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# Shear-Stress and Wall-Stress Regulation of Vascular Remodeling After Balloon Angioplasty

## Effect of Matrix Metalloproteinase Inhibition

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***Background***—Constrictive vascular remodeling (VR) is the most significant component of restenosis after balloon angioplasty (PTA). Whereas in physiological conditions VR is associated with normalization of shear stress (SS) and wall stress (WS), after PTA the role of SS and WS in VR is unknown. Furthermore, whereas matrix metalloproteinase inhibition (MMPI) has been shown to modulate VR after PTA, its effect on the SS and WS control mechanisms after PTA is unknown.

***Methods and Results***—PTA was performed in external iliac arteries of 12 atherosclerotic Yucatan pigs, of which 6 pigs (7 vessels) received the MMPI batimastat and 6 pigs (10 vessels) served as controls. Before and after the intervention and at 6-week follow-up, intravascular ultrasound pullback was performed, allowing 3D reconstruction of the treated segment and computational fluid dynamics to calculate the media-bounded area and SS. WS was derived from the Laplace formula. Immediately after PTA, media-bounded area, WS, and SS changed by 20%, 16%, and −49%, respectively, in both groups. VR was predicted by SS and WS. In the control group, SS and WS had been normalized at follow-up with respect to the reference segment. In contrast, for the batimastat group, the SS had been normalized, but not the WS. The latter is attributed to an increase in wall area at follow-up.

***Conclusions***—Vascular remodeling after PTA is controlled by both SS and WS. MMPI inhibited the WS control system. **(*Circulation*. 2001;104:91-96.)**

**Key Words:** stress ■ angioplasty ■ metalloproteinases

Although balloon angioplasty (percutaneous transluminal angioplasty, PTA) is a well-accepted method to reduce arterial stenosis, an important disadvantage of the method is the restenosis that develops in 30% to 50% of the patients.[1] Although it has been accepted that intimal hyperplasia causes the restenosis,[2] it recently became clear that restenosis after PTA is caused mainly by shrinkage of the vessel wall ("constrictive vascular remodeling").

Vascular remodeling has been observed in physiological conditions in response to changes in shear stress (SS), where it is aimed at restoring the original values of SS.[3] Although it has been postulated that this mechanism is of importance in vascular remodeling after PTA, experimental data underlying this theory are currently lacking.[1] This is of importance, because it has been shown that the endothelium plays an essential role in vascular remodeling.[4] Immediately after PTA, the endothelium is disrupted and the regenerated endothelial layer is dysfunctional.[5] Furthermore, because the vascular tissue is damaged after PTA, factors not involved in vascular remodeling during more physiological conditions might become of importance. Hence, the first question addressed in the present study was whether vascular remodeling after PTA is controlled by SS and if so, to which reference value the SS values will be restored during the remodeling process. To that end, we developed a method based on a combination of intravascular ultrasound (IVUS) and computational fluid dynamics that enables us to calculate regional SS over time.

The vessel wall responds to increments in blood pressure, at an unchanged flow, by increasing vessel wall thickness.[6] The wall stresses (WS) calculated before and after these pressure elevations appear to be similar, implying that WS is normalized during these conditions. PTA increases local WS, and the constrictive vascular remodeling may be a consequence of WS normalization. Therefore, the second aim of the present study was to evaluate

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the existence of a WS feedback loop in constrictive vascular remodeling after PTA.

In a previous study, de Smet et al[7] showed a reduction in vascular remodeling after PTA by inhibition of matrix metalloproteinase (MMP). Because the expression of MMP mRNA is coupled to both the shear-stress and wall-stress changes,[8] we hypothesized that pharmacological MMP inhibition will affect the negative feedback loops that control the SS and WS. The third aim of the present study was to investigate the regional SS and WS normalization after MMP inhibition.

## Methods

### General Protocol

Animals were treated according to the *Guide for the Care and Use of Laboratory Animals* published by the US National Institutes of Health (NIH publication No. 85-23, revised 1985), and treatment was approved by the Ethical Committee on Animal Experiments of the Faculty of Medicine, Utrecht University.

The left and right external iliac arteries of 12 atherosclerotic Yucatan minipigs[7] were treated by PTA. Subsequently, 6 animals were given an MMP inhibitor, BB-94 (batimastat, British Biotech Pharmaceuticals Ltd; 64 mg/kg IP, 20 mg/mL, every 2 weeks), and the others served as controls.

### Animal Instrumentation

All animals were anesthetized with metomidate (4 mg/kg IV) and ventilated (Servo, EM 902) with a mixture of $O_2$:$N_2O$ 1:2 and halothane 1% to 2%. During each procedure, heparin (thromboliquine 100 IU/kg, Organon Technika) and atropine (0.25 mg every 15 minutes) were administered.

The arterial tree was accessed through the carotid artery. A guiding catheter was placed at the entrance of the iliac artery, and angiography was performed (Philips). The image with the highest contrast was selected and recorded on DAT tape. One day before PTA, acetylsalicylic acid (125 mg) was given and continued for 2 weeks. As the target area for PTA, the minimum lumen diameter was selected from angiographic images in both external iliac arteries. Subsequently, IVUS catheters (2.9F; 30 MHz; Du-MED) were used to record the target area by a continuous pullback, starting from the first distal side branch to the entrance of the guiding catheter. To relocate the target area at different time points (before and after PTA and at follow-up), the position of the distal side branch was documented by angiography.[7] A standard angioplasty balloon was selected to induce a dilation ratio of 1.2. The balloon was inflated 3 times at a pressure of 10 atm. After PTA, the IVUS measurements were repeated.

At 6-week follow-up and before termination, angiography and an IVUS pullback documented the treated area. Before and during PTA and at the day of termination, a continuous infusion of nitroglycerin (20 $\mu$g/min) was given to prevent spasm.

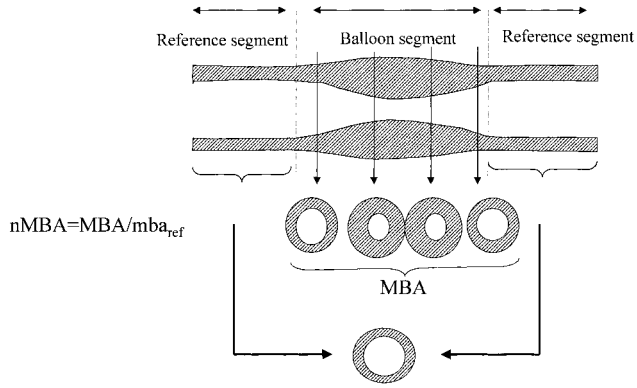


**Figure 1.** Definition of normalization of parameters in balloon-dilated segment by dividing them by average reference value. In this example, parameter MBA is divided by reference value $mba_{ref}$ to obtain nMBA.

### 3D Reconstruction and Computational Fluid Dynamics

The IVUS images were digitized at intervals of 0.5 mm from the videotape. Lumen and media were traced semiautomatically by a well-validated software package.[9] The lumen and media contours were positioned perpendicular to the IVUS catheter axis at intervals of 0.5 mm, and a 3D reconstruction of the lumen and wall of the iliac arteries was obtained.

To calculate SS by a finite-element software package (Sepran, Sepra), the lumen of the artery was filled by 3D finite elements as described previously.[10] The axial resolution of the mesh was 0.75 mm, and the cross-sectional resolution was 0.25 mm. We assumed a Newtonian fluid (viscosity 3 cP; density 1050 kg/m$^3$), a parabolic velocity profile (flow 80 mL/min[11]), no-slip conditions at the wall, and zero stress conditions at the exit. Finally, the media was processed similarly to the lumen to obtain a 1-to-1 matching of lumen and wall with the resolution of the mesh data. Furthermore, each set of iliac arteries (before PTA [pre], after PTA [post], and at follow-up) was processed to allow comparison of similar locations of each artery at each time point with in-house–developed software.

### Analysis and Statistics

We computed the lumen area (LA), the wall area (WA), and the media-bounded area (MBA). The SS was averaged over each cross section. Regional WS was derived from the Laplace formula. Next, all cross-sectional parameters were normalized by dividing by the average value of the reference segment (Figure 1A). Because arterial spasm might influence the reference segments immediately after PTA, the reference segment before PTA was used to calculate relative values for the post-PTA parameters. On the basis of these normalized values, several parameters were defined as a function of time (Table 1). For comparison of the LA, MBA, WA, SS, WS, and

**TABLE 1. Definition of Applied Parameters**

| | Parameter | Formula | Description |
|---|---|---|---|
| Lumen change | $\Delta nLA_{fuppost}$ | $nLA_{fup}-nLA_{post}$ | Change in normalized lumen area in the follow-up period |
| Vascular remodeling | $\Delta nMBA_{fuppost}$ | $nMBA_{fup}-nMBA_{post}$ | Change in normalized MBA in the follow-up period |
| Vessel wall growth | $\Delta nWA_{fuppost}$ | $nWA_{fup}-nWA_{post}$ | Change in normalized wall area in the follow-up period |
| Acute lumen gain | AG | $LA_{post}-LA_{pre}$ | Change in lumen area due to PTA |
| | $\Delta nSS_{fuppre}$ | $nSS_{fup}-nSS_{pre}$ | Shear stress relative to preangioplasty values |
| | $\Delta nWS_{fuppre}$ | $nWS_{fup}-nWS_{pre}$ | Wall stress relative to preangioplasty values |
| | $\Delta nSS_{fupref}$ | $(nSS_{fup}-1)\times100\%$ | Shear stress normalization at follow-up |
| | $\Delta nWS_{fupref}$ | $(nWS_{fup}-1)\times100\%$ | Wall stress normalization at follow-up |

fup indicates at follow-up; post, after PTA; AG, acute gain; pre, before PTA; and ref, reference segment.

**TABLE 2. Geometric and Biophysical Parameters Within the Balloon-Dilated Segment Obtained From 3D Reconstructions of Iliac Arteries of Atherosclerotic Yucatan Pigs Receiving Either Placebo (10 Vessels) or Batimastat (7 Vessels)**

| | Control | | | Batimastat | | |
|---|---|---|---|---|---|---|
| | Pre | Post | Fup | Pre | Post | Fup |
| LA, $mm^2$ | 15.9±2.8 | 19.0±3.1* | 12.2±2.6†‡ | 13.8±2.8 | 18.6±4.6* | 12.6±2.6†‡ |
| MBA, $mm^2$ | 20.8±4.4 | 24.7±4.2* | 17.6±2.9† | 18.2±3.1 | 23.8±5.2* | 19.3±4.5† |
| WA, $mm^2$ | 5.7±2.1 | 5.7±1.9 | 5.4±0.6 | 4.4±1.5 | 5.2±1.9 | 6.6±3.2 |
| SS, $N/m^2$ | 0.6±0.2 | 0.3±0.1* | 1.0±0.6† | 0.7±0.2 | 0.3±0.2* | 0.8±0.3† |
| WS, $kN/m^2$ | 85±24 | 101±24 | 68±13†‡ | 96±39 | 113±44 | 70±26†‡ |
| nLA | 0.95±0.35 | 1.19±0.43* | 1.05±0.23† | 0.92±0.22 | 1.32±0.60* | 0.98±0.35† |
| nMBA | 0.98±0.37 | 1.18±0.43* | 1.04±0.21 | 0.95±0.20 | 1.30±0.52* | 1.16±0.46 |
| nWA | 1.10±0.47 | 1.14±0.50 | 1.05±0.23 | 1.03±0.19 | 1.25±0.29 | 1.73±0.87§ |
| nSS | 1.35±0.64 | 0.69±0.44* | 1.11±0.40† | 1.32±0.55 | 0.61±0.49* | 1.21±0.86† |
| nWS | 0.93±0.28 | 1.08±0.26 | 1.03±0.21§ | 0.94±0.19 | 1.04±0.29 | 0.65±0.16§ |
| $LA_{ref}$, $mm^2$ | 17.3±5.1 | ... | 12.4±4.5‡ | 15.6±4.2 | ... | 14.6±5.6‡ |
| $MBA_{ref}$, $mm^2$ | 22.7±6.1 | ... | 17.8±5.3‡ | 19.9±5.1 | ... | 18.5±6.8‡ |
| $WA_{ref}$, $mm^2$ | 5.4±1.4 | ... | 5.4±1.3 | 4.2±1.3§ | ... | 4.0±1.4§ |
| $SS_{ref}$, $N/m^2$ | 0.6±0.3 | ... | 1.0±0.8‡ | 0.6±0.2 | ... | 0.6±0.2‡ |
| $WS_{ref}$, $kN/m^2$ | 95±21 | ... | 69±22‡ | 108±22 | ... | 106±20‡ |

Pre indicates before PTA; post, after PTA; Fup, follow-up; and MLA, minimal lumen area. The prefix n means that the parameter has been divided by its reference value.

*$P<0.05$, pre vs post; †$P<0.05$, post vs fup; ‡$P<0.05$, pre vs fup; §batimastat vs control.

their normalized (n) values, a 2-way ANOVA was applied with an appropriate post hoc test for multiple comparisons.

SS and WS were studied by use of regression analysis versus acute lumen gain. To obtain a gaussian distribution of the SS and WS, a log transformation was performed. $nSS_{post}$ and $nWS_{post}$ were tested as predictors of vascular remodeling and vessel wall growth (Table 1) after PTA. The regression model studying vascular remodeling included several dummy variables. Two dummy variables per animal corrected for an offset and slope, and the third tested for the control versus batimastat group. The partial derivatives of the regression line in combination with the range were used to determine the partial contribution of SS and WS to vascular remodeling. All values are expressed as mean±SD.

## Results

### Animal Population

In the control group, 10 arteries (30 3D reconstructions) were studied, because 1 artery was lost because of technical failure and in 1 artery no balloon was inflated. For the batimastat group, 1 pig died during the follow-up period, and in 2 arteries no balloon was inflated. One 3D reconstruction failed because of technical failure, and because the analyses required 3 complete 3D reconstructions for each artery (before and after PTA and at follow-up), the batimastat group includes 7 arteries (21 3D reconstructions).

We selected data within the balloon-dilated segment and excluded 12.5% at each site for further analysis to avoid inaccuracies at the edges. Furthermore, to exclude the influence of spasm in the balloon-dilated segments, only cross sections with positive acute lumen gain were selected. Finally, vessel segments containing side branches were excluded. This process of data selection resulted in 218 and 87 cross sections for each of the 3 time points for the control group and the batimastat group, respectively.

### Changes in Geometric Parameters After PTA

Because LA, MBA, and WA were not different between the control and the batimastat groups, the data were pooled. PTA increased LA and nLA (by 29%) and MBA and nMBA (by 23.4%), whereas WA and nWA remained unchanged (Table 2). At 6-week follow-up, LA decreased to values 15% below preangioplasty values, whereas nLA, MBA, and nMBA returned to their preangioplasty values. WA remained unchanged in the control group, whereas nWA increased in the batimastat group ($P<0.05$). The reference values decreased during follow-up (Table 2), which explained most of the difference between absolute and normalized values.

Regression analysis on all data points revealed that the slopes of the relationships between LA and MBA at follow-up (fup) were different for the control group [$MBA_{fup}=(1.00\pm0.06)\times LA_{fup}+(5.12\pm0.63)$] and for the batimastat group [$MBA_{fup}=(2.10\pm0.14)\times LA_{fup}-(5.64\pm1.70)$], whereas the equations were similar before angioplasty [control: $MBA_{pre}=(1.50\pm0.05)\times LA_{pre}-(1.51\pm0.73)$; batimastat: $MBA_{pre}=(1.35\pm0.08)\times LA_{pre}$]. As a consequence, batimastat reduced the contribution of constrictive vascular remodeling to lumen decrement in the follow-up period [control: $\Delta nLA_{fuppost}=(1.05\pm0.03)\times\Delta nMBA_{fuppost}$; batimastat: $\Delta nLA_{fuppost}=(-0.46\pm0.25)+(0.27\pm0.08)\times\Delta nMBA_{fuppost}$ $P<0.05$].

### Changes in SS and WS After PTA

SS and nSS decreased after PTA by 60% for both groups (Table 2). Analysis showed that for high acute gains, the decrease in normalized SS was more extreme (up to 87%) for both the control group (Figure 2A and 2B) and the batimastat group (Figure 2D and 2E). Furthermore, the SS returned to its reference values at follow-up over the entire range of acute

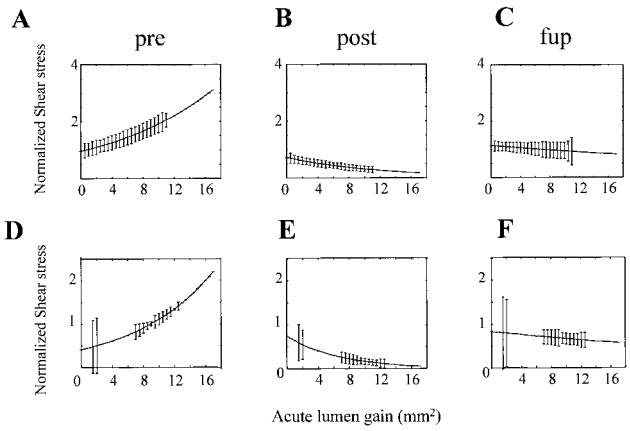


**Figure 2.** Normalized SS before (A, D) and after (B, E) PTA and at follow-up (C, F) vs acute lumen gain for control (A, B, C) and batimastat (D, E, F) groups. Note that ranges of figures of control group and batimastat group are different.

gains for both the control group (Figure 2C) and the batimastat group (Figure 2F). When we subtracted the nSS before angioplasty from the nSS at follow-up, the difference displayed a monotonically decreasing function in the control group (Figure 4A). Consequently, the SS returned to the follow-up reference values but not to preangioplasty values (compare Figure 2C with Figure 4A). In the batimastat group, the normalized SS values returned to both the preangioplasty values (Figure 4B) and the values of the reference segments at follow-up (Figure 2F), mainly because of a different preangioplasty distribution.

After PTA, WS and nWS increased by 20% for both groups (Table 2). Analysis showed that for the batimastat (Figure 3E) group, the WS changes in the low acute gain range were not well defined, in contrast to the control group (Figure 3B). During follow-up, the absolute WS values declined to values below the preangioplasty and postangioplasty values (Table 2). In contrast, normalized WS returned to values of the reference segment (Figure 3C) and the preangioplasty values (Figure 4C) for the control group and remained below the reference segment values (Figure 3F) and preangioplasty values (Figure 4D) in the batimastat group.

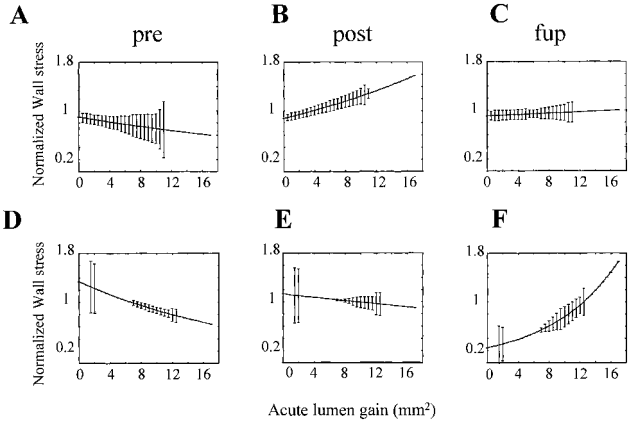


**Figure 3.** Normalized WS before (A, D) and after (B, E) PTA and at follow-up (C, F) vs acute lumen gain for control (A, B, C) and batimastat (D, E, F) groups.

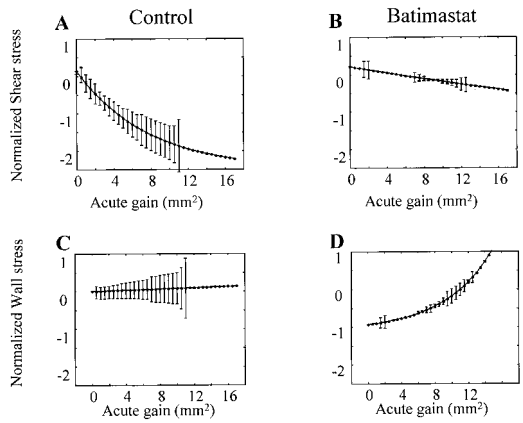


**Figure 4.** Normalization of SS and WS for control group (A, C) and batimastat group (B, D) vs acute gain. Zero on abscissa indicates normalized SS and WS values. Zero on ordinate means that values in balloon-dilated segment are equal to reference segments. Error bars indicate SEM.

## Correlation Between Geometric Factors and Biophysical Factors

A multivariate model including $nWS_{post}$ and $nSS_{post}$ significantly predicted vascular remodeling. After administration of batimastat, the contribution of WS to vascular remodeling was changed such that now a positive relationship between WS and vascular remodeling was observed [Figure 5B; control: $\Delta nMBA_{fuppost}=(0.40\pm0.95)+(0.11\pm0.04)\times nSS_{post}-(0.58\pm0.08)\times nWS_{post}$; batimastat: $\Delta nMBA_{fuppost}=(0.68\pm0.15)+(0.11\pm0.04)\times nSS_{post}+(0.38\pm0.13)\times nWS_{post}$; $r^2=0.73$, $P<0.05$]. Consequently, administration of batimastat changed the relative contribution of SS (control 0.27, batimastat 0.26) and WS (control 0.72, batimastat 0.63) to vascular remodeling. Vessel wall growth for the batimastat group was related to $nWS_{post}$ [$\Delta nWA_{fuppost}=(0.88\pm0.18)\times nWS_{post}$, $r^2=0.71$, $P<0.05$]. In the control group, no predictor for vessel wall growth was found.

## Discussion

Vascular remodeling is known to be the most important component of restenosis after PTA. Because SS and WS have been implicated as regulators of vascular remodeling during physiological conditions, we evaluated their role in vascular remodeling after PTA. The major findings of the present

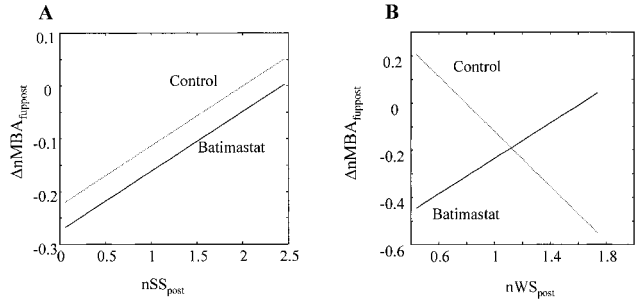


**Figure 5.** Vascular remodeling ($\Delta nMBA_{fuppost}$) vs normalized SS ($nSS_{post}$) (A) and vs normalized WS ($nWS_{post}$) (B) after PTA for control group (dotted line) and for batimastat group (solid line) derived from multivariate prediction model.

study are that regional SS and regional WS returned to their reference values after PTA after a 6-week follow-up. This "normalization" of SS and WS occurs predominantly through vascular remodeling, because both WS and SS immediately after PTA are important predictors of vascular remodeling. In contrast, administration of batimastat resulted in a hampered WS control.

### Geometric Factors

As expected from previous studies, vascular remodeling was the major factor in the lumen change after PTA.[7] Batimastat reduced this contribution of vascular remodeling to the lumen shrinkage in the balloon-dilated segment, as deduced from our regression analysis on MBA versus LA.

The additional increase in WA at follow-up after administration of the MMP inhibitor was an unexpected finding.[12] Because the observed increments in wall thickness are well beyond the resolution of the IVUS technique (200 $\mu$m), they must reflect an increase in the layers of the vessel wall. From the literature, it is known that administration of an MMP inhibitor fails to decrease the neointimal thickness.[12] This observation has been explained by an increase in proliferation of smooth muscle cells in the intima during the second week after PTA.[13] Because the measurements in the present study were made later (6 weeks) after PTA, the increments in wall thickness might be in accordance with these previous findings.

### SS and WS Control Mechanisms

Under physiological conditions and pathophysiological conditions like those in experimental atherosclerosis, the diameter of the arteries is regulated by the local SS and/or by local WS. Thus, changes in SS/WS induce adaptations of the arterial wall to keep the SS/WS within normal limits.[4] We argued that if SS and WS are important regulators in vascular remodeling after PTA, then they should comply with the following constraints. First, SS or WS should change after PTA; second, the change of WS or SS induced by PTA should be predictive of vascular remodeling; and third, vascular remodeling should stop when SS or WS has returned to "normal values." The last constraint requires that the follow-up measurements be performed at the moment the healing process is stopped and no morphological changes occur. Because we performed our measurements at 6-week follow-up, which is thought to be close to the stationary situation,[14] we could conclude that both regional WS and regional SS fulfilled all 3 requirements. Although the WS changes in the low acute gain range were not well defined for the batimastat group, an average increase in WS was still observed after PTA. To investigate to which SS and WS values the balloon-dilated segment returned, we compared the values at follow-up with the values before PTA and the reference values at follow-up. Remarkably, both SS and WS returned during follow-up to their reference values and not to their preangioplasty values in the control group. Although this investigation was not intended to study the underlying mechanism, one might argue that this is due to the growth of newly formed endothelial cells from upstream and from downstream into the balloon-dilated segment. Because these endothelial cells are newly formed and the atherogenic diet was stopped at the moment of PTA, the set point of the SS and WS of these newly formed endothelial cells may be close to the reference values.

In the present study, the modulating effect of batimastat on the SS/WS regulation was studied. Batimastat hampered the WS regulation, whereas the SS regulation remained unaffected. In geometric terms, batimastat induced iliac arteries with a "normal" lumen and a thick vessel wall.

Although the underlying mechanisms of these findings were not studied, one may speculate that the high WS gradients after PTA are not compensated for by smooth muscle cell migration, as in the control group, but rather by smooth muscle cell replication in the batimastat group.

### Limitations

Some systemic constrictive remodeling of the reference segment occurred, possibly induced by the discontinuation of the atherosclerotic diet during the follow-up period. Batimastat clearly abolished this constrictive remodeling effect.

Because the control group showed that acute lumen gain was an important factor in both the SS and WS normalization, the SS and WS in the batimastat group were also related to acute lumen gain. The distribution of data over the acute lumen gain values, however, was less homogeneous than in the control group. As a consequence, the power of the tests for detecting differences in the batimastat group was lower than in the control group.

We applied a steady-state, Newtonian fluid model in inelastic vessels in the present numerical analysis, whereas it is known that blood exerts non-Newtonian properties at low shear-rate values; the walls of blood vessels are elastic, and flow is pulsatile. Cho et al,[15] applying non-Newtonian fluid properties, showed from simulations that the SS was only slightly different from the simulations applying Newtonian fluid conditions. Furthermore, Perktold et al[16] showed that the effect of elasticity of the vessels in time-dependent flow on average SS is relatively small in the shear-rate range applied in the present study. It cannot be excluded, however, that the time-dependent flow conditions could change the local SS distribution, which could be the explanation of the unexplained noise in the prediction of vascular remodeling.

We applied the Laplace equation to calculate WS in our blood vessels. Because the external iliac arteries exhibited only small curvature, the 2D assumption seems justified. Tissue anisotropy and local spots of very high WS, however, are not accounted for in the present study. This may lead to an underestimation of the role of average WS in vascular remodeling.

In conclusion, constrictive vascular remodeling after PTA is controlled by an SS-negative and a WS–negative feedback mechanism aimed at keeping SS and WS constant. Reduction in vascular remodeling by administration of batimastat inhibited the WS control system but not the SS control mechanism.

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