Simvastatin Prevents Coronary Microvascular Remodeling in Renovascular Hypertensive Pigs

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Patients with hypertension and chronic kidney disease are at risk for cardiovascular diseases, possibly related to inflammation. Statins have beneficial anti-inflammatory effects on vascular structure regardless of cholesterol reduction. It was hypothesized that alterations in myocardial microvascular structure in swine renovascular hypertension (RVH) would be improved by simvastatin treatment. Three groups of pigs were studied after 12 wk: Normal (n = 7), RVH (n = 7), or RVH+simvastatin (RVH+S; 80 mg/d; n = 6). Left ventricular muscle mass and myocardial perfusion were determined in vivo using electron beam computed tomography, and myocardial samples then were scanned ex vivo using micro-computed tomography for measurement of the spatial density of myocardial microvessels (80 to 500 μm) in situ. Capillary density and myocardial expression of inflammatory and growth factors were determined in myocardial tissue. The effects of simvastatin on inflammation-induced tube formation were evaluated in vitro in human umbilical vein endothelial cells that were exposed to TNF-α. RVH and RVH+S had similarly increased arterial pressure and serum creatinine. However, left ventricular hypertrophy was prevented by simvastatin, and myocardial perfusion was increased. Compared with normal, RVH showed increased spatial density of microvessels (169.6 ± 21 versus 107.7 ± 15.2 vessels/cm²; P < 0.05), which was decreased in RVH+S (72.5 ± 14.9 vessels/cm²), whereas capillary density remained similar to normal. RVH also increased myocardial expression of inflammatory and growth factors, which were reversed by simvastatin. Furthermore, simvastatin attenuated TNF-α–induced angiogenesis in vitro. Simvastatin prevents myocardial microvascular remodeling and hypertrophy in experimental RVH independent of lipid lowering. This protective effect is partly mediated by blunted expression as well as angiogenic activity of inflammatory cytokines.


Patients with chronic kidney disease (CKD) and hypertension are at particularly high risk for cardiovascular diseases, characterized by cardiomyopathy and high prevalence of heart failure. The underlying mechanisms are not clear (1–3) but may be partly mediated by increased systemic and local inflammation in target organs (4). Microvascular remodeling and dysfunction often precede overt large-vessel injury in cardiovascular diseases and represents a strong, independent predictor of prognosis in hypertrophic cardiomyopathy (5). Microvascular remodeling, which may include remodeling of the wall; three-dimensional (3D) architecture; and spatial density of the arteries, arterioles, and capillaries, contributes critically to elevated peripheral resistance and complications of hypertension by interfering with blood supply and leading to ischemia. We previously demonstrated in pigs that renovascular hypertension (RVH) impairs coronary microvascular function (6). Indeed, CKD is often accompanied by hypertension, which may be partly responsible for its association with impaired coronary flow reserve and left ventricular (LV) dysfunction.

A number of large clinical trials have established the benefits of statins for the prevention of major cardiovascular events (7,8) and suggested that mechanisms of statins beyond lipid lowering are likely involved in the reduction of coronary events. Both in vivo and in vitro studies support the notion that statins counteract chronic subclinical vascular inflammation (9) and induce regression of cardiac myocyte hypertrophy (10). Statins exert anti-inflammatory actions through their ability to prevent the isoprenylation of members of the Rho family of small G proteins, resulting in functional inactivation of these G proteins (11). However, data on the effects of statins on patients with CKD are limited (12), and the efficacy of statin treatment to attenuate cardiac microvascular remodeling in RVH has not been fully explored.

The aim of this study was to test the hypothesis that cardiac remodeling in RVH, likely driven by inflammation, would be
attenuated by chronic simvastatin supplementation. Micro-computed tomography (μ-CT), a powerful imaging technique that permits assessment of the 3D pattern of the microvascular structure in situ (13), was used to evaluate 3D microvascular remodeling.

**Materials and Methods**

All protocols that used animals were approved by the Institutional Animal Care and Use Committee. Age- and body weight–matched female domestic pigs were studied after 12 wk of no intervention (normal; n = 7), RVH (n = 7), or RVH supplemented with simvastatin (RVH + S; Merck & Co., White House Station, NJ; 40 to 80 mg/d adjusted for body size, starting at induction of RVH; n = 6). We previously showed that simvastatin supplementation at this dosage, which is clinically efficacious in humans, was associated with pleiotropic effects in the swine in the absence of a decrease in lipid levels (14,15). Gradual development of unilateral renal artery stenosis was induced by placement of a local-irritant coil in the main renal artery at baseline in all RVH pigs, as described previously (6,16,17). The degree of stenosis was subsequently assessed by selective renal angiography as the decrease in luminal diameter (18). Mean arterial pressure was obtained by use of a PhysioTel telemetry system (Data Sciences International, St. Paul, MN) implanted at baseline in the left femoral artery (6,16).

After 12 wk of intervention, the pigs were anesthetized (ketamine 17.5 mg/kg per h and xylazine 2.3 mg/kg per h in saline), and a pigtail catheter was placed in the right atrium for contrast media injections during electron beam CT scanning. Blood samples were taken through the catheter, and serum creatinine, lipid profile (Roche, Nutley, NJ), and TNF-α (R&D System, Minneapolis, MN) levels were determined.

Pigs were then scanned by electron beam CT (Imatron C-150, South San Francisco, CA) during contrast injection. Cross-sections of the myocardium were harvested for in vitro studies.

**μ-CT Procedure**

Before μ-CT scanning, an intravascular microfil silicone rubber (MV-122; Flow Tech, Carver, MA) was perfused through a cannulated left anterior descending coronary artery at physiologic pressure closely matched to the pig’s BP, at a flow rate of 0.9 ml/min (6,20). The flow rate was measured in each experiment using the same size of syringe. A transmural portion of the LV anterior wall (approximately 2 × 1 × 1 cm) was then sectioned, prepared, and scanned at 0.49° angular increments, providing 721 views around 360°. Images were digitized for reconstruction of 3D volume images, which consisted of cubic voxels of 20 μm on a side, and were displayed at 40-μm cubic voxels for subsequent analysis (6,20).

Using the Analyze software package (Biomedical Imaging Resource, Mayo Clinic, Rochester, MN), the transmural myocardium was then tomographically divided into subepicardium (outer two thirds) and subendocardium (inner one third), as described previously (6,20). In each region, myocardial microvessels (diameters 80 to 500 μm) were counted in seven to 14 tomographic cross-sections by the Object Counting feature of the software, and their spatial density was calculated by dividing the vessel numbers by the cross-section area (20). Similarly, average microvascular diameter and vascular volume fraction (sum of all vessel cross-sectional area/total area of the region of interest) were calculated in each region (21). Vessels that were <80 μm (two voxels) in diameter were considered to be below the lower limit of spatial resolution and were not counted.

**Myocardial Tissue**

Myocardial inflammation was evaluated by protein expression of TNF-α, its downstream mediator NF-κB, the NF-κB inhibitor IκB, and monocyte chemoattractant protein-1 (MCP-1). Angiogenic factors were evaluated by the expression of vascular endothelial growth factor (VEGF), its receptor 2 (Flk-1), and its major regulator hypoxia inducible factor-1α (HIF-1α). Microvascular remodeling processes were assessed by the expression of tissue transglutaminase (tTG), RhoA, and α-smooth muscle actin (α-SMA), and myocardial fibrosis was assessed by trichrome staining and expression of TGF-β.

**Western Blotting**

A standard Western blotting protocol was used, as described previously (20). The antibodies used were against TNF-α, RhoA, NF-κB, IκB, TGF-β, VEGF, Flk-1, and HIF-1α (all 1:200; Santa Cruz Biotechnology, Santa Cruz, CA); tTG (1:200; Novus Biologic, Littleton, CO); and MCP-1 (1:500; BioVision, Mountain View, CA). β-Actin (1:1000; Sigma, St. Louis, MO) was used as the loading control.

**Histopathology**

Paraffin-embedded, 5-μm-thick sections were stained with hematoxylin and eosin or trichrome or exposed to antibodies against α-SMA (1:50; Dako, Glostrup, Denmark), following standard immunohisto logic protocols, as described previously (22). Cross-sections of the myocardium (one per animal) were examined using a computer-aided image-analysis program (MetaMorph, Meta Imaging System 4.6; Molecular Device Corp., Downingtown, PA). In each representative slide, microvessels with diameters between 80 and 500 μm were selected, perivascular trichrome (blue) was traced with the software, perivascular fibrosis was expressed as percentage of trichrome of field area, and the results from six to 10 vessels averaged (22). In addition, the microvascular media/lumen ratio was measured in α-SMA–positive microvessels (80 to 500 μm in diameter) with the aid of the same software (22). In hematoxylin and eosin sections under ×800 magnification, capillaries were identified as vessels at approximately 8 μm in diameter constituted of a single layer of endothelial cells; capillary density was then assessed as the ratio of capillaries to muscle fibers (23).

**Human Umbilical Vein Endothelial Cell Tube Formation**

To explore the mechanisms of the effects of simvastatin on inflammation-elicted microvessel formation, we performed in vitro experiments using cultured human umbilical vein endothelial cells (HUVEC) that were exposed to TNF-α, an important inflammatory cytokine, with and without co-incubation with simvastatin. The BD BioCoat angiogenesis system (BD Biosciences, Bedford, MA) was used to evaluate HUVEC tube formation. HUVEC (2 × 10⁴) were plated in each well and incubated at 37°C for 16 h with endothelial cell growth medium. HUVEC were studied after exposure to no additional intervention.
perfusion was selectively increased in RVH (Table 1). However, both subendocardial and subepicardial perfusion was increased by simvastatin (Table 1). These effects of simvastatin were independent of lipid lowering, because total cholesterol and LDL levels were similar among the three groups (Table 1).

**Effects of Simvastatin on Microvascular Remodeling in RVH**

Compared with normal pigs, RVH had significantly higher spatial density of transmural microvessels as assessed by µ-CT (169.6 ± 21 versus 107.7 ± 152 vessels/cm²; P < 0.05), which was normalized in RVH+S (72.5 ± 14.9 vessels/cm²). The increased density in RVH seemed to result from increased microvascular sprouting from small intramyocardial arteries (Table 1, Figure 1), which was observed only in subendocardial vessels that were smaller than 300 μm, and was normalized by simvastatin. It is interesting that the density of small subepicardial vessels in RVH hearts was not significantly increased compared with normal yet decreased after simvastatin treatment. Furthermore, capillary density (relative to myofibers) remained unchanged among the three groups, suggesting that the vascular changes were restricted to larger microvessels. In addition, RVH had increased vascular volume fraction, whereas tomographic intramyocardial microvascular diameter was not significantly changed (Table 1). Accordingly, the ex-

**Table 1. Lipid profile, MAP, and structural characteristics of myocardial microvessels in normal, RVH, and RVH+S pigs**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Normal (n = 7)</th>
<th>RVH (n = 7)</th>
<th>RVH+S (n = 6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum creatinine (mg/dl)</td>
<td>1.4 ± 0.1</td>
<td>1.9 ± 0.1b</td>
<td>1.8 ± 0.1b</td>
</tr>
<tr>
<td>Total cholesterol (mmol/L)</td>
<td>2.1 ± 0.2</td>
<td>2.2 ± 0.2</td>
<td>1.9 ± 0.1</td>
</tr>
<tr>
<td>LDL (mmol/L)</td>
<td>0.9 ± 0.1</td>
<td>1.1 ± 0.1</td>
<td>1.0 ± 0.1</td>
</tr>
<tr>
<td>TNF-α (pg/ml)</td>
<td>67.8 ± 4.5</td>
<td>134.9 ± 37.1b,c</td>
<td>63.1 ± 5.3</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>102.6 ± 1.6</td>
<td>140.9 ± 10.4b</td>
<td>137.6 ± 11.1b</td>
</tr>
<tr>
<td>Degree of stenosis (%)</td>
<td>-</td>
<td>70.9 ± 6.7b</td>
<td>66.2 ± 4.6b</td>
</tr>
<tr>
<td>LV muscle mass (g/kg body wt)</td>
<td>2.1 ± 0.1</td>
<td>2.7 ± 0.2b,c</td>
<td>2.1 ± 0.1</td>
</tr>
<tr>
<td>Myocardial perfusion (ml/min per g)</td>
<td>0.9 ± 0.1</td>
<td>0.9 ± 0.1c</td>
<td>1.4 ± 0.2b</td>
</tr>
<tr>
<td>subendocardial</td>
<td>0.84 ± 0.11</td>
<td>1.17 ± 0.08b,c</td>
<td>1.55 ± 0.18b</td>
</tr>
<tr>
<td>subepicardial</td>
<td>1.10 ± 0.14</td>
<td>0.85 ± 0.12c</td>
<td>1.41 ± 0.35</td>
</tr>
<tr>
<td>Spatial density (vessels/cm²)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>subendocardial (μm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤200</td>
<td>101.5 ± 7.3</td>
<td>188.9 ± 20.1b,c</td>
<td>74.1 ± 18.7</td>
</tr>
<tr>
<td>201 to 300</td>
<td>9.3 ± 3.6</td>
<td>20.2 ± 2.7b,c</td>
<td>7.4 ± 1.1</td>
</tr>
<tr>
<td>301 to 500</td>
<td>3.3 ± 0.8</td>
<td>4.5 ± 2.9</td>
<td>4.1 ± 0.8</td>
</tr>
<tr>
<td>subepicardial (μm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤200</td>
<td>89.3 ± 15.8</td>
<td>110.4 ± 12.5c</td>
<td>53.7 ± 8.2b</td>
</tr>
<tr>
<td>201 to 300</td>
<td>8.4 ± 2.1</td>
<td>12.3 ± 2.1c</td>
<td>3.4 ± 0.8b</td>
</tr>
<tr>
<td>301 to 500</td>
<td>3.5 ± 0.8</td>
<td>2.9 ± 1.7</td>
<td>2.2 ± 0.3</td>
</tr>
<tr>
<td>Capillary density (relative to myofibers)</td>
<td>0.28 ± 0.02</td>
<td>0.28 ± 0.01</td>
<td>0.32 ± 0.04</td>
</tr>
<tr>
<td>Vascular volume fraction (%)</td>
<td>2.5 ± 0.1</td>
<td>4.6 ± 0.7b,c</td>
<td>2.8 ± 0.3</td>
</tr>
<tr>
<td>Average microvascular diameter (μm)</td>
<td>141.3 ± 9.1</td>
<td>139.6 ± 5.7</td>
<td>145.4 ± 5.7</td>
</tr>
</tbody>
</table>

aLV, left ventricular; MAP, mean arterial pressure; RVH, pigs with renovascular hypertension; RVH+S, pigs that had RVH and were treated with simvastatin.

bP < 0.05 versus normal.

cP < 0.05 versus RVH+S.
expression of HIF-1α, an important regulator of VEGF, was increased in RVH, as was the expression of VEGF and its receptor Flk-1 (Figure 2), indicating angiogenic activity. All of these parameters were preserved in pigs that had RVH and received treatment with simvastatin.

**Simvastatin Inhibits Inflammation in Hypertensive Pigs**

The systemic levels and myocardial tissue expression of the inflammatory cytokine TNF-α were significantly increased in RVH, and both were attenuated by simvastatin (Table 1, Figure 3). NF-κB, the downstream mediator of TNF-α, was also activated, whereas the expression of its inhibitor IkB was decreased in RVH (Figure 3). Furthermore, RVH increased expression of MCP-1, suggesting inflammatory cell recruitment in the myocardi-um (Figure 3). All of these inflammatory changes were blunted by simvastatin treatment.

**Simvastatin Modulates Vascular Wall Remodeling Factors in the Hypertensive Heart**

Compared with normal, RVH increased expression of tTG and RhoA, which simvastatin normalized (Figure 3). RVH also exhibited greater microvascular media-to-lumen ratio (in vessels 80 to 500 μm in diameter), increased perivascular fibrosis, and increased TGF-β1 expression, which were also attenuated by simvastatin (Figures 2 and 4).

**Discussion**

This study demonstrates, for the first time, that simvastatin prevents myocardial microvascular remodeling in normocholesterolmic RVH by attenuating both the expression and angiogenic activity of inflammatory factors. The acute phase of adaptive cardiac growth during pressure overload is associated with coronary angiogenesis (26), which reflects in sprouting, branching, or lengthening of preexistent arterioles or capillaries. At the chronic and stable stage of LVH, microvascular density may reach a plateau (27), whereas at an advanced phase, it may decrease in parallel with decreased contractility (26). Our RVH pig model is at a phase of cardiac growth and therefore shows LVH accompanied by increased intramyocardial microvascular density, supporting the concept that adapted microvascular plasticity allows compensatory cardiac hypertrophy (28). The peripheral microcirculation often shows capillary rarefaction in hypertension, but our observation that RVH increased intramyocardial microvascular density is consistent with previous studies that showed increased myocardial arteriolar (6,29,30) or capillary (26,31) density in rat and mouse models of RVH. The slight variability in the size and the location of the affected cardiac vessels may be due to the different phase, animal, or hypertension models used in the different studies. In our model, density increased only in subendocardial vessels that were smaller than 300 μm, whereas capillary density remained unchanged. This was accompanied by increased basal perfusion in this region, although we previously demon-
strated that microvascular response to increased cardiac demand was impaired in RVH (6,19).

This study demonstrates that the increased density of small intramyocardial arteries in RVH was normalized by simvastatin and is underscored by previous studies that showed that statins inhibited angiogenesis that is induced by angiogenic growth factors (32,33) and advanced glycation end products (34). We previously demonstrated that simvastatin attenuates vasa vasorum neovascularization in the coronary artery wall in experimental hypercholesterolemia (35). This study further demonstrates that simvastatin blunted RVH-induced myocardial angiogenesis in association with attenuation of both myocardial and systemic inflammation. By preventing LVH, simvastatin might have decreased the stimulus for microvascular proliferation, but its ability to decrease tube formation in vitro that was induced in HUVEC by the inflammatory cytokine TNF-α indicates a direct effect of this drug on preventing inflammation-induced angiogenesis. The increased intramyocardial microvascular density in RVH was localized mainly in the subendocardium, possibly because of the unique sensitivity of this region to hypoxia (36). It is interesting that the decrease in vascular density after simvastatin treatment was also observed in the subepicardium. The significant increase in myocardial perfusion that was observed in RVH+S argues against an adverse effect of this decreased density on microvascular function. Indeed, the increased perfusion in the face of decreased vessel number supports the notion that the proliferating vessels in RVH are not fully functional, as we recently suggested (6). It is not unlikely that similar to vasa vasorum, new fragile microvessels in fact contribute to tissue injury and interstitial fibrosis (37) and that their pruning may be favorable.

In addition, simvastatin may improve vascular function and increase myocardial perfusion by upregulating endothelial nitric oxide synthase expression (14) and thereby nitric oxide availability.

The inhibitory effect of simvastatin on myocardial neovascularization in RVH might have been modulated via VEGF expression. Accordingly, both VEGF and its receptor Flk-1, the principal mediator of angiogenic and permeability-enhancing effects of VEGF (38), were increased in RVH and normalized by simvastatin treatment. VEGF expression is often regulated by the transcription factor HIF (39,40). We have shown that RVH leads to myocardial microvascular dysfunction (6,19,41) and thereby upregulation of HIF-1α, which may ultimately lead to microvascular angiogenesis. In hypercholesterolemic pigs, simvastatin improved coronary endothelial function (14) and myocardial perfusion (15). Hence, decreased neovascularization may have resulted from improved vascular function and decreased hypoxia. Furthermore, under normoxic conditions, TNF-α may also increase HIF and VEGF expression by activation of NF-κB (42). Indeed, HUVEC incubation with TNF-α increased VEGF expression, as well as tube formation, an effect that was also inhibited by simvastatin, indicating that simva-

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**Figure 4.** (Top) Trichrome staining (blue) showing perivascular fibrosis in RVH. (Middle) α-Smooth muscle actin staining (α-SMA). (Bottom) Quantification of interstitial fibrosis and media/lumen ratio from the trichrome and α-SMA staining, respectively, which both were decreased by simvastatin. *P < 0.05 versus normal. Magnification, ×20.
statin may attenuate angiogenesis by inhibiting inflammatory cytokine–induced VEGF expression.

Vascular remodeling in RVH also reflects in increased wall thickness of the intramyocardial microvessels. The beneficial effects of statins on microvascular remodeling in RVH may be due to multiple mechanisms, among which their anti-inflammatory effect may be a pivotal step. It has been shown that inflammatory cells infiltrate the cardiac tissue of renovascular hypertensive rats and induce cardiac and coronary fibrosis (43). Notably, this study shows in RVH increased myocardial expressions of TNF-α, NF-κB, and MCP-1, which are important inflammatory factors. TNF-α directly induces angiogenesis (24,44), activates the endothelium, and increases the expression of adhesion molecules and chemokines (45), including MCP-1, the major regulator of macrophage recruitment that in turn can also promote angiogenesis (46). The increased expression of NF-κB and decreased IκB in RVH further confirmed activation of inflammatory signal transduction downstream to TNF-α. Furthermore, MCP-1 may in turn participate in instigation of myocardial fibrosis by upregulating TGF-β expression and fibroblast proliferation in the perivascular space (47). Simvastatin decreased both the systemic levels and myocardial expression of TNF-α, NF-κB. Indeed, the ability of simvastatin to attenuate MCP-1 expression may have been responsible for the decrease in TGF-β expression that was observed in this study. Moreover, we observed that simvastatin attenuated TNF-α-stimulated HUVEC tube formation, suggesting that simvastatin inhibits not only the expression but also the angiogenic activity of TNF-α.

Simvastatin may have also attenuated myocardial microvascular remodeling by downregulation of tTG expression. It has been shown that tTG increased inward remodeling of small arteries both in vivo and in vitro and that its activity was dependent on pressure (48). In RVH, a change in the pattern of shear stress may decrease nitric oxide production, increase vasomotor tone, and enhance tTG binding to integrins, leading to activation of RhoA/Rho-associated coiled-coil forming protein kinase. Similarly, RVH-related increase in intracellular calcium provides additional activation of tTG, which in turn activates the RhoA/Rho-associated coiled-coil forming protein kinase pathway. It was shown recently that RhoA/protein kinase–dependent activation of NF-κB stimulates adhesion molecular expression in endothelial cells (49), establishing RhoA as signal mediator that contributes to vascular inflammation. It is interesting that this study suggests that statins may inhibit this process by decreasing expression of tTG and RhoA. In hypertensive patients, greater media-to-lumen ratio of subcutaneous small arteries (50) was significantly associated with the occurrence of cardiovascular events (51). Their improvement in our study may therefore suggest that statins might be beneficial for the outcomes of hypertension.
In addition to the heart, we previously demonstrated that simvastatin improved single-kidney perfusion and GFR in the ischemic kidney in RVH, although serum creatinine remained elevated (52), possibly as a result of lingering renal injury. However, it is yet unclear whether statins would be of benefit in patients with CKD, because the Die Deutsche Diabetes-Dialyse Study (4D) study showed that atorvastatin had no significant effect on the composite primary end point of cardiovascular events in patients who had diabetes and received hemodialysis (12), and the results of A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events (AURORA) (53) and Study of Heart and Renal Protection (SHARP) (54) are yet unavailable. Nevertheless, because simvastatin preserved myocardial microvascular architecture and prevented LVH, our study suggests that statins may improve cardiac outcome in RVH.

Notably, our study is limited by the use of relatively young animals that may have been more sensitive to the effect of hypertension (55) and statins on vascular development. Furthermore, changes in small resistance arterioles under 80 μm in size were not fully addressed by our method and could account for some of the discrepancies with other studies. In addition, simvastatin was added at the time of induction of RVH, and its effects were therefore more in prevention than reversal of microvascular injury. The effects of TNF-α on angiogenesis may also vary with different experimental conditions and TNF-α levels (56).

Conclusion

We observed that simvastatin prevents intramyocardial microvascular remodeling and LVH in experimental RVH, partly by blunting expression as well as angiogenic activity of inflammatory cytokines. This study therefore suggests that statins may improve cardiac outcomes in RVH.

Acknowledgments

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Disclosures

None.

References


