A Physical Model for the Formation of Evaginations:
A Prospective Precursor to the Creation of Saccular Aneurysms*

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SUMMARY The actual spatial geometry of separate regions of normal and enlarged fenestrations from the internal elastic lamina of human cerebral arteries have been replicated in sheets of latex rubber from scanning electron microscope (SEM) photomicrographs. Geometrical models which assume a constant diameter for the fenestrations, a constant ligament efficiency for the regions of fenestrations and a uniform array of rows and columns have also been created in sheets of latex rubber. The stress (load per unit of cross-sectional area) and strain (percent elongation) were computed for each of the samples during uniaxial stretching. The elongation of the sample representing the region of enlarged fenestrations increased an average of 47% compared to the similar representation of normal fenestrations, at the same increments of stress. This suggests that regions of enlarged fenestrations would form a bulge, indicative of an evagination of the internal elastic lamina.

The model configurations demonstrate very similar stress/strain characteristics to the replications. This finding justified the use of the modelling technique using equivalent ligament efficiencies, to represent the actual spatial geometry. During elongation, the average area of the enlarged fenestrations increased at a rate which was an order of magnitude greater than the normal fenestrations. Since a number of observations associated with the development of intracranial saccular aneurysms can be correlated to a region of enlarged fenestrations, the region of enlarged fenestrations may be a defect in the internal elastic lamina which could play a prominent role in the development of intracranial saccular aneurysms.

DESPITE CONSIDERABLE RESEARCH on the etiology of intracranial saccular aneurysms, the mechanism for their creation remains unresolved. At present, there are two main theories about their etiology, viz., congenital defects and developmental defects. Consideration of the factors which invalidate the congenital theory are extensively discussed by Stehbens.3-2 The current evidence strongly supports the degenerative theory of development.

Many factors may cause degeneration of the arterial wall. Medial gaps alone, representing a loci minoris resistentiae, were first described by Forbus and suggested to be a predisposing factor for aneurysm formation. This has been since repudiated by a number of authors.3-5-7 Sahs observed that "when this area (medial gap) was bridged by an intact elastic membrane, no bulge was found."

Stehbens has identified three early changes related to the development of saccular aneurysms: i) areas of thinning; ii) funnel-shaped dilatations; and iii) microscopic evaginations. Areas of thinning was characterized by "... gross thinning of the wall accompanied by extensive loss of elastic tissue and thinning of the media and adventitia." Histologically, funnel-shaped dilatations have a markedly attenuated wall, slight intimal thickening, gross deficiency of the internal elastic lamina and thinning of the media and elastica. The micro-evaginations are essentially small bulges of the luminal surface (including the internal elastic lamina) into the wall of the media. Stehbens commented that one micro-evagination "... exhibited a fragmented elastic lamina, with a small mural thrombus and fibrin and red-cell infiltration of the wall." Sahs attached considerable importance to the evagination, commenting "... they (small outpouchings) may be the precursor of saccular aneurysms." A further observation was that the elastic layer had undergone conspicuous fragmentation and that further fragmentation would result in widening, which may progress to a recognized saccular aneurysm. The significance of fragmentation of the internal elastic lamina during the formation of saccular aneurysms has also been mentioned by other investigators.8-9

The internal elastic lamina of human cerebral arteries has been described as a fenestrated sheet.3-10-11 Regions of enlarged fenestrations in the apical region of cerebral arterial bifurcations have been observed by ourselves,11 as well as by Merei and Gallyas.9 The regions of enlarged fenestrations were more prevalent in the apical region of bifurcations (46% of specimens examined) than straight segments (6% of specimens examined). We have also deduced that serial sections (typically 4-7 µm thick), which are cut through areas of enlarged fenestrations with an average diameter of 7 µm,11 would appear fragmented since regions of enlarged fenestrations in the internal elastic lamina would appear as numerous gaps with intervening bands of elastin, while the adjacent regions with normal fenestrations (diameter 2.1 µm) would resemble a solid sheet. It is significant that enlarged fenestrations have been reported at the mouth of saccular aneurysms.8,12

Since it could be logically concluded that regions of enlarged fenestrations may stretch more readily than the adjacent areas of normal fenestrations, the regions of enlarged fenestrations could transform into a micro-evagination. In this communication it is our intention...
to analyze the tensile properties, as well as the spatial geometry, for regions of normal and enlarged fenestrations with the use of perforated latex models.

Method

Since the internal elastic lamina is buried within the arterial wall, isolation of the desired region of the internal elastic lamina, in a form suitable for mechanical testing is at present impractical. Most existing methods of isolation require the application of excessive heat (50°C or greater) which might cause irreversible protein damage that could influence the mechanical characteristics of the tissue, but this has not been confirmed to our knowledge. The technical difficulties in handling such a thin, fragile tissue along with the lack of an appropriate testing procedure have necessitated consideration of an alternative technique. The technique to be presented here, entails replicating the image of the actual fenestrations (both normal and enlarged) from a photomicrograph in a latex rubber sheet, followed by uniaxial tensile stretching.

Part A — Geometrical Parameters

Photomicrographs obtained with the scanning electron microscope for regions of normal and enlarged fenestrations from the same specimen, are illustrated in figure 1. The specimen is a bifurcation from the anterior circulation of a 50-year old female, obtained at autopsy. The procedure for isolating the internal elastic lamina from the arterial wall has been described elsewhere and will not be repeated here. An analysis of the shrinkage during preparation of cylindrical specimens and of bifurcations (unpublished) has revealed a linear shrinkage of only 6.9%. Since the intent of this study was to compare the relative tensile properties, the geometric characteristics reported subsequently for both the normal and enlarged fenestrations have not been corrected for the shrinkage.

The negative for each photomicrograph was mounted in an enlarger and the image projected on the platen of a Hewlett Packard digitizer (model 9864A) interfaced with a Hewlett Packard 9830A microcomputer. Both images in figure 1 represent the same final magnification of 2250.

Since the fenestrations are generally round or elliptical in shape, two sets of two points each, which represented the lengths of the major and minor axes for the inside border of each fenestration, were digitized and entered into the microcomputer for further processing and storage. Only fenestrations which appeared to pass completely through the internal elastic lamina were measured. The area for each fenestration was computed with the use of the equation for an ellipse.

Four geometric characteristics were computed:

i) Diameter. The diameter of a circle with an area equivalent to the ellipse.

ii) Density. The number of fenestrations per square millimeter.

iii) Percentage Area. Proportional surface area of all fenestrations with respect to the total area of the field of view (expressed as percentage), for the photomicrograph.

iv) Ligament Efficiency. The minimum width of a solid band of material divided by the centre-to-centre distance between two or a series of adjacent holes. A high value for ligament efficiency (values are between 0 and 1) indicates the combination of small holes with substantial centre-to-centre distances, while a lower value represents larger holes and/or the distance between the holes is reduced. This term and the associated equation have been adopted directly from the reference.

The equations for computing the preceding characteristics, including the derivation of the expression for computing a ligament efficiency for the case of a random pattern of holes with unequal diameters is presented elsewhere.

Part B — Mechanical Testing

A replication of the fenestrations in the internal elastic lamina for both photomicrographs was produced by tracing the inside border of each fenestration shown on a 50.8 x 50.8 mm glossy print (magnification of 770) onto the surface of a sheet of latex rubber (Dental Dam Material, The Hygiene Corporation, Akron, Ohio 44310, U.S.A.). Latex rubber is a readily available elastomer with mechanical characteristics of high resilience, high extensibility, and low elastic modulus which are similar to elastin.

Models of the spatial geometry of the fenestrations

![Figure 1. Photomicrographs of the surface of the internal elastic lamina (human cerebral) illustrating: (a) a region of normal fenestrations; (b) a region of enlarged fenestrations. The short white bars represent 10 μm.](http://stroke.ahajournals.org/DownloadedFrom)
were created with a single (average) diameter, a uniform array of rows and columns, and the same ligament efficiency. Since the number of rows/columns for the actual geometry was not an integer (*i.e.*, 6.6 for the normal and 4.6 for the enlarged) it was necessary to create two geometrical models for each replication. One geometrical model consisted of the number of rows/columns with the closest integer value less than the actual number, while the other geometrical model consisted of the closest integer value greater than the actual number. The square border of the model must also be scaled accordingly. The outline of the holes and external border were again traced on the latex sheet. These models, of spatial geometry will henceforth be referred to as "uniform pattern."

Two opposing ends of each latex sheet were trimmed along the edge while the remaining edges were sandwiched between two strips of 1.3 mm aluminum sheet that were aligned along the transverse border of the model. The aluminum strips were attached to the latex rubber with double-sided masking tape. The aluminum strips were then mounted in the grips of a constant-rate-of-crosshead-movement testing machine (model 1125, Instron Corporation, Canton, Massachusetts, 02021, USA). The latex samples (unperforated) were stretched in uniaxial tension at a crosshead speed of 100 mm/min to a maximum elongation (strain) of 30%, through three sequences of loading and unloading. The load/deformation record for each sample was subsequently converted into a stress/strain curve. The stress (engineering stress) is defined as the load applied to the sample divided by the cross-sectional area of the sample:

\[ \sigma = \frac{P}{A} \]  
\[(1)\]

where \(\sigma\) = stress (kg/cm²)  
\(P\) = load (kg)  
\(A\) = original cross-sectional area (cm²)

The strain represents the percentage elongation of the sample or the change in length divided by the original length:

\[ \varepsilon = \frac{dL}{L} \times 100 \]  
\[(2)\]

where \(\varepsilon\) = strain (%)  
\(dL\) = change in length (cm)  
\(L\) = original length of the sample (cm)

Therefore, the stress/strain curve represents the tensile properties of the sample with variations in either the cross-sectional area or length of the sample accounted for. Any difference between the relationship of perforations to thickness of the latex sheet, and fenestrations to thickness of the internal elastic lamina were judged irrelevant because of two reasons: 1) the primary interest of this study is a relative comparison between different configurations of perforations in uniform sheets; and 2) the thickness of the sample is accounted for in the preceding computations.

Perforations were cut in both the replication and uniform pattern samples. The samples were again mounted in the testing machine and the tensile test repeated, except the samples with the larger perforations were elongated to 60%. The stress/strain curves for the perforated samples were subsequently computed.

The condition of the latex rubber samples with the holes marked but not perforated will subsequently be termed "solid." Samples with the perforations cut out will henceforth be referred to as "perforated." The samples with either a replication or uniform pattern representing normal fenestrations, henceforth will be referred to (collectively) as "smaller perforations." Alternatively, the samples with a replication or uniform pattern representing enlarged fenestrations will be referred to as "larger perforations."

**Part C — Spatial Geometry**

Following each uniaxial tensile test (described previously in Part B), photographs were taken of each sample mounted in the testing centre. The photographs for the replications of the normal fenestrations were obtained in the unstretched condition, as well as at 10, 20 and 30% elongation (strain). A similar series was obtained for the replications of the enlarged fenestrations, except that the series was extended to the 40, 50 and 60% elongation, for the perforated condition only. Since we found during preliminary studies that stretching to 60% was not followed by immediate return to the initial length, an extended series was not obtained for the solid condition. This procedure was selected since we believe that the material properties of the latex itself should not change between the tests on the solid and the perforated conditions.

Figure 2 illustrates the perforated replication and 7 x 7 uniform pattern of the normal fenestrations, in both the unstretched and 30% elongated conditions. A similar arrangement for the replication and 5 x 5 uniform pattern of the enlarged fenestrations is presented in figure 3.

The image from the negative for each photograph depicting the stretched condition of the sample, was projected on the platen of the Hewlett Packard Digitizer. Since the circular holes transform into an ellipse when the rubber is stretched, the longitudinal and transverse dimensions of a single row of holes (solid or perforated) closest to the centre of the sample were recorded and averaged along with the width of the sample corresponding with the series of holes.

The series of measurements were converted into the following set of spatial parameters:

i) Area. The area of the ellipse.

ii) Ligament Efficiency. The ligament efficiency for both the longitudinal and transverse directions.

iii) Eccentricity. The eccentricity for an ellipse will be used in this case to represent the shape factor since the eccentricity has a value of '0' for a circle and '1' for a slit.
iv) Expansion Ratio. Linear expansion of the hole in the longitudinal direction in relation to the original length of the solid sheet is expressed by Burton as:

\[ N = \frac{dh}{dL/L} \]

where 
- \( N \) = the expansion ratio
- \( dh \) = axial change in hole (mm)
- \( h \) = original dimension of the hole (mm)
- \( dL \) = change in length of the sample (mm)
- \( L \) = original length of the sample (mm)

For the case of a solid material with circles marked on it, the value would be unity, regardless of elongation. The equations associated with the above parameters are presented elsewhere (18).

Results

A) Geometrical Parameters

Table 1 presents the characteristics of the normal and enlarged specimens, computed from the photomicrographs illustrated in figure 1. The values for both the normal and enlarged fenestrations compare favourably with the mean values for the larger group of specimens, presented previously.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Normal</th>
<th>Enlarged</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diameter (μm)</td>
<td>43</td>
<td>21</td>
</tr>
<tr>
<td>Density (#/sq. mm)</td>
<td>1.5</td>
<td>5.9</td>
</tr>
<tr>
<td>Percentage area (%)</td>
<td>9861</td>
<td>4821</td>
</tr>
<tr>
<td>Ligament efficiency</td>
<td>2.2</td>
<td>17.4</td>
</tr>
</tbody>
</table>

B) Mechanical Testing

The corresponding characteristics for the perforations in the latex, which model the spatial geometry of the fenestrations, are presented in table 2. The stress/strain curves for the solid condition were essentially identical and have been combined on figure 4. The stress/strain curves (fig. 4) for the perforated replication of the normal fenestrations demonstrated a slight but distinct shift towards increased strain (elongation) at the same stress values as the solid sheet. That is to say, the replication tended to stretch slightly more under the same stress conditions.

The stress/strain curves for the perforated replication of the enlarged fenestrations exhibited a pronounced shift to increased strain (elongation) at the same stress values for the solid sheet. The mean in-
crease in the elongation of the replication of the enlarged in relation to the normal fenestrations (based upon 16 increments of stress from 0.2 to 3.2 kg/cm²) was 47% ± 0.06% SD.

In order to compare the relative change in the stress/strain characteristics for the solid condition to the perforated condition for both the replication and geometrical models, the stress/strain characteristics for the perforated condition were standardized with respect to the solid condition. The results (in terms of standardized stress) for the samples representing normal fenestrations, presented in fig. 5, exhibited a reduction to about 0.92 of the original value (solid condition). There is close agreement between the uniform pattern and replicate configurations.

The standardized stress values for replication of enlarged fenestrations decreased to about 0.66 of the value for the solid condition (fig. 5). The agreement between the uniform pattern and replicate configurations for the enlarged fenestrations is reasonable but not as close as the preceding relationship for normal fenestrations. In both cases the agreements were remarkable between the uniform pattern configurations (6 × 6 and 7 × 7 representing normal, 4 × 4 and 5 × 5).

**TABLE 2** Characteristics of Perforations (Based Upon Table 1)

<table>
<thead>
<tr>
<th>Models</th>
<th>Diameter (mm)</th>
<th>Centre-to-Centre Distance (mm)</th>
<th>Ligament Efficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>6 × 6, 7 × 7</td>
<td>1.2</td>
<td>7.7</td>
</tr>
<tr>
<td>Enlarged</td>
<td>4 × 4, 5 × 5</td>
<td>4.6</td>
<td>11.1</td>
</tr>
</tbody>
</table>

**FIGURE 3.** Photographs showing the replication and 5 × 5 uniform pattern representing the enlarged fenestrations, mounted in the grips of the uniaxial tensile testing machine. (a) replication (perforated) in the unstretched condition; (b) replication (perforated) at 30% elongation; (c) 5 × 5 model (perforated) in the unstretched condition; (d) 5 × 5 model (perforated) at 30% elongation.

**FIGURE 4.** The stress-strain curves for the solid latex as well as the perforated replications of the normal and enlarged fenestrations.
5 representing enlarged). This finding eliminated the necessity to interpolate between the uniform patterns to account for the difference between the actual numbers of rows/columns and the nearest integers.

C) Spatial Geometry

The satisfactory agreement between the uniform patterns and replications for the regions of normal and enlarged fenestrations demonstrated in the preceding section, has facilitated analysis of the changes in the Spatial Geometry. Measurements were taken from the uniform pattern of perforations in the geometrical models rather than the irregular shape and pattern of perforations in the replications.

It is evident from figures 2 (c,d) and 3 (c,d) that progressive elongation of the latex sheets transformed the circular holes into elliptical holes. The width of the sheet was also reduced. The results for the two uniform patterns representing each specimen have been combined and a linear regression (least squares) fit has been applied to the data for diameter, area, and ligament efficiency. The $r^2$ (coefficient of determination) values for the slopes were 0.92 or greater ($p < 0.001$) except for slopes near the horizontal which were considerably less. Since the slope is approaching zero for this latter situation, the $r^2$ computation is not a reliable indication of the fit.

The comparable results for the tensile properties of the two uniform patterns created for both the normal and the enlarged regions were also reflected in the results for the spatial geometry. Consequently, the results have been reported in this section for only one of the two uniform patterns of each specimen.

The results for the transverse diameter (solid and perforated) for the uniform patterns representing both normal and enlarged fenestrations are presented in figure 6. None of the curves appear to deviate substantially from the initial diameters. This observation is further confirmed by the low value of the slopes which are presented in table 3. The slopes for the perforated condition of the axial diameters for both the normal and enlarged fenestrations are greater than the solid condition as shown in figure 7 and confirmed in table 3. It is also interesting that the rate of increase of the axial diameter for the uniform pattern representing en-

![Figure 5](image-url)  
**Figure 5.** Standardized stress-strain curves for the replications and uniform patterns representing the normal and enlarged fenestrations.

![Figure 6](image-url)  
**Figure 6.** Graphs demonstrating the change in transverse diameter with increasing strain.

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Slopes of Linear Regression</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Transverse diameter</td>
</tr>
<tr>
<td>Normal</td>
<td></td>
</tr>
<tr>
<td>marked</td>
<td>$-0.002$</td>
</tr>
<tr>
<td>perforated</td>
<td>$-0.013$</td>
</tr>
<tr>
<td>perforated/marked</td>
<td>$(1)$</td>
</tr>
<tr>
<td>Enlarged</td>
<td></td>
</tr>
<tr>
<td>marked</td>
<td>$-0.015$</td>
</tr>
<tr>
<td>perforated</td>
<td>$-0.006$</td>
</tr>
<tr>
<td>perforated/marked</td>
<td>$(1)$</td>
</tr>
<tr>
<td>Enlarged/normal</td>
<td></td>
</tr>
<tr>
<td>marked</td>
<td>$(1)$</td>
</tr>
<tr>
<td>perforated</td>
<td>$(1)$</td>
</tr>
</tbody>
</table>

Notes: (1) = not relevant; (2) = not defined.
larged fenestration, exceeds the rate of increase for the normal fenestration by a factor of 2.7 (table 3).

The expansion ratios computed for the uniform patterns representing normal and enlarged specimens were 3.02 ± 0.6 SEM and 2.26 ± 0.01 SEM respectively. Therefore, although the rate of increase of the axial diameter for the uniform pattern representing enlarged fenestrations greatly exceeded the rate for the normal fenestrations, the expansion ratio for the larger diameter perforations was actually less.

When the transverse and axial diameters are combined for the calculation of the relevant areas, the perforated conditions again increased more rapidly than the solid condition (fig. 8, table 3). However, the more startling observation is that the rate of increase of the area for the uniform pattern representing the enlarged fenestrations is an order of magnitude greater than that for the normal fenestrations.

The results for the transverse ligament efficiencies (uniform pattern of normal and enlarged) shown in figure 9 and confirmed in table 3, exhibit horizontal slopes. The slope for axial ligament efficiency for the solid condition is also horizontal (fig. 10, table 3). However, the axial ligament efficiency for the perforated condition decreases with increasing strain as depicted in figure 10. The relative rate of this decrease listed in table 3 is 1.2 for the uniform patterns representing enlarged with respect to the normal fenestrations, which indicates that the rates are comparable.

The eccentricity for both the solid and perforated conditions of both uniform patterns (normal and enlarged) increased rapidly with initial strain, with pro-
Figure 11. Plots of eccentricity (ellipse) with increasing strain.

Discussion

The characteristics of the fenestrations for both the normal and enlarged fenestrations listed in Table 1 are in good agreement with the previous results for the larger population of specimens. Replication in latex rubber of the actual geometry for both the normal and enlarged fenestrations at the same magnification, has provided a means for comparing the tensile properties of the same material with two distinct perforated configurations. The obvious increase in elongation at comparable stress levels for the sample with larger perforations (illustrated in figure 4) indicates that a region with larger perforations would be expected to stretch more than the surrounding region of smaller perforations.

If the stretching forms a bulge which is depicted to be elliptical in cross-section, as shown in Figure 12, then the height of the bulge (H) can be related to a proportional increase in the length (K) of a localized region with respect to the adjacent material. The relationship (see Appendix for derivation) may be expressed as:

\[ H = L(0.81K^2 - 1)^{1/2} \]  

where \( H \) = height of the bulge
\( K \) = the proportional increase in length of the region
\( L \) = one-half the original length of the region

In order to consider the influence of larger perforations on the distention of the wall of a tube, the wall is conceived to be multilaminate consisting of adjacent perforated and solid layers in intimate contact. The perforated layer is considerably more elastic than the solid layer, but under the influence of an internal pressure the perforated layer distends first and continues to distend. This structure would maintain an internal pressure while permitting the elastic, perforated layer to distend in response to an internal pressure, without constraint by the solid layer. This structure is analogous to the wall of cerebral arteries. A study by Roach and Burton showed that the initial elastance of the artery represented elastin (highly distensible) and the final elastance represented collagen (stiff) which concurs with the description of the response of the multilaminate wall presented above. We, therefore, propose that this simple model reasonably mimics the condition in the arterial wall.

An internal pressure would cause a uniform distension of an elastic sheet with perforations of consistent size (fig. 12a,b). However, a region of larger perforations would distend more readily (as illustrated in figure 4) than the surrounding smaller perforations, which would create a bulge. In order to assess the factors affecting the creation of a bulge in regions of larger perforations, three conditions are considered:

1) Bulge Apparent Only With Pressure

The regions of normal and enlarged fenestrations when examined by the scanning electron microscope, usually appear as a continuous flat surface without any discernible evidence of a permanent bulge in the region of enlarged fenestrations. Nevertheless, the technique of mounting the specimen on a flat surface along with the small size of the regions of enlarged fenestrations could account for the flat appearance. Under the influence of transmural pressure, a stress would be induced in the arterial wall resulting in stretching of the internal elastic lamina.

The results depicted in figure 4 demonstrated that the region of larger perforations would stretch more than the circumjacent region with smaller perforations. The increased elongation of 47% presented earlier for the region of larger perforations in relation to the smaller perforations, may be converted to an appropriate proportion of perimeter to major axis (K) by the expression:

\[ K = 1 + (k_s \times k_E) \]  

where \( k_s = \frac{L}{K} \)
\( k_E = \) proportional increase in elongation of the regions of larger to smaller perforations

Solution of equation (4) with the substitution for K of 1.147, 1.294 and 1.441 for 10%, 20% and 30% strains respectively, results in corresponding bulge heights (H) of 0.13, 0.30 and 0.41 per unit length of the semi-major axis. That is, the height of the bulge for the 30% strain, would represent 0.41 or 41% of the length of the semi-major axis. The dimensions of the bulge representing 30% strain, shown in Figure 12d, have been drawn to scale, in order to demonstrate this relationship.
ii) Permanent Bulge

An alternate consideration is that the enlargement of the fenestrations has created a permanent bulge. In this instance, the increase in the linear dimension in the region of the enlarged fenestrations is attributable to an increase in the centre-to-centre distance, since it is assumed that the average width of the ligament between fenestrations remains constant, while the fenestration diameter increases. In order for this to occur it is presumed that normal fenestrations have increased in size, but not coalesced.

Computation of the average ligament width for the model configurations representing the two samples presented in Figure 1 was 8.54 µm for the normal fenestrations and 8.52 µm for the enlarged fenestrations. Similarly, the ligament width computed from the previous publication on enlarged fenestrations11 revealed average values of 12.8 µm for the normal fenestrations and 13.0 µm for the enlarged fenestrations. The exceptional agreement for each of the two groups, confirms the above supposition that the fenestrations could have enlarged without consuming the internal elastic lamina. This finding also suggests that the conversion from normal to enlarged fenestrations, perhaps as a consequence of accommodation to increased stress, could create a permanent bulge. A further discussion about enlargement of the fenestrations will be presented later.

A proportional increase in the length of the region of enlarged fenestrations (K) is calculated as the ratio of the average centre-to-centre distance for the enlarged in relation to the normal fenestrations. For the value of the regions of enlarged and normal fenestrations presented in this communication, the result for 'K' is 1.44. Substitution of this value into equation (4) yields a height for the bulge of 0.41 per unit length of the semi-major axis. This result is depicted in Figure 12e with the dimensions of the bulge drawn to scale.

iii) Effect of Transmural Pressure On Permanent Bulge

Under the influence of transmural pressure, the permanent bulge described in the preceding section (ii) would increase in size. The increase represents a summation of the proportional increases presented in sections i) and ii):

\[ K = k_i + (k_s \times k_E) \]

where \( k_i \) = ratio of centre-to-centre distances for enlarged to normal (section ii).

Substitution into equation (4) for K values of 1.587, 1.734 and 1.881 for strains of 10%, 20% and 30% respectively, resulted in corresponding bulge heights of 0.51, 0.60 and 0.68 per unit length of the semi-major axis. An illustration has been presented in figure 12f with the dimensions of the bulges representing a permanent bulge (section ii), as well as a superimposed 30% strain, drawn to scale.

We acknowledge that the relative influence of the internal elastic lamina in relation to the other components in the arterial wall, on the mechanical characteristics of the artery are not well understood. Also, the shape of a bulge is three-dimensional, whereas, the relative elastic characteristics used in this analysis were determined from uniaxial tensile measurements without constraining the lateral edges. A further investigation of the relative characteristics with a three-
dimensional model is anticipated at some future date. It cannot be reliably predicted whether a three-dimensional model (with all edges constrained) would result in any change from the relative differences determined in the present study between the replications of the regions of normal and enlarged fenestrations.

The preceding analysis suggests that the formation of evaginations in the elastic lamina may be attributable to regions of enlarged fenestrations. Consideration of whether enlargement of the fenestrations is a primary effect which directly results in an evagination or whether there is a dependency upon another effect such as a medial defect or thinning, is beyond the scope of this investigation.

The agreement for the standardized stress between the replication and uniform pattern configurations representing both the regions of normal and enlarged fenestrations, substantiates the rationale for the use of the uniform pattern configurations based upon equivalent ligament efficiencies, to represent the average spatial geometry of fenestrations during progressive stretching. In a complementary investigation the same modelling technique for straight segments of cerebral arteries of various external diameter with variation in the characteristics of the fenestration and photomicrographs at different magnification, also provided similar excellent agreement between the stress/stretch characteristics of the replication and uniform pattern configurations.

It was evident from figures 6 and 9 that progressive elongation did not diminish the transverse diameter nor affect the transverse ligament efficiency. Nevertheless, the axial diameter for the larger perforations increased at a faster rate than the smaller perforations. This effect resulted in a progressive decrease in the ligament efficiency, as well as a substantial increase in the average area of the larger perforations, in relation to the normal perforations. It is interesting that the eccentricities which represent the shape factor for both the larger and smaller perforations are equivalent, even though the increase in their respective axial diameters and areas are considerably different.

Infiltration by fibrin and red blood cells into the arterial wall between the internal elastic lamina and the media has been reported by a number of authors. The pronounced increase in the average area for the larger perforations in relation to the smaller perforations may demonstrate the basis for a role in this infiltration.

Stehbens has also studied the degenerative changes in the intimal cushions or pads present at bifurcations. He cited their susceptibility to lipid accumulation to substantiate his hypothesis that the cushions are sites of mild but persistent injury, indicative of an early stage of atherosclerosis. One of the degenerative changes identified for the formation of cushions was elastin fragmentation which suggests that perhaps enlarged fenestrations may play a role in the development of atherosclerosis.

Klynstra and Böttcher have shown that the preferred sites of fatty streaks and spots in pig thoracic aorta demonstrate enhanced permeability. Others have demonstrated with the use of rats that hypertension will accelerate the infiltration of mononuclear cells as well as fluorescent proteins and colloidal carbon proteins into the arterial wall. Olsen further observed with the use of serial sections that in the permeable areas, the internal elastic lamina is either lacking or depicted as "disconnected fragments."

Oka and Nimi et al have stated that the permeability of the endothelium is enhanced by wall shear stress, stretch, vibration, circumferential tension and high stress concentrations. A previous study by Hassler demonstrated that the diameter of fenestrations (anterior cerebral artery) increased to a peak at about the third decade of life, and then subsequently decreased at a moderate rate. In a recent study by Hayashi et al, the circumferential wall stress (constant transmural pressure of 100 mm Hg was assumed for all ages) computed for the intracranial vertebral artery also increased to a peak at about the second decade of life (values for the third decade of life were not reported) with a moderate decrease thereafter. This decrease in wall stress is attributable to the increased thickness of the arterial wall which includes a concomitant increase in thickness of the internal elastic lamina. The remarkable similarity in the shape of the curves for change in the diameter of the fenestrations and wall stress associated with age, suggests that the fenestration diameters may be influenced by the stress induced in the internal elastic lamina.

Preliminary results of a recent study by other members of our group have shown that the average diameter of fenestrations from the thoracic aortas of rabbits, enlarged with an increase in the diameter of poststenotic dilatation. This finding provides further supporting evidence for the possible influence of increased wall stress on the enlargement of the fenestrations. We have also suggested that regions of enlarged fenestrations create stress concentrations which may further influence their growth. Ferguson has concluded from model studies, that the impingement of blood at the apex of intracranial bifurcations increases the shear stress at the apex. The combined influence of this effect along with transmural pressure could be an important factor contributing to a focal degeneration of the internal elastic lamina. Macfarlane has shown that increasing the transmural pressure has the effect of increasing the radius of curvature (caudal-dorsal) at the apex of the bifurcation but also results in flattening of the central portion. He has attributed the flattening to very high wall stresses in the apical region of the bifurcation. Therefore, localized regions of increased wall stress induced perhaps by haemodynamic flow, the geometry of the artery at a bifurcation and/or changes in the structure of the arterial wall may contribute to the creation of enlarged fenestrations.

Although the modelling technique presented in this communication has limitations, nevertheless, it has demonstrated that regions of enlarged fenestrations could produce small evaginations and, perhaps, increased permeability of the internal elastic lamina.
Even though the progression from a small evagination to a fully-developed aneurysm has not been conclusively proven, other investigators\(^2\)\(^3\)\(^6\)\(^7\) have suggested that fragmentation of the internal elastic lamina and evagination are a necessary precursor to the formation of a saccular aneurysm. The observation by Hassler\(^2\) and Merei and Gallyas\(^8\) of enlarged fenestrations at the mouth of saccular aneurysms provides further evidence to suggest that the enlargement of fenestrations may play a significant role in the etiology of intracranial saccular aneurysms.

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References


Appendix

The purpose of this appendix is to derive the expression for determining the depth of an elliptically shaped bulge from a flat surface. The standard solution (approximate) for computing the perimeter of an ellipse is:

\[
P = 2\pi \left( L^2 + H^2 \right)^{\frac{1}{2}} \quad (1)
\]

where \(P\) = perimeter

\(L\) = semi-major axis (i.e., one-half of the length of the region of large perforations)

\(H\) = semi-minor axis (i.e., the height of the bulge)

This expression may be re-arranged:

\[
H = \left( \frac{p^2}{2\pi^2} - L^2 \right)^{\frac{1}{2}} \quad (2)
\]

For a proportional increase in one-half of the perimeter, in relation to the major axis, the applicable expression is:

\[
K = \frac{P}{2L} \quad (3)
\]

Substitution of equation (3) into equation (2) and re-arranging, yields the result:

\[
H = L \left( 0.81K^2 - 1 \right)^{\frac{1}{2}} \quad (4)
\]
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G J Campbell and M R Roach

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