Impact of coronary vasa vasorum functional structure on coronary vessel wall perfusion distribution

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Gössl, M., N. M. Malyar, M. Rosol, P. E. Beighley, and E. L. Ritman. Impact of coronary vasa vasorum functional structure on coronary vessel wall perfusion distribution. Am J Physiol Heart Circ Physiol 285: H2019–H2026, 2003.—Noncoronary vasa vasorum have been described as networks of microvessels in the wall of arteries and veins. However, we have shown, using microcomputerized tomography (micro-CT) imaging methods, that porcine coronary vasa vasorum have a tree-like branching structure similar to the vasculature in general. In this study, we elucidate functional aspects of coronary vasa vasorum perfusion territories. Three pig hearts were injected with radiopaque Microfil via the coronary sinus to fill the left anterior descending coronary arteries (LADs) retrogradely at atmospheric pressure. In three other hearts, LADs were injected antegradely at 100-mmHg pressure via the left main carotid artery. Additionally, six LADs were injected in vivo with a suspension of 100- or 300-μm-diameter microspheres before harvesting of the hearts and injection of the LADs with Microfil. All harvested LADs were scanned intact with micro-CT (20 μm cubic voxels). The spatial density of vasa vasorum (no. of vasa/mm2) was measured in 20-μm-thick cross sections (at 0.4-mm intervals). Retrogradely injected LADs showed high and uniformly distributed vasa vasorum densities in the adventitia (means ± SE; 5.38 ± 0.09 vs. 3.58 ± 0.1 vasa/mm2 in antegrade prepared LADs; P < 0.001). Antegrade preparation of LADs showed patchy distribution, low-vasa-vasorum-density territories especially on the myocardial side of the coronary artery wall (epicardial density: 4.29 ± 0.13 vasa/mm2 vs. myocardial density: 2.80 ± 0.1 vasa/mm2, P < 0.001). Microembolization reduced vasa vasorum densities significantly (100-μm-diameter microspheres: 3.26 ± 0.07 vasa/mm2, P < 0.05; 300-μm-diameter microspheres: 2.66 ± 0.07 vasa/mm2, P < 0.001 vs. antegrade controls) and increased the size of low-vasa-vasorum-density territories. We conclude that coronary vasa vasorum are functional endarteries not connected via a plexus. This characteristic may have a significant impact on the spatial distribution of perfusion and drainage of the coronary vessel wall.

Intraluminal coronary artery pressure; microembolization; microcomputerized tomography

Vasa vasorum have been described as a “network” or “plexus” of microvessels located in the vessel wall of arteries and veins responsible for nutrient supply to and drainage from the vessel wall (2, 9, 21, 24, 25). A recent study by our group (5) using microcomputerized tomography (micro-CT) showed, however, that the general structure of coronary vasa vasorum is “treelike,” consistent with endarteries. Furthermore, we could show that despite the constrained topology of the space in which they proliferate, the hemodynamic characteristics of coronary vasa vasorum are surprisingly similar to that of the vasculature in general. Although several investigators (6, 14, 17) have shown that blood flow in vasa vasorum can be regulated by different vasoactive agents such as adenosine, endothelin-1, or acetylcholine, the question as to whether vasa vasorum function as networks or endarteries has not been resolved. Both structures (network or endartery) have different implications as to the perfusion of the coronary vessel wall. A network can maintain perfusion more easily by virtue of shunting and retrograde perfusion, whereas the occlusion of a proximal endartery branch will stop perfusion of all distal branches. However, even if there is an anatomic plexus of vasa vasorum, local occlusion of that network by the compressive forces inside the coronary artery wall could make the vasa vasorum functionally endarteries.

Hence, the present study was designed to investigate the functional branching structure of vasa vasorum through the impact on their perfusion in two different conditions of coronary artery wall compressive forces relative to the perfusion pressure within the vasa vasorum. The first condition studied was experimental microembolization. The occlusion of proximal segments of a vasa vasorum structure may indicate which functional structure is predominant. If it was the network or plexus, then the occlusion of a single proximal segment should not have much impact on the perfusion of more distally located vasa vasorum segments. If, however, the vasa vasorum were endarteries, the impact would be significant, because none of the more distal vasa vasorum segments would be perfused. The second condition studied was a change of coronary artery intramural pressure. The intraluminal coronary artery pressure produces compressive forces inside the coronary artery wall [Lame’s Law (3)] and thus may occlude those distal vasa vasorum segments that have

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reduced intraluminal pressure due to resistive forces [Poiseuille’s Law (22)] compared with the compressive forces surrounding them.

METHODS

Animal Studies and Specimen Acquisition

All animal studies were approved by the Mayo Foundation’s Institutional Animal Care and Use Committee. Twelve female, juvenile, domestic, cross-bred swine (31–42 kg body wt) were fed normal laboratory chow for 3 mo. Six animals were divided into two equal groups: group a received in vivo injections of suspensions of 300-μm-diameter, nonradioactive microspheres (2 × 10^2 microspheres), and group b received injections of 100-μm-diameter microspheres (5 × 10^3 microspheres). Swine were anesthetized, intubated, and ventilated with room air as described previously (10). Under sterile conditions, the neck was dissected on the left side, and the left jugular vein and carotid artery were isolated. A catheter was positioned in the left anterior descending coronary artery (LAD) between the first and second septal branch (monitored by fluoroscopy). Finally, intracoronary injections of the different amounts of microspheres were performed (Fig. 1). Microspheres were prepared as described previously (16). Electrodes on the limbs were used to monitor the electrocardiogram.

The results of our previous study (5) showed that there are two types of arterial vasorum in the porcine coronary artery wall: vasa vasorum externa (VVE) and vasa vasorum interna (VVI). The average diameter of a major LAD branch that leads to a VVE origin is 0.191 ± 0.147 mm, and the average diameter of a VVI origin is 0.054 ± 0.063 mm (5). Accordingly, we chose 100- and 300-μm-diameter microspheres for this study.

An additional six swine served as controls. Microembolized and control animals were euthanized with a weight-adjusted intravenous injection of Sleepaway (Fort Dodge Laboratories; Fort Dodge, IA). After the heart was harvested, we used two different preparation techniques as follows.

Preparation 1. In the six microembolized and three control hearts, we cannulated the LAD ostium with 2-mm-diameter plastic cannulas. To clear the coronary network of blood, we then infused 60 ml of heparinized saline (0.9% sodium chloride with 10,000 units heparin) via an automated injector at a nominal pressure of 100 mmHg. Next, we infused a radiopaque, lead-containing, liquid, low-viscosity polymer (Microfil MV-122, Flow Tech; Carver, MA). This infusion (at 100 mmHg) was continued until the compound flowed freely from the coronary sinus.

Preparation 2. In the three remaining control hearts, we infused Microfil via the coronary sinus so as to fill the LAD retrogradely, but without the high intra-arterial pressure. This involved filling the ventricles and atria with low-melting point paraffin (to prevent leakage of Microfil through arteriovenous shunts like the Thebesian veins (23)) and suturing all openings that were produced by the harvesting process to maintain pressure in the venous system. By infusing the polymer retrogradely, the low pressure (open to atmosphere) inside the LAD lumen prevented the compression of vasa vasorum within the coronary vessel wall.

The hearts were immersed in 10% neutral buffered formalin and placed in refrigeration at 4°C overnight to allow polymerization of the compound. On the following day, the intact epicardial coronary arteries and concomitant veins were removed from the heart with a margin of at least 1 cm on each side of the artery, well outside the adventitia. The specimens were then placed in a 75% alcohol solution. At 15-min intervals, the alcohol concentration was changed to 85%, 95%, and absolute alcohol to dehydrate the tissue. The coronaries were encased in paraffin wax for micro-CT scanning and three-dimensional (3-D) reconstruction.

Microscopic 3-D CT Reconstruction

Specimens up to 10 cm long were scanned intact by a micro-CT system consisting of a spectroscopy X-ray tube, a fluorescent crystal plate, a microscopic objective, and a charge-coupled device (CCD) camera (8). To preserve the connectivity of the vasa vasorum, the arteries were scanned in 2-cm increments along the coronary artery luminal axis (i.e., without cutting the 6- to 10-cm-long coronary artery into pieces). The resulting 3-D images were displayed using image analysis software (Analyze 4.0, Biomedical Imaging Resource, Mayo Clinic, Rochester, MN). Computer-generated displays were generated at different angles of view and gray scale values of voxels. For this study, the micro-CT scanner was configured so that the dimension of the cubic voxels was 20 μm (16-bit gray scale).

Delineating the Coronary Vessel Wall and Quantitative Morphometric Analyses

After the arteries had been scanned with micro-CT, we obtained histological cross sections (Lawson’s Elastic Van Gieson staining) from all arteries (1 cross section every 2 cm) and took digitized microscopic photographs. On these images, we measured the circumferences (C) of 1) the lumen, 2) the interface of media and adventitia (i.e., the outer elastic membrane), and 3) the outer surface of the adventitia using Analyze software. Next, we calculated the radius \( r = C/(2\pi) \) for each of these three parameters. The ratio of the radii (denominator was the lumen radius) gave us the scale factor.
for the transfer of these radii onto the corresponding micro-CT cross section. We used matching anatomic markers in both the histological section and micro-CT cross section to assure the correct correspondence of the micro-CT image to the histological image. For those micro-CT cross sections between the histological sections, we used the subtle intensity difference in the micro-CT image (appearing as a "halo"), which matched well with the calculated interface of the adventitia and the surrounding fat tissue. This finding provided us with the opportunity to determine and measure the coronary artery wall (including the intima + media and adventitia) in every single micro-CT cross section we analyzed without obtaining histology for each of them (5).

The spatial "density" of the vasa in the wall was obtained by manually counting the number of vasa per 20-μm-thick cross-section divided by the total cross-sectional area (no. of vasa/mm²) of vessel wall depicted in the tomographic image. That way, vasa vasorum were counted in cross sections spaced at 0.4-mm intervals along the LAD segments distal to the microsphere injection site and in corresponding control segments. Branching points were excluded from the analysis. In summary, a total of 1,511 cross sections (i.e., 137 ± 30 cross sections/specimen) was included in the analysis.

The differentiation of arterial and venous vasa vasorum was done by using the 3-D information of the micro-CT data set as described earlier (5). In brief, if the vasa vasorum could be connected to the main lumen (VVI) or to a major branch (VVE), they were considered arterial. In contrast, if they could be connected to a concomitant vein, they were considered venous vasa vasorum.

Subdivision of the Vessel Wall into Epicardial and Myocardial Quadrants

To calculate the distribution of vasa vasorum densities throughout the vessel wall, we subdivided the delineated vessel wall into four quadrants (epicardial left (Epi-L), epicardial right (Epi-R), myocardial left (Myo-L), and myocardial right (Myo-R)). This subdivision was done in every cross section analyzed (see illustration for subdivision in Fig. 4).

Statistical Analysis

All data are presented as means ± SE for all arteries. One-way ANOVA, followed by a Tukey-Kramer post hoc test with correction for multiple comparisons, was used to identify the statistical differences among groups. Individual group comparisons were performed by an unpaired Student t-test. P < 0.05 was considered significant in all analyses.

RESULTS

Densities and Spatial Distribution of Perfused Coronary Vasa Vasorum

Impact of microembolization. In vivo microembolization with 100- or 300-μm-diameter microspheres decreased the spatial density of coronary vasa vasorum significantly (Table 1 and Fig. 2). The overall decrease in vasa vasorum density after 300-μm-microsphere microembolization was significantly higher than that with the 100-μm-diameter microsphere microembolization (Table 1 and Figs. 2 and 3). Figure 3 shows the impact of the different-sized microspheres on each of the four vessel wall quadrants alone (subdivision of coronary vessel wall in quadrants is illustrated in Fig. 4). Microembolization with 300-μm-diameter microspheres decreased the density of vasa vasorum in all four quadrants of the vessel wall significantly. Microembolization with 100-μm-diameter microspheres decreased only the vasa vasorum density in the epicardial quadrants significantly.

Furthermore, Fig. 3 shows that in antegrade (physiologically) prepared LADs, the epicardial side of the vessel wall (Epi-L plus Epi-R) showed consistently higher vasa vasorum densities than the myocardial side (Myo-L plus Myo-R, P < 0.001). A subanalysis in these arteries (Fig. 5) with exact differentiation of venous and arterial vasa vasorum demonstrated that only venous vasa vasorum showed significantly higher spatial densities on the epicardial than on the myocardial side of the coronary artery wall. Arterial vasa vasorum, however, were distributed equally between the two sides of the coronary vessel wall.

Figure 4 shows the displays of spatial vasa vasorum densities in all four quadrants of the coronary vessel wall, referenced to the endothelial surface. The spatial distribution of vasa vasorum densities in each vessel wall quadrant along the coronary artery is encoded in gray scale. Control LADs infused antegrade at a physiological pressure of 100 mmHg showed a patchy distribution of low-vasa-vasorum-density territories (indicated by black areas). Consistent with the above-mentioned average vasa vasorum densities (Fig. 3), these low-density territories were preferentially located on the myocardial side (Myo-L and Myo-R) of the arterial wall. In addition, as shown in Fig. 4 with

Table 1. Quantitative results of computerized digital micro-CT image analysis

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<th>Control Segments</th>
<th>Embolized Segments</th>
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<td></td>
<td>Antegrade</td>
<td>Retrograde</td>
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<tr>
<td>n</td>
<td>364</td>
<td>429</td>
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<tr>
<td>Lumen radius, mm</td>
<td>0.85 ± 0.01</td>
<td>0.51 ± 0.02</td>
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<tr>
<td>Vessel wall area, mm²</td>
<td>2.87 ± 0.06</td>
<td>3.22 ± 0.07?</td>
</tr>
<tr>
<td>&quot;Spatial&quot; density of vasa vasorum (entire coronary vessel wall, vasa/mm²)</td>
<td>3.58 ± 0.1</td>
<td>5.38 ± 0.09°</td>
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<tr>
<td>Vasa vasorum diameter, mm</td>
<td>0.056 ± 0.001</td>
<td>0.069 ± 0.001‡</td>
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Data are means ± SE; n, no. of cross sections analyzed. micro-CT, microcomputed tomography. *P < 0.001, †P < 0.01, and ‡P < 0.05 vs. control antegrade injected segments; §P < 0.01 vs. 100-μm-diameter microsphere-embolized segments.
representative examples, microembolization with 100- and 300-μm-diameter microspheres increased the size of those patchy distributed low-density territories significantly [antegrade controls: 4.99 ± 1.78 mm²; 100-μm-diameter microspheres: 11.26 ± 1.82 mm² ($P < 0.05$ vs. controls); 300-μm-diameter microspheres: 18.09 ± 1.94 mm² ($P < 0.001$ vs. controls and $P < 0.05$ vs. 100-μm-diameter microspheres)].

**Impact of change in coronary artery intramural pressure.** Figure 4 also shows that, in contrast to antegrade (i.e., with 100-mmHg intraluminal coronary artery pressure) prepared LADs, retrogradely perfused LADs (i.e., with intraluminal coronary artery pressure open to atmosphere) showed fewer, relatively small, patchy distributed low-vasa-vasorum-density territories [1.65 ± 0.39 mm² ($P < 0.001$ vs. antegrade controls)]. Consistently, under atmospheric intraluminal pressure, the average spatial density of coronary vasa vasorum was significantly higher in all coronary artery vessel wall quadrants (Fig. 3 and Table 1) and there was no significant difference between the epicardial and myocardial quadrants (5.5 ± 0.3 vs. 5.2 ± 0.3 vasa/mm², not significant). The vasa vasorum diameter increased ~23% compared with antegradely prepared coronary arteries (Table 1).

**DISCUSSION**

3-D micro-CT imaging offers the particular important capability to conveniently analyze large 3-D volumes of coronary arteries without the need for physical sectioning, thus preserving the continuity of the vascular structures. It allows quantification of the vasa vasorum without the need to prepare hundreds of time- and cost-intensive histological sections (not to mention the technical difficulties in preventing distortion, accurate section-to-section registration, and visualization of the presence of vasa vasorum in histology). Hence,
we could precisely calculate vasa vasorum densities in more than 1,500 digital cross sections and reference them to the endothelial surface of the host vessel. In the present study, the micro-CT scanner was configured to generate 20 µm/side cubic voxels so as to maximize the intact volume that could be scanned while maintaining a reasonable spatial resolution. Consequently, the 20-µm voxel size of our 3-D micro-CT data limited the diameter of vessels that could be visualized, so that there are possibly smaller vasa vasorum inside the media or adventitia that were not resolvable in our micro-CT images.

Several investigators (2, 9, 21, 24, 25) have described the vasa vasorum as a network or plexus of microvessels in the wall of arteries, although these results were based on observations in the presence of vascular disease. The results of the present study in normal porcine coronary arteries, however, provide evidence that coronary vasa vasorum are functional endarteries rather than a functional network or plexus. An endartery, by definition, is not connected to other vessels’ perfusion territories, in contrast to a network or plexus, where different vessels’ perfusion territories may communicate, both antegrade and retrograde, with each other. Hence, the occlusion of a segment that is part of a network still allows perfusion of more distally located segments by virtue of redirected flow in the network. The compression or occlusion of a proximal segment of an endartery, however, leads to a stop of perfusion of the more distal segments of the endartery. It is important to know which of the two possibilities is predominant in coronary vasa vasorum to un-

Fig. 4. Display of vasa vasorum densities (arterial and venous vasa vasorum in the vessel wall of the LAD) in all four vessel wall quadrants, referenced to the endothelial surface, shown in representative examples of an antegrade control LAD (data from 128 cross sections at 0.4-mm intervals), a 100-µm-diameter microsphere-embolized artery (117 cross sections), a 300-µm-diameter microsphere-embolized artery (155 cross sections), and a retrogradely infused control LAD (101 cross sections). The densities of vasa vasorum are encoded in grayscale. This display shows the presence of a patchy distribution of low-vasa-vasorum-density territories (black) in the antegrade control. These low-density territories enlarge after 100- and 300-µm-diameter microsphere injections (+48% and +61%, respectively). The retrograde control shows almost no low-vasa-vasorum-density territories (−92%).
understand how far disturbances in their structure can impact on the perfusion of the coronary vessel wall.

We demonstrated a feasible method for the retrograde, minimal pressure filling of a coronary artery. This method essentially eliminates the pressure gradient within the arterial wall. In conjunction with the method of antegrade (physiological) filling, these two experiments allowed us to analyze the impact of the intraluminal coronary artery pressure alone and hence the different intramural compressive forces (radial stress) on the distribution and diameter of vasa vasorum inside the coronary artery vessel wall.

We deduced from the increase in vasa vasorum diameters (>23%) under atmospheric intraluminal coronary artery pressure that the compressive forces inside the coronary artery wall have significant impact on flow through the vasa vasorum. The results show, furthermore, that a physiological coronary arterial intraluminal pressure (100 mmHg) by virtue of compressive forces in the arterial wall leads to a significant decrease in the number of perfused vasa vasorum (Fig. 3) and a patchy distribution of low-vasa-vasorum-density territories (Fig. 4). If vasa vasorum are a network or plexus, as postulated by several investigators, the compression of segments of that network should be compensated by redirected flow through the multiple connections of the network. However, the patchy distribution of the low-density territories (Fig. 4) strongly indicates that vasa vasorum are functional endarteries with a treelike branching structure, consistent with our earlier findings (5). Hence, the compression of proximal segments of the treelike structure leads to nonperfused, distal tree segments, creating patchy distributed low-vasa-vasorum-density territories. In contrast, under a minimal (atmospheric) coronary arterial intraluminal pressure (i.e., minimal intramural compressive forces after retrograde perfusion), there were only a few, small low-density territories in the coronary artery wall (Fig. 4), and the number of perfused vasa vasorum is significantly higher (Fig. 3). These findings have two implications: 1) that the reduced compressive forces within the arterial wall only compress the very distal vasa vasorum branches or 2) that a few small regions within the coronary vessel wall contain no vasa vasorum at all.

Our results are based on static data, and this is a possible limitation in that oscillating changes of vasa vasorum intraluminal pressure may log the phase of the compressive forces inside the coronary artery wall. The high number of vasa vasorum filled under minimal coronary arterial intraluminal pressure (i.e., retrograde filling of the LAD; Fig. 3) may indicate that during certain time points within the cardiac cycle, those vessels might be recruitable as well. Another possible limitation may be seen in the number of animals studied, but because the intragroup variability was statistically insignificant, we are confident that our results are representative.

More evidence for vasa vasorum being functional endarteries can be deducted from our microembolization experiments. Microembolization, by virtue of occlusion of proximal vasa vasorum segments, decreased the number of perfused arterial vasa vasorum (Figs. 2 and 3) and increased the size of patchy distributed low-vasa-vasorum-density territories in the coronary artery wall (Fig. 4). If vasa vasorum form a functional plexus, the occlusion of some proximal segments of the vasa vasorum by microemboli should be compensated for by redirected flow within the network. The probability for a high number of interconnecting branches in a network being embolized and causing the same or even higher impact on vessel wall perfusion is negligible and, moreover, not consistent with our earlier, detailed analysis of the anatomic structure of porcine coronary vasa vasorum (5). The number of vasa vasorum perfused (Fig. 3), and hence the size of low-vasa-vasorum-density territories (Fig. 4, black areas), is conceivably dependent on the hierarchical location of the occlusion within the tree structure, as indicated by the use of different-sized microspheres in our experi-

**Fig. 5.** Spatial density of venous and arterial porcine coronary vasa vasorum. Only venous vasa vasorum show a significant difference in density between the myocardial and epicardial sides of the coronary vessel wall. Arterial vasa vasorum are uniformly distributed. *P < 0.001.
ments. Coronary microembolization with 300-μm-diameter microspheres had a significantly higher impact than that with 100-μm-diameter microspheres because 300-μm-diameter microspheres occlude more proximal branches of the vasa vasorum tree structure, which leaves all hierarchically more distal-located vasa vasorum segments nonperfused, or they even occlude major LAD branches, which leaves complete vasa vasorum trees nonperfused (as we have shown earlier (5), LAD branches feed the majority of arterial vasa vasorum).

Our subanalysis with differentiation of venous and arterial vasa vasorum (Fig. 5), by virtue of their connection to either an artery or vein, shows that especially the perfusion of venous vasa vasorum on the myocardial side of the coronary vessel wall is altered under physiological intraluminal pressure. The consistently lower vasa vasorum densities on the myocardial side of the coronary arteries (in physiologically antegrade) perfused LADs; Fig. 3) suggest a possible relationship to plaque formation predominant on the myocardial side of coronary arteries (7, 15, 19). Future studies will need to be performed to determine whether the distribution of low-vasa-vasorum-density territories precisely correlates with early, patchy, atherosclerotic changes in the coronary artery wall (11). Nonetheless, Nakata et al. (13) showed in rats that the obstruction of the venous side of aortic vasa vasorum causes atherosclerotic lesions. In conjunction with the “response to retention” model, as recently proposed by Skalen et al. (18), the results of Nakata et al.’s study and the present study emphasize the need to further explore the relative role of supply to, and drainage from, the coronary vessel wall in disease.

Finally, experimental microembolization does not only help us to define the functional structure of vasa vasorum, it is, moreover, a model worth pursuing because it shows the immediate impact of disturbances within the coronary artery’s microcirculation on the perfusion of its vessel wall. Earlier experimental studies (1, 12, 13) on various animal arteries (not coronary arteries) have shown that the impairment of nutrient flow through the vasa vasorum leads to atherosclerotic lesions. Moreover, as others (4, 20) have shown that coronary microembolization leads to an increased myocardial inflammatory response, which is associated with a progressive contractile dysfunction, it seems plausible that microembolization of coronary vasa vasorum may also induce microinflammation in the coronary vessel wall. This possibility, however, has to be tested in further chronic experiments before any stronger conclusions of the role of microembolization in coronary atherosclerosis can be drawn. Nonetheless, knowing the functional structure of vasa vasorum may elucidate their role in determining the size and location of atherosclerotic lesions.

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DISCLOSURES

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REFERENCES


