (125 ± 6 N/m<sup>2</sup>) and vessels from 6-wk-old intact rats (120 ± 4 N/m<sup>2</sup>). This was the case within a broad range of pressures (e.g., 60-160 mmHg) (data not shown). To estimate wall shear rate, the blood flow measured in vivo was combined with the internal diameters observed in vitro at 100 mmHg. This estimate did not differ significantly among HF (665 ± 96 s<sup>−1</sup>), LF (590 ± 106 s<sup>−1</sup>), and Sham vessels (692 ± 54 s<sup>−1</sup>) and vessels from 6-wk-old intact rats (745 ± 60 s<sup>−1</sup>).
Contractile reactivity. In HF, LF, and Sham vessels equilibrated at 100 mmHg in the presence of 2.5 mM Ca$^{2+}$, the administration of 100 μM sodium nitroprusside and the removal of extracellular Ca$^{2+}$ failed to induce significant dilatation (data not shown). This indicates the absence of basal tone in all three experimental groups.

All HF and Sham vessels constricted in response to a high K$^+$ solution (125 mM) and to NE (10 μM). Twenty-five percent of the LF vessels failed to respond to these vasoconstrictor stimuli and were not included in this study. Constrictor responses to K$^+$ and NE did not differ between vessels from intact 6-wk-old rats and Sham control rats (Table 3, Fig. 5). The percent diameter reduction induced by K$^+$ was significantly larger, but the accompanying reduction in media stress was comparable in HF compared with Sham vessels (Table 3). Constrictor responses to K$^+$ were markedly smaller in LF than in Sham vessels. In HF vessels, the maximal response to NE was increased vs. control vessels when expressed as percent diameter reduction but not when expressed as change in media stress (Table 3, Fig. 5). In LF vessels, the maximal constrictor responses to NE were significantly reduced in both respects.

**DISCUSSION**

In rat mesenteric small arteries that had been chronically exposed to altered blood flow, both the wall mass and lumen diameter were modified. Elevated blood flow resulted in outward hypertrophic remodeling and reduced blood flow in inward hypertrophic remodeling (32). These seem to involve different cellular changes.

The superior mesenteric artery supplies the arterial blood flow to most of the small intestine. In the rat, the third-order side branches of this vessel run parallel to the gut and interconnect with the ~20 first-order branches. Thanks to these anastomoses, most of the outflow of every other first-order mesenteric artery side branch could be obstructed without noticeable necrotizing injury to the ileum as has previously been reported (32, 33). Although flow was drastically reduced in the obstructed vessels, blood flow increased acutely to approximately the same extent in the parallel vessels that had not been obstructed. Four weeks after this intervention, the ligated vessels were still present and perfused, possibly due to the small side branches of these vessels that perfuse the mesentery. Blood flow was still drastically reduced in the ligated vessels, and blood flow was still markedly enhanced in the nonligated parallel vessels. In 10-wk-old rats that had been subjected at 6 wk of age to a sham procedure, blood flow did not differ significantly between first-order mesenteric artery side branches. Furthermore, wall structure, lumen diameter, and vasoconstritor responses did not differ between vessels of 6-wk-old rats and those of 10-wk-old Sham rats. Collectively, these observations indicate that persistent reductions and elevations in blood flow could be induced in parallel mesenteric small arteries of the same rats and that these changes

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**Table 3. Constrictor responses to high K$^+$ solution and NE in mesenteric small arteries exposed for 4 wk to HF or LF compared with vessels in nonoperated 6-wk-old and sham-operated rats**

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<th>6 Wk Old</th>
<th>Sham</th>
<th>HF</th>
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<tr>
<td>K$^+$ (125 mM)</td>
<td></td>
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<tr>
<td>ΔID, %</td>
<td>75.2 ± 2.1</td>
<td>65.2 ± 5.0</td>
<td>83.7 ± 1.8</td>
<td>32.5 ± 2.6</td>
</tr>
<tr>
<td>ΔWS, N/m²</td>
<td>−135 ± 15</td>
<td>−113 ± 14</td>
<td>−150 ± 11</td>
<td>−48 ± 9</td>
</tr>
<tr>
<td>NE (10 μM)</td>
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<tr>
<td>ΔID, %</td>
<td>−75.0 ± 2.3</td>
<td>−67.3 ± 5.0</td>
<td>−82.3 ± 1.6</td>
<td>−36.5 ± 5.3</td>
</tr>
<tr>
<td>ΔWS, N/m²</td>
<td>−141 ± 14</td>
<td>−119 ± 12</td>
<td>−149 ± 12</td>
<td>−59 ± 16</td>
</tr>
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Values are means ± SE; n, no. of rats. NE, norepinephrine; Δ, change in. Significant difference from Sham rats: *P < 0.05; †P < 0.01; ‡P < 0.001.
were superimposed on stable vessel wall structure and reactivity.

Measurements of lumen diameter and wall thickness in isolated cannulated arteries and morphometric measurements of immersion-fixed preparations were used to evaluate the structure of the vessels. These approaches indicate that both wall mass and lumen diameter were increased in the HF arteries and that both wall mass and lumen diameter were reduced in the LF vessels. Pressure-diameter curves indicate that the alteration of lumen diameter was statistically significant over a broad range of intraluminal pressures. These lumen diameter changes are primarily structural in nature because, for all experimental groups, removal of extracellular Ca\(^2+\) and a high concentration of sodium nitroprusside failed to modify lumen diameter. When evaluated at identical pressure (e.g., 100 mmHg), circumferential wall stress in HF and LF vessels did not differ from control values. Collectively, these observations indicate that 4 wk of elevated blood flow resulted in outward hypertrophic remodeling, that 4 wk of reduced blood flow resulted in inward hypotrophic remodeling, and that both sets of structural alterations led to a restoration of circumferential wall stress. The latter is in line with earlier findings in the circulation of the cremaster muscle (34, 35) and mesentery of the rat (32, 33) as far as adaptation to elevated flow is concerned. It is tempting to speculate that wall shear stress was also normalized by the structural responses to altered blood flow (14, 17, 36). This cannot be directly concluded from our observations but is supported by calculated wall shear rate based on flows and diameters measured in vivo and in vitro, respectively.

The increase in wall mass noted in the HF vessels was accompanied by a substantial increase in the DNA content of these vessels (+100%) and by a significant increase in the number of nuclear profiles in cross sections of the media and adventitia (+45 and +120%, respectively). The reduction in wall mass seen in the LF vessels was not accompanied by a reduction in DNA content, and a comparable number of nuclear profiles could be observed in the media of these vessels. Nonetheless, a marked increase in the number of nuclei was noted in the adventitia (+100%). The role of the adventitia in the overall structure of the blood vessel wall is largely unknown. Yet, because we observed different changes in adventitial and medial cells in LF vessels, future mechanistic analyses will require techniques with a high degree of spatial resolution rather than biochemical studies of the entire vessel segments. Because two independent techniques, aimed at changes in cell number, yielded conflicting results, analysis of the changes in cell number, cell volume, and ploidy in the present experimental setting will require more sophisticated techniques. That different cellular changes are involved in the structural responses to flow elevation and flow reduction is also indicated by the observed alterations in contractile reactivity. In the HF vessels, the absolute and relative reductions in lumen diameter evoked by either high K\(^+\) or a high concentration of NE were increased, but the accompanying reduction in media stress did not differ from that in vessels from Sham animals. So, in this condition, new contractile elements (e.g., cells) seem to have been added both in series and in parallel to the preexisting ones (23). In the LF vessels, the vasoconstrictor responses were markedly reduced, not only when assessed as an absolute reduction in diameter but also in terms of alteration in media stress. So, in the LF vessels, hyporeactivity to vasoconstrictor stimuli seemed to involve a reduction in both mass and contractility of the arterial smooth muscle.

The structural and functional changes that we noted in rat mesenteric small arteries exposed to altered blood flow (HF vessels: a 25% increase in lumen diameter, a 35% increase in media cross-sectional area, and a 100% increase in DNA content; LF vessels: a 40% reduction in lumen diameter, a 30% reduction in media cross-sectional area, and a 50% reduction in contractility) are large compared with earlier investigations (14, 17, 36) of flow-induced remodeling in large conduit arteries. Considerable diameter increases have previously been described for collateral vessels in the rabbit hindlimb after femoral arterial occlusion (19) and in the rat mesentery after ligation of multiple mesenteric artery side branches (32, 33). This could be due to the muscular nature of the small arteries and may be helpful for future analyses of the mechanisms underlying flow-induced structural changes. Most arterial vasomotor (15, 28) and structural responses (3, 17) to blood flow elevation have been observed to be endothelium dependent. Endothelium-derived mitogens (25) and macrophages recruited through enhanced endothelial expression of adhesion molecules (29) have been proposed to participate in flow-induced arterial remodeling. Another possibility, which is not mutually exclusive from the former, takes into account that vasomotor responses to changes in flow affect the mechanical factors within the vessel wall. First-order mesenteric artery side branches exhibit basal vasomotor tone (24) and experience a transmural pressure that is slightly but significantly smaller than aortic pressure (31). Reduction and elevation in tone will be accompanied by an increase and a decrease, respectively, in transmural pressure in the distal part of these vessels. In view of the size of the vessels, these changes in pressure may be anticipated to be rather small. On acute local elevation in blood flow, endothelium-derived mediators such as NO and prostaglandins induce vasodilatation (15). This entails an elevation in circumferential wall stress as lumen diameter increases and wall thickness decreases. This alteration, indirectly brought about by the endothelium, has been considered to be an important direct (21) or indirect (1) hypertrophic stimulus for the arterial wall. We propose that this mechanical factor overrules the potential antimitogenic effects of the acute endothelium-derived vasodilators NO and prostaglandins (6, 9, 30). In line with this, a recent investigation (13) of arteriovenous shunts in patients
revealed a positive correlation between wall shear rate and mitogenicity of vascular smooth muscle cells. Conversely, on acute local reduction in blood flow, vasoconstrictor tone is increased as a result of a reduced supply of endothelium-derived relaxing factors and possibly increased endothelial release of the potent vasoconstrictor and mitogenic substance endothelin (20). Circumferential wall stress is thereby reduced, and in the long run, atrophy of the arterial wall may develop. Also in this case, changes in wall stress are suggested to override the mitogenic effect of reduced and increased supply of NO and endothelin, respectively. The accompanying hyporeactivity could result from prolonged excessive vasoconstriction (2). Alternatively, this may be a consequence of long-term exposure to endothelin. In deoxycorticosterone acetate salt hypertensive rats, which exhibit elevated tissue and circulating levels of endothelin (18), mesenteric small artery contractile reactivity is reduced, and this can be prevented by chronic treatment with the endothelin-receptor antagonists bosentan (18).

We are not the first who evaluated structural changes in rat mesenteric small arteries in response to chronic changes in blood flow (32, 33). Still, our study revealed aspects that were not addressed before. These include 1) the possibility that structural adaptation to reduced flow evolves through mechanisms other than those to elevated flow, 2) changes in the adventitia, and 3) changes in contractile reactivity accompanying changes in arterial diameter.

In summary, we observed that after chronic exposure to elevated and reduced blood flow, circumferential wall stress was normalized by outward hypertrophic remodeling and inward hypotrophic remodeling, respectively. The former may involve an increase in arterial cell number, the latter a reduction in arterial smooth muscle cell volume and contractility. Wall mass changes in response to chronic changes in blood flow contrast with suspected effects on arterial smooth muscle cell growth of endothelium-derived vasoactive agents implicated in the acute control of wall shear stress.

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Address for reprint requests: J. G. R. De Mey, Dept. of Pharmacology, University of Bordeaux II, 146 Rue Leo Saignat, 33076 Bordeaux Cedex, France.

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