Elasticity of passive blood vessels: a new concept

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The mechanical properties of blood vessels are of fundamental importance for the function of the circulation: in large vessels, compliance influences pulse pressure. In the resistance circulation, the pressure-dependent caliber of individual segments at full dilation sets the limits for organ perfusion. These mechanical properties are subject to physiological regulation (4) and are also affected by cardiovascular disease. Indeed, substantial research is currently devoted to macrovascular and microvascular remodeling in relation to cardiovascular pathology (see Refs. 18 and 22). Remodeling is characterized by a change in the pressure-diameter or stress-strain relation, and therefore understanding the link between vascular wall mechanics and elastic fiber embedding and turnover becomes crucial.

The passive mechanics of the vascular wall involve elastin and collagen. Elastin fibers are easily distended (elastic moduli ($E_s$) of $\sim 0.4$ MPa (8)) and have linear stress-strain relations up to $\sim 300\%$ distensions. Collagen fibers are extremely stiff ($E_c$ $\sim 100$–1,000 MPa) and are believed to break above distensions of 3–4% (8). The nonlinear stress-strain and pressure-diameter curves of blood vessels are generally explained by a contribution of only elastin at low distensions, followed by recruitment of collagen stiffness at higher distensions. Such recruitment is frequently imagined by “hook on” of parallel-arranged collagen fibers with high but finite and linear stiffness (2, 5, 7, 29, 30). A major concern of this concept, however, is the prediction of substantial distension of individual collagen fibers, while in reality the fibers would break at strains above a few percent. Moreover, these hook-on models have to assume the contribution of very few collagen fibers to allow sufficient distension given their large collagen stiffness. Consequently, these models are based on low collagen recruitment fractions, while the majority of collagen does not contribute to the mechanical properties (2, 5).

Here, we propose an alternative, conceptually different model explaining vascular wall mechanics on the basis of elastin and collagen stiffness. The model is based on series arrangement of an infinite number of units, each consisting of elastin and fully rigid collagen fibers arranged in parallel. The collagen fibers switch stepwise from slack (zero stress) to rigid (infinite stiffness) upon ongoing element strain. A comparable model was previously reported by Maksym and Bates (15) for the explanation of lung parenchymal tissue mechanical characteristics. The current model is designed to explain the shape of the stress-strain curves of blood vessels at full dilation, the effects of dissolving collagen by proteolytic enzymes, and the effects of fiber turnover, as may occur during remodeling, on wall mechanics. We have chosen to evaluate relatively simple, one-dimensional models to compare the concepts of hook-on of parallel collagen and series arrangement of elastin/collagen units. It is well appreciated that more complex models, including two- or three-dimensional fiber orientation and tension distribution (10, 11, 24), will be required to account for specific aspects of wall mechanics, but such models are outside the scope of this study.

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In this study, we evaluated two fundamentally different models for the passive mechanical behavior of blood vessels: the classic hook-on (HO) model and a new series element (SE) model. The predicted stress-strain relations will be compared with experimental data on small arteries before and after collagenase digestion. We first explain the experimental procedures; subsequently, the models are presented and their mathematics are derived (see the Glossary for a description of the parameters used). Finally, we explain how the models were fitted to the data.

Experimental procedures. All animal experiments were done in accordance with institutional guidelines and were approved by the local committee on animal experimentation. Rat mesenteric first- and second-order small arteries were isolated and mounted on isometric force transducers (model 610 M, Danish MyoTech; allowing four segments to be studied simultaneously) using two 40-μm wires, according to common procedures (19). The vessel distension was measured manually with a micrometer screw at a resolution of 3 μm. The length of the mounted segment was measured (usually 2 mm) to calculate wall tension from force. The vessels were heated to 37°C in nominally calcium-free MOPS-buffered physiological saline solution (composed of (in mmol/l) 145.0 NaCl, 4.7 KCl, 1.17 MgSO 4·7H 2O, 1.2 NaH 2PO 4·H 2O, 5.0 glucose, and 2.0 pyruvate; pH 7.35 ± 0.02), to which 4 M papaverin was added. A normalization procedure was performed to determine the inner diameter of the vessel at an equivalent pressure of 100 mmHg (D 100 ), assuming Laplace’s law. A diameter-tension relation was then made starting at 1.05-D 100 , releasing in eight steps to 0.5-D 100 , and stretching again to 1.05-D 100 . Of the four simultaneously studied segments, three were then incubated in collagenase (0.1 mg/ml, type I, Sigma, in MOPS-buffered solution containing 0.4 mM Ca 2+ ), whereas the fourth served as a time-matched control. During incubation, vessels were gradually stretched to maintain an equivalent pressure of roughly 100 mmHg. After 20–25 min, the collagenase was washed out extensively, and a new diameter-tension relation was made by releasing in small steps to zero tension and stretching again to the equivalent pressure of 100 mmHg. A second round of collagenase incubation was then performed, and a new diameter-tension curve was made for all vessels. For all curves, stresses during shortening and stretch were averaged before fitting of the two models. In one-half of the experiments, trypsin inhibitor (0.03 mg/ml, Sigma) was added to the digestion solution. This appeared not to have any effect, and results with and without trypsin inhibitor were pooled.

Stiffness of the mechanical setup itself was found to be 4.5 mN/μm. On the basis of this stiffness and the segment length (~2 mm), vessel shortening averaged 0.75% (range 0.43–1.29%) at the highest measured tensions in the experiments. The effect of this shortening on the diameter-tension relations is minimal and was ignored.

Three digested vessels and one control vessel were processed for transmission electron microscopy (TEM). Vessels were fixed in 4% formaldehyde and 1% glutaraldehyde in 0.1 M sodium phosphate buffer while kept at the maximal applied
stretch and were postfixed with 1% osmium tetroxide and 1% lanthanum nitrate. The vessels were embedded in LX112 while still on the wires. The plastic was then manually trimmed to remove the wires, and ultrathin cross sections were made of the free part of the vessels between the wires. Digital TEM pictures were obtained with a built-in charge-coupled device camera and analyzed using ImageJ (NIH).

**Description of the HO model.** The HO model (Fig. 1A) consists of a single elastin fiber with linear elasticity and parallel arrangement of multiple collagen fibers with linear elasticity and varying unstressed lengths. The collagen fibers carry zero stress below their slack length. On distension (Fig. 1B), these fibers become increasingly recruited or “hooked on.” The nonlinear stress-strain relation of blood vessels is thus explained by the increasing contribution of collagen fibers, as schematically shown in the stress-strain curve in Fig. 1. This model can be described mathematically as follows: the stress carried by elastin fibers $\sigma_e$ relates to the vessel strain $\varepsilon$ (i.e., dimensionless relative distension) and elastin elastic modulus $E_e$ (in N/m$^2$) according to

$$\sigma_e(\varepsilon) = E_e \cdot \varepsilon$$  \hspace{1cm} (1)

To derive the stress carried by collagen ($\sigma_c$), let $\varepsilon_c$ be the vessel strain where a specific collagen fiber becomes recruited. Upon ongoing distension, the strain of this fiber ($\varepsilon_c$) then relates to vessel strain ($\varepsilon$) as (see the APPENDIX)

$$\varepsilon_c = \frac{\varepsilon - \varepsilon_r}{\varepsilon + 1} \quad \varepsilon > \varepsilon_r$$  \hspace{1cm} (2)

On the basis of linear collagen elasticity above slack length, stress on this collagen fiber as a function of vessel strain will be

$$\sigma_c(\varepsilon, \varepsilon_r) = E_c \cdot \varepsilon_c = E_c \cdot \frac{\varepsilon - \varepsilon_r}{\varepsilon + 1} \quad \varepsilon > \varepsilon_r$$  \hspace{1cm} (3)

$$\sigma_c(\varepsilon, \varepsilon_r) = 0 \quad \varepsilon \leq \varepsilon_r$$

where $E_c$ is the collagen elastic modulus (in N/m$^2$). When considering a collection of collagen fibers with a distribution in $\varepsilon_c$ according to the density function $f_c(\varepsilon_c)$, the mean stress of the collagen compartment (based on standard stochastic theory, e.g., Ref. 1) equals

$$\overline{\sigma_c}(\varepsilon) = \int_{-\varepsilon_r}^{\varepsilon} \sigma_c(\varepsilon, \varepsilon_r) \cdot f_c(\varepsilon_c) \text{d}\varepsilon_c$$  \hspace{1cm} (4)

Substituting Eq. 3 and assuming that no fibers hook on below the resting length of the vessel reveals

$$\overline{\sigma_c}(\varepsilon) = E_c \cdot \int_{-\varepsilon_r}^{\varepsilon} \frac{\varepsilon - \varepsilon_r}{\varepsilon + 1} \cdot f_c(\varepsilon_c) \text{d}\varepsilon_c$$  \hspace{1cm} (5)

The vessel wall consists of elastin, collagen, and other constituents that will be assumed not to carry any stress. Taking $A_e$ and $A_c$ as the relative volume fractions of elastin and collagen, respectively, the stress as averaged over the whole wall can be expressed as

$$\sigma(\varepsilon) = A_e \cdot \overline{\sigma_e}(\varepsilon) + A_c \cdot \overline{\sigma_c}(\varepsilon)$$  \hspace{1cm} (6)

or, substituting Eq. 5

$$\sigma(\varepsilon) = A_e \cdot E_e \cdot \varepsilon + A_c \cdot E_c \cdot \int_{-\varepsilon_r}^{\varepsilon} \frac{\varepsilon - \varepsilon_r}{\varepsilon + 1} \cdot f_c(\varepsilon_c) \text{d}\varepsilon_c$$  \hspace{1cm} (7)

For $f_c(\varepsilon_c)$, we applied Weibull distributions (see below). Goodness of fit to experimental data was essentially equal with this distribution compared with a truncated ($\varepsilon_c > 0$) normal distribution (data not shown).

To be able to relate the model predictions to experimental data on wire-mounted vessels, Eq. 7 was converted to a strain-wall tension relation, where wall tension $T$ is the force per vessel length (in N/m)

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**Fig. 1.** Schematic drawing of the classic hook-on (HO) model, consisting of a parallel arrangement of linear springs representing elastin and collagen. A: HO model at zero stress. Here, the elastin element is at its resting length and all collagen springs are detached. B: a stress $\sigma$ is applied to the vessel, resulting in a strain $\varepsilon$. The two top collagen springs have hooked on, whereas the third spring is still slack. C: stress-strain curves for the individual springs and their parallel combination, showing hooking on of the lower and middle collagen fiber. $\varepsilon_r$ indicates the vessel strain at which the middle collagen fiber is recruited.
\[ T(\varepsilon) = W \cdot A_e \cdot E_e \cdot \varepsilon + W \cdot A_e \cdot E_e \cdot \int_{\varepsilon_i=0}^{\varepsilon_f} \frac{\varepsilon - \varepsilon_i}{\varepsilon_f + 1} f_i(\varepsilon) \, d\varepsilon_i \quad (8) \]

where \( W \) is the wall thickness (in m), which was assumed to remain constant. Variation of wall thickness, elastic fiber content, or elastic moduli has similar scaling effects on the above relation, and therefore these parameters cannot be separately fitted to experimental strain-tension relations. These parameters were therefore lumped in this study, resulting in a four-parameter classic HO model \([WAE_{el}, WAE_{col}, \varepsilon_r, \varepsilon] \) of the Weibull distribution \( f(\varepsilon_r) \); see below.

\[ T(\varepsilon) = WAE_{el} \cdot \varepsilon + WAE_{col} \cdot \int_{\varepsilon_i=0}^{\varepsilon_f} \frac{\varepsilon - \varepsilon_i}{\varepsilon_f + 1} f_i(\varepsilon) \, d\varepsilon_i \quad (9) \]

Degradation of collagen fibers by collagenase will cause a shift in the theoretical strain-tension curves, which was implemented in the HO model as follows: we assumed that all collagen fibers have equal chances of being removed, i.e., the density function \( f_i(\varepsilon_i) \) remains unchanged. Thus only the amount of collagen was assumed to decrease (or collagen stiffness, which seems unrealistic but in any case would be mathematically identical), and degradation is reflected by a lower value for \( WAE_{col} \). The product of wall thickness \( (W) \) and relative content \( (A_e) \) equals the absolute “collagen layer thickness.” Thus, for a remaining fraction of collagen \( \beta \) \(( \beta = 1 \) reflecting an untreated vessel), the following relation holds:

\[ WAE_{col}(\beta) = \beta \cdot WAE_{col}(1) \quad (10) \]

Thus, in the simulations, the effect of collagenase was implemented by modifying \( WAE_{col} \) and keeping the other parameters constant.

**Description of the SE model.** The fundamental element in the SE model is a parallel arrangement of elastin with linear elasticity and collagen fibers of varying length that carry no stress when kept slack but have infinite stiffness once straightened, thereby fully blocking further extension of the individual element (Fig. 2A). Hence, distension of an individual element is limited by the shortest of its collagen fibers. While the longer fibers are irrelevant for the mechanical behavior under untreated conditions, their presence affects probability distributions of element extensibility and the effect of collagenase treatment (see below). The model con-

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**Fig. 2.** Schematic drawing of the new serial element (SE) model. The basic element (shown in A under zero stress) consists of a linear elastin spring and parallel collagen fibers that may bend but become fully rigid once straightened. B: three such elements in series under stress \( \sigma \). Note that stresses in the 3 elements are equal by definition. The right element is still distensible at this stress, whereas the middle and left elements became rigid once strain reached their specific \( \varepsilon_r \). C: stress-strain curves for the individual elements and their serial combination. At each stress, strain (i.e., relative distension) of the combination of these 3 elements equals the average of individual strains. \( \varepsilon_r \) and \( \sigma_r \) indicate the strain and stress, respectively, at which the left element is straightened.
sists of a large number of such elements in series, with equal unstressed lengths but with a dispersion in strains at which these elements become taut. Three of such elements are shown in Fig. 2B. To simplify the mathematics, the limiting case of an infinite number of elements will be used below. Each element will consequently be infinitesimally short. For a finite number of elements in series, the model predictions would be much harder to calculate but virtually identical when based on a large amount of elements (say, 1,000). For small numbers of elements, the predictions would become stochastic in the sense that individual simulations would provide different results. Because of the series arrangement, all elements carry the same stress \( \sigma \). The right element is still distensible at this stress, whereas the left two elements have become rigid, their distension being limited to \( \epsilon_r \). The assumption of a dispersion in \( \epsilon_r \) and the associated stress \( \sigma_r \) is essential for this model. The diagram shown in Fig. 2C indicates the stress-strain relation of these three elements and their serial combination. While the nonlinear stress-strain relation of the blood vessel was in the HO model the result of collagen recruitment, here it is the result of exclusion of part of the series-arranged elastin.

The stress-strain relation of the SE model can be derived as follows: for a single element, the strain \( \epsilon_e \) on the applied stress to the wall (\( \sigma \)) and the stress where this element becomes rigid (\( \sigma_r \)), according to

\[
\epsilon_e(\sigma, \sigma_r) = \frac{\sigma}{A_e \cdot E_e} \quad \sigma \leq \sigma_r
\]

\[
\epsilon_r(\sigma, \sigma_r) = \frac{\sigma - \sigma_r}{A_e \cdot E_e} \quad \sigma > \sigma_r
\]

(11)

where \( A_e \) is the relative volume occupied by elastin and \( E_e \) is the elastic modulus of elastin. Because all elements have equal resting lengths, the strain of the whole wall \( \epsilon(\sigma) \) equals the average of the individual element strains \( \epsilon_e(\sigma, \sigma_r) \). These elements have varying collagen tightening stresses \( \sigma_e \). Let \( f_e(\sigma_r) \) be the density function for the collagen tightening stress. The vessel strain then follows from

\[
\epsilon(\sigma) = \epsilon(\sigma) = \epsilon(\sigma) \int_{\sigma_r}^{\sigma} f_e(\sigma_r) d\sigma_r
\]

(12)

Substituting Eq. 11, assuming that \( f_e(\sigma_r) = 0 \) for \( \sigma_r < 0 \), and splitting the integral into rigid (left term) and distensible elements (right term) reveals

\[
\epsilon(\sigma) = \frac{1}{A_e \cdot E_e} \int_{\sigma_{e,0}}^{\sigma} \sigma_r f_e(\sigma_r) d\sigma_r + \frac{\sigma}{A_e \cdot E_e} \int_{\sigma_{e,0}}^{\sigma} f_e(\sigma_r) d\sigma_r
\]

(13)

or

\[
\epsilon(\sigma) = \frac{1}{A_e \cdot E_e} \int_{\sigma_{e,0}}^{\sigma} \sigma_r f_e(\sigma_r) d\sigma_r + \frac{\sigma}{A_e \cdot E_e} \left[ 1 - F_e(\sigma) \right]
\]

(14)

where \( F_e(\sigma) \) is the cumulative density function, i.e., the fraction of elements that have tight collagen.

For the shape of the density function for collagen tightening stress in the SE model, \( f_e(\sigma_r) \), we considered the following: the collagen in each element consists of a group of fibers with varying lengths (Fig. 2A). Each element will become distensible as soon as the shortest of its collagen fibers tightens. The minimum of a collection of equally distributed stochastics with a lower physical boundary, such as collagen length here, can be modeled by a Weibull distribution (21). These distributions are commonly used in failure analysis of technical systems, where the parameter of interest is the time to first failure. Here, we use Weibull distributions to describe the dispersion in \( \sigma_r \). The characteristic stress and sets the scale of this distribution, whereas the left two elements have become rigid, their distension being limited to \( \epsilon_r \). The assumption of a dispersion in \( \epsilon_r \) and the associated stress \( \sigma_r \) is essential for this model. The diagram shown in Fig. 2C indicates the stress-strain relation of these three elements and their serial combination. While the nonlinear stress-strain relation of the blood vessel was in the HO model the result of collagen recruitment, here it is the result of exclusion of part of the series-arranged elastin.

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\epsilon_e(\sigma, \sigma_r) = \frac{\sigma}{A_e \cdot E_e} \quad \sigma \leq \sigma_r
\]

\[
\epsilon_r(\sigma, \sigma_r) = \frac{\sigma - \sigma_r}{A_e \cdot E_e} \quad \sigma > \sigma_r
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\]

(13)

or

\[
\epsilon(\sigma) = \frac{1}{A_e \cdot E_e} \int_{\sigma_{e,0}}^{\sigma} \sigma_r f_e(\sigma_r) d\sigma_r + \frac{\sigma}{A_e \cdot E_e} \left[ 1 - F_e(\sigma) \right]
\]

(14)

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The effect of collagenase treatment was derived in the SE model as follows: as indicated in Fig. 2A, each element consists of multiple collagen fibers in parallel, only the shortest of which sets the behavior of this element. Removing fibers by collagenase treatment will cause a rightward shift of the density function \( f_e(\sigma_r) \) because the shortest fibers in each element have a chance of being removed, such that the next longer collagen fiber will take over. To arrive at this new density function, the chance that a slack element becomes straight upon a unit increase in tension is required. This tightening rate (TR), in analogy to the failure rate in failure analysis (21), can be expressed as

\[
TR/T(\sigma) = \frac{\gamma}{\alpha_T} \left( \frac{T}{\alpha_T} \right)^{-1}
\]

(18)

TR is directly proportional to the number of parallel collagen fibers in each element

\[
TR(\sigma, \beta) = \beta \cdot TR(T, 1)
\]

(19)

where \( \beta = 1 \) indicates an untreated vessel. While the scaling of TR depends thus on the number of parallel fibers, the shape is independent of this number and is determined by \( \gamma \). For the special case of \( \gamma = 1 \), TR is constant, leading to an exponential density function. The rate constant for this exponential distribution (in \( 1/\alpha_T \)) will become larger, or \( \alpha_T \) will become smaller, if more fibers are present in each element. The proportionality between TR and \( \beta \) can be expressed as a dependence of parameter \( \alpha_T \) on the collagen content as follows

\[
\alpha_T(\sigma) = \alpha_T(1/\beta)^{1/\gamma}
\]

(20)
Thus, in the simulations, the effect of collagenase was implemented in the SE model by modifying \( \sigma_T \) according to the above relation, keeping the other two parameters (\( WAE_{el} \) and \( \gamma \)) constant. Elastase effects were theoretically analyzed as well but turned out to provide no clues for discrimination between both models (not shown).

**Model fitting to experimental data.** To fit the models, the experimentally applied diameters need to be converted to strains relative to the unloaded vessel diameter. The isometric setup is not very accurate in determining the unloaded diameter, because diameter is the independent variable here and tension is very low in a wide range of diameters (~0.5–0.6 \( D_{100} \)), rising increasingly faster at higher distensions. However, we (27) previously found a consistent relation between passive diameter at low pressure (measured at 5 mmHg) and 100 mmHg in this same type of vessel when vessels were mounted on cannulas and pressurized. On the basis of this, we took the unloaded diameter of all vessels in this study as equal to \( D_s = 0.54 \times D_{100} \).

While the parameter fitting for the HO model provides \( \alpha_e \) and \( \gamma \) in \( f_e(\varepsilon_e) \), the best-fitting density function in the SE model is expressed as \( f_s(T) \). To compare the parameter \( \alpha \) of both models, the characteristic tension of the SE model (\( \alpha_T \)) was converted to a characteristic element strain (\( \alpha_e \)) according to \( \alpha_e = (1/\epsilon_{el}) \times \alpha_T \). The shape parameter \( \gamma \) is invariant under the linear transformation from \( T \) to \( \varepsilon_e \).

Matlab was used for model analysis, fitting, and visualization. Integrals were quantitated by summation over 1,000 classes for the HO model and 3,000 classes for the SE model, thereby covering the highly asymmetric predicted density functions in the latter model. For fitting of the models to experimental data, a multidimensional unconstrained nonlinear minimization (Nelder-Mead) method was used. With the use of this method, the sums of squared differences between model and data were minimized with a parameter and function tolerance of \( 10^{-6} \). The squared correlation coefficient representing the match between data and optimal model was calculated as 1 – RSSQ/SSQ, where RSSQ is the remaining sums of squared differences between data and their prediction and SSQ is the sums of squares of data around their mean value. Model fitting was performed to the strain-tension curve of each individual undigested vessel, as obtained before collagenase incubation. This involved optimization of four and three parameters, respectively, for the HO and SE models. Subsequently, on the basis of the found parameters, we theoretically analyzed the effect of collagenase treatment by varying the digestion factor \( \beta \) in both models, as indicated above. We then qualitatively compared these predictions to the stress-strain curves obtained after digestion. In addition, for the SE model, we estimated the degree of digestion \( \beta \) as follows: we considered that the maximal possible strain of the vessel, where all elements are rigid, is equal to the mean of \( f_e(\varepsilon_e) \) and is thus proportional to \( \alpha_e \). Furthermore, the largest applied strains, where tension rapidly rose, were assumed to be only slightly smaller than this maximal strain. By rearranging Eq. 20 and realizing that \( \gamma \) is not affected by digestion, this leads to

\[
\beta = \left( \frac{\text{maximum applied strain of undigested vessel}}{\text{maximum applied strain of digested vessel}} \right)^{\gamma} \tag{21}
\]

**RESULTS**

**Experimental data.** Figure 3 shows the relation between applied diameter and measured wall tension for eight vessels. In six of these vessels (Fig. 3, A–F), these curves were again measured after one and two rounds of collagenase digestion. The vessels in Fig. 3, G and H, served as time-matched controls. As can be seen, undigested vessels have the expected nonlinear shape with increasing stiffness at higher diameters. The effect of digestion was characterized by both a considerable rightward shift of the steep part of this curve and a loss of tension at lower distensions. The dashed lines in Fig. 3 indicate the 100-mmHg isobar, as based on Laplace’s law. While we did not always obtain equivalent pressures exceeding 100 mmHg after digestion, the intersection of the isobar with the (extrapolation of) these curves (\( D_{100} \)) reveals that, due to the nonlinear elastic properties, stable diameters can be obtained in control as well as after digestion. Some vessels (Fig. 3, D and E) had a more than doubled \( D_{100} \) value after two rounds of digestion.

The above results were obtained in the presence of maintained stress during digestion. When vessels were digested at minimal tension, subsequent stretching caused a transient increase in tension followed by remarkably large stress relaxation, such that steady-state tension remained minimal up to a stretch level where it suddenly rose. Therefore, the diameter-tension curve of vessels treated this way was qualitatively similar to the above data on vessels digested under tension: a sudden shift from very low tension to high stiffness at a critical stretch.

Figure 4A shows an example of the vascular ultrastructure in an undigested vessel. This control vessel contained a clear internal elastic lamina, a media consisting of smooth muscle cells (SMCs) interspersed by collagen (mostly type III, based on elastin pattern and diameter as established at higher magnification TEM), a small external elastic lamina, and an adventitia containing densely packed bundles of type I collagen, orientated in both the longitudinal and tangential direction and frequently covered by fibroblast processes. Despite the high stretch during fixation, adventitial collagen bundles had wavy patterns in series with more straight sections. Quantitative image analysis of the undigested vessel revealed a total thickness of collagen fibrils of 3.35 ± 1.54 μm (mean ± SD, based on 20 locations in 1 section). Total wall thickness was 10.76 ± 3.64 μm. Thus collagen constituted 31% of the vessel wall. Collagen was present in the media (1.74 ± 0.87 μm) and adventitia (2.80 ± 0.85 μm). Thicknesses of the internal and external elastic lamina were 1.04 ± 0.33 μm and 0.30 ± 0.02 μm, respectively. These numbers provide a collagen-to-elastin content ratio of 3.39.

An example of the effect of two rounds of collagenase digestion is depicted in Fig. 4B. Collagenase treatment caused disorganization of the medial and adventitial collagen layers. This was characterized by a large increase in distance between individual fibrils and the presence of large apparently empty spaces. The internal elastic lamina appeared swollen and disrupted. In other vessels, part of the SMCs had also disappeared. We did not try to quantitate the degree of collagen digestion because of the highly irregular thickness and fibril spacing of this layer. As a rough visual estimate,
~50–80% of the collagen was removed by the two rounds of digestion.

**Fitting of model predictions to undigested vessels.** Both the HO and SE models could adequately fit the diameter-tension curves of the vessels before digestion. Figure 5 shows an example for the HO model. In Fig. 5A, both the experimental data and the fitted model are shown. Figure 5B indicates the associated distribution of collagen recruitment strain, whereas Fig. 5C plots the fraction of recruited fibers as a function of vessel strain. Figure 5C shows that at the highest applied strain of 0.944, 36% of the collagen fibers are recruited, whereas 64% are still slack. Twelve percent of all fibers became recruited at strains of 0.8 or less, causing the rapid increase in stiffness (Fig. 5A) in this range of strains. At the highest applied strain, these collagen fibers have been extended by at least 18%.

Figure 5D shows the pressure-diameter relation based on Laplace’s law. Table 1 summarizes the fitted parameters for the eight vessels. We found that this model could adequately fit the data for widely varying values of WAE\(_{\text{col}}\). Thus fixing WAE\(_{\text{col}}\) to 69.5 N/m, the average of the individual fits, left estimations of the other three parameters essentially unchanged. For a 10-fold larger WAE\(_{\text{col}}\), the HO model could appropriately fit the data for higher levels of the characteristic strain \(\varepsilon_c\) (Table 1), with a consequently rightward shift of the collagen recruitment curve. This is also illustrated in the example of Fig. 5 (dotted curves, superimposed on the solid line in Fig. 5A), where only 2.4% of the collagen fibers are predicted to be recruited at the highest applied strain. In other words, the classic HO model could be

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Fig. 3. Wall tension as a function of diameter for 8 vessels. **A–F:** six vessels before digestion (●) and after one round (○) and two rounds (□) of collagenase digestion. For **F,** results were obtained for only one round of collagenase digestion due to technical problems. **G** and **H:** two time-matched controls. Dashed lines, 100-mmHg isobar based on Laplace’s law.
fitted to the data on the basis of either low collagen stiffness or content (low WAE\text{col}) or low recruitment (high $\alpha_c$ and thus high mean collagen recruitment strains).

Figure 6A demonstrates an example of fitting the SE model (solid line). In Fig. 6B, the predicted density function $f_i(\epsilon_c)$ for tightening of individual elements is indicated. This highly asymmetric function was characterized by Weibull parameters $\alpha_c = 0.517$ and $\gamma = 0.499$. Figure 6C reflects the fractional number of elements that become straight on ongoing vessel stretch. Thus, at 50% strain, 80% of the elements is rigid. Also, this fit predicts a maximal strain of $\sim$103%, where all elements become rigid.

Table 1 summarizes the fitted parameters based on the serial element model. While this model has three degrees of freedom (WAE\text{el}, $\alpha_c$, and $\gamma$), several alternative combinations of these parameters could be found that almost equally well fitted the data. When WAE\text{el} was fixed to the mean value of this three-parameter model (WAE\text{el} = 0.310) and only characteristic strain $\alpha_c$ and shape parameter $\gamma$ were fit to the data, a somewhat larger $\alpha_c$ and similar $\gamma$ was found (Table 1). For approximately threefold higher fixed values of WAE\text{el}, relatively tight fits were still found (Table 1), but the fitted curves deviated systematically from the data (not shown). When the special case of an exponential distribution of tightening strain ($\gamma = 1$) is considered, still very tight fits were found, as illustrated by the dashed curve in Fig. 6A. Moreover, the variation in $\alpha_c$ between the experiments in this case was minimal. The remaining variation in WAE\text{el} based on this exponential density function was strongly correlated with the vascular caliber ($r^2 = 0.78$, WAE\text{el} vs. slack diameter $D_s$, $n = 8$); the ratio of WAE\text{el}/$D_s$ equaled 3.65 ± 0.18 kPa (mean ± SE, $n = 8$).

**Predicted effects of collagen digestion.** As indicated in METHODS AND MODELS, the effect of collagen digestion can be mimicked in the HO and SE models by changing WAE\text{el} and $\alpha_c$, respectively, based on their dependence on the digestion parameter $\beta$ ($\beta = 1$ reflecting an undigested vessel). Figure 7 depicts the effect of digestion based on the HO model with WAE\text{el} set constant to 69.5 N/m (Table 1). The linear stress-strain relation at low strain (Fig. 7A) remained unchanged, in accordance with the involvement of only elastin in this range. The predicted effect of digestion on the steep part of the curve was characterized by a gradual decrease in slope, essentially without any rightward shift until 80% of all collagen was digested. The density function of collagen recruitment strain (Fig. 7B) was unaffected because fibers of each tightening strain had equal probabilities of being digested. Likewise, the collagen recruitment fraction remained unchanged (Fig. 7C). The consequences of digestion for the strain in pressurized vessels, assuming Laplace’s law, are shown in Fig. 7D. Predictions for the HO model based on a much larger WAE\text{col} (695 N/m; Table 1) were essentially similar (data not shown).

Figure 8 shows the predictions for collagenase treatment based on the SE model and the exponential distribution ($\gamma = 1$; Table 1). The vertical asymptote, i.e., the strain where all elements become rigid, is predicted to gradually shift rightward over a substantial range (Fig. 8A). This is the result of a shift in $\alpha_c$ and thus in the density function of collagen tightening strain (Fig. 8B). Figure 8C indicates a reduction in the fraction of rigid elements at any strain as a result of collagenase treatment. In Fig. 8D, the predicted pressure-diameter relations are indicated, reflecting a substantial increase in diameter while stable diameters are maintained at all pressures. Predictions based on alternative sets of parameters for the SE model (Table 1) were essentially similar (data not shown).

The SE model predictions far more closely resembled the experimental data. However, the experimental curves after collagenase treatment had very low tensions at submaximal strains. Neither the HO nor SE model predicted this aspect. The tested vessels were $\sim$2 mm in length, and the recorded tensions are an average over this length of vessel. We considered the
possibility that collagen digestion was rather variable along the vessel length. Such variability has remarkably dissimilar effects on predictions by both models. In the HO model, all collagen fibers are parallel and an uneven digestion along the length would therefore have no effect on the recorded tension at all. According to the SE model, however, the least digested part would set the strain where tension suddenly rises. Below this strain, the tension would reflect an average over all more or less digested parts of the vessel and would be lower than expected on the basis of homogeneous digestion. This is illustrated by the simulation in Fig. 9, where strain-tension curves are depicted for the exponential model with digestion parameter $\beta = 0.7$ (left dashed line) and $\beta = 0.3$ (right dashed line) as well as for varying digestion along the length with $\beta$ ranging between 0.7 and 0.3 (solid line). This solid line, with a sharp switch from low tension development to rigidity, more closely resembles the observations.

While a SE model with a varying degree of digestion along the length could possibly be fitted to the data, the fitting procedure is quite cumbersome. We therefore followed a more practical approach and estimated $\beta$ for the least digested part of each vessel from the highest applied strain, i.e., a strain close to the vertical asymptote where all element become rigid (see METHODS AND MODELS). The values of $\gamma$ needed for this estimate were taken from the fits of the undigested vessels, because $\gamma$ is invariant under digestion. The estimates for $\beta$ are indicated in Fig. 10 based on the SE model with parameter sets (Table 1) including either varying $\gamma$ (A) or $\gamma = 1$ (B). While these two choices provided quantitatively different estimates for $\beta$, both show a gradual reduction in $\beta$ over the two incubation periods. The

![Graph A](image1.png)
![Graph B](image2.png)
![Graph C](image3.png)
![Graph D](image4.png)

Table 1. Parameter estimation based on model fitting to experimental vessels

<table>
<thead>
<tr>
<th>Model</th>
<th>$WAE_{col}$ N/m</th>
<th>$WAE_{el}$ N/m</th>
<th>$\alpha$</th>
<th>$\gamma$</th>
<th>$r^2$</th>
<th>Mean Collagen Strain</th>
<th>Recruitment at 100 mmHg, %</th>
<th>$A_c E_c / A_e E_e$</th>
</tr>
</thead>
<tbody>
<tr>
<td>HO model</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Four parameters</td>
<td>69.5 ± 9.2</td>
<td>0.800 ± 0.096</td>
<td>1.11 ± 0.08</td>
<td>8.09 ± 1.05</td>
<td>0.993–0.997</td>
<td>1.04 ± 0.07</td>
<td>31.9 ± 3.5</td>
<td>91.8 ± 10.6</td>
</tr>
<tr>
<td>$WAE_{col} = 69.5$</td>
<td>0.801 ± 0.097</td>
<td>1.14 ± 0.09</td>
<td>8.30 ± 1.21</td>
<td>0.993–0.997</td>
<td>1.06 ± 0.08</td>
<td>32.6 ± 5.5</td>
<td>99.8 ± 16.4</td>
<td></td>
</tr>
<tr>
<td>$WAE_{col} = 695$</td>
<td>0.811 ± 0.100</td>
<td>1.93 ± 0.28</td>
<td>6.00 ± 0.66</td>
<td>0.992–0.997</td>
<td>1.78 ± 0.25</td>
<td>3.2 ± 0.5</td>
<td>989 ± 161</td>
<td></td>
</tr>
<tr>
<td>SE model</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Three parameters</td>
<td>0.310 ± 0.057</td>
<td>0.550 ± 0.089</td>
<td>0.542 ± 0.064</td>
<td>0.988–0.999</td>
<td>1.06 ± 0.03</td>
<td>97.2 ± 0.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$WAE_{col} = 0.310$</td>
<td>(0.310)</td>
<td>(0.616 ± 0.054)</td>
<td>(0.578 ± 0.049)</td>
<td>(0.997–0.999)</td>
<td>(1.04 ± 0.03)</td>
<td>(97.3 ± 0.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$WAE_{col} = 1$</td>
<td>(1)</td>
<td>(1.016 ± 0.088)</td>
<td>(4.35 ± 0.98)</td>
<td>(0.983–0.997)</td>
<td>(0.92 ± 0.01)</td>
<td>(99.5 ± 0.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\gamma = 1$</td>
<td>0.554 ± 0.047</td>
<td>0.944 ± 0.010</td>
<td>(1)</td>
<td>(0.995–0.999)</td>
<td>(0.94 ± 0.01)</td>
<td>(97.4 ± 0.5)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values are means ± SE; $n = 8$ experimental vessels. For $r^2$, the range is indicated. The four parameters of the HO model were $WAE_{col}$, $WAE_{el}$, $\alpha$, and $\gamma$ of the Weibull distribution, and the three parameters of the SE models were $WAE_{col}$, $\alpha$, and $\gamma$. Mean collagen strain was derived from $\alpha$, and $\gamma$. Recruitment at 100 mmHg is the percentage of recruited fibers (HO model) or rigid elements (SE model) at this pressure. $A_c E_c / A_e E_e$ indicates the ratio of the collagen and elastin content-stiffness product, as derived from $WAE_{col}$ and $WAE_{el}$. See Glossary for abbreviations.
second incubation period was somewhat less effective than the first one. Moreover, larger vessels were much more resistant to collagen digestion than smaller ones. No attempt was made to estimate the degree of digestion based on the HO model because the predictions for this model were fully incompatible with the collagenase results.

**DISCUSSION**

**Summary of results.** We analyzed the adequacy of two fundamentally different models in predicting passive mechanical properties of rat mesenteric small arteries. Both the classic HO model and a new SE model could be fitted to the observed strain-tension relations.

![Fig. 6. Example of fitting the SE model to experimental data. A: strain-tension data (○) and fitted curve for a three-parameter model (solid line) as well as a model with an exponential collagen tightening strain density function (dotted line). B: density functions $f_1(\varepsilon)$ of the collagen tightening strain for the three-parameter (solid line) and exponential (dotted line) models. C: fraction of elements with straight collagen as a function of vessel strain. D: predicted pressure-diameter relation of this vessel.](image-url)

![Fig. 7. Predictions of the effect of collagen digestion based on the HO model. Shown are predictions for digestions of 0–90% of all collagen in the wall in steps of 10%. A–D are as in Fig. 5, A–D; dashed lines in A and D are 100-mmHg isobars.](image-url)
of untreated vessels. However, the SE model far better predicted the effect of collagenase treatment. Moreover, unrealistically large distension of individual collagen fibers, as found in the HO model, is absent in this SE model. Finally, this model requires one parameter less (collagen stiffness and content), and even a still-further simplification by assuming an exponential collagen tightening density function did not affect the adequacy of fitting the data. We thus propose that the SE model provides a useful concept for the understanding of vascular mechanics.

**Motivation of model choices.** We kept the models as simple as possible. Aspects that were ignored include the active smooth muscle, viscous properties, three-dimensional organization of the vascular wall, and zero stress state. Some of these aspects have been studied in the past on the basis of the HO model (5, 29), and it is clear that such work needs to be done on the SE model as well. Recently, Maksym and Bates extended their SE model of lung tissue mechanics (15) in two dimensions, predicting complex features such as self-orga-

![Fig. 8. Predictions of the effect of collagen digestion based on the SE model. A–D are as in Fig. 6, A–D.](image)

![Fig. 9. Predicted effect of heterogeneous digestion along the vessel length according to the SE model. Shown are digestion at β = 0.7 (left dashed line) and β = 0.3 (right dashed line) and a homogeneously (hom) distributed degree of digestion between 0.7 and 0.3 (solid line).](image)

![Fig. 10. Estimation of digestion parameter β for 6 digested vessels (closed symbols) and 2 time-matched controls (open symbols) based on the maximum diameter that could be applied during the experiments and the SE model with varying γ (A; see also Table 1) or γ = 1 (B). Numbers indicate initial D100 values (in μm). Control, before digestion; D1 and D2, after one and two digestion periods, respectively. See Glossary for a description of parameters.](image)
nized criticality and preferential pathways of force transmission (16).

The TEM pictures make clear that collagen is present in both the media (mainly type III) and adventitia (type I), and collagen type IV may be present at the basal side of the endothelial cell. In the model, we did not aim to discriminate between the various collagen types and locations. Indeed, it is not clear which collagen is carrying the stress under normal conditions and how this stress distribution is altered by the collagenase. Clearly, future work will be needed to unravel this and refine the model accordingly.

Vascular diameter is determined by both the passive elements and SMCs. For the HO model, SMC activity has been included in the past as a single compartment parallel to the collagen and elastin, with the inclusion of extra collagen in series (29). In the future, the SE model should also be extended with these SMC properties. This could be done by adding a SMC component parallel to the elastin and collagen in each of the elements. This way, this model would have cross-connections between the SMC and extracellular fibers at the boundary between each two elements. Because the active elements, cytoskeleton, and extracellular elements form a continuum, this design seems to be a more realistic starting point. We do believe that ignoring the SMC in the current passive, static models is justified: previous work (28) from our laboratory justifies the SMC in the current passive, static models is justified: previous work (28) from our laboratory showed that passive isolated SMCs do not maintain stress even on severe distension, even though collagen is carrying the stress under normal conditions. Indeed, it is not clear which collagen is carrying the stress under normal conditions and how this stress distribution is altered by the collagenase digestion. Importantly, this large increase in stress on severe distension, even though collagen is carrying the stress under normal conditions.

The substantial rightward shift of the strain-tension curve after digestion seems fully incompatible with the HO model. According to this model (Fig. 7), digestion would result in pivoting of the steep part of the strain-tension curve around the point where collagen recruitment starts rather than in a rightward shift. This is a consequence of the shape of the collagen recruitment function (Fig. 7C) and the presence of substantial “spare” collagen with recruitment strains only marginally larger than the highest strains in the control runs.

One could argue that the SE model is still unnecessarily complex because it assumes multiple parallel collagen fibers in each compartment (Fig. 2) rather than a single fiber. For the undigested vessels, this would make no difference. However, during digestion, some of the elements would then lose all collagen, resulting in linear stress-strain relations of these elements and a consequent loss of vessel stiffening upon ongoing strain. When incorporating this simplified model, we found such reduction in vessel stiffness to result in instability at constant pressure (i.e., absence of an intercept with the Laplace relation); at 100 mmHg, such instability occurred after removal of ~40% of the collagen. This model was therefore not further considered.

Adequacy in predicting experimental data. Both models could adequately fit the data obtained on undigested vessels. In both cases, alternative sets of parameters could be found (Table 1) with similar goodness of fit. For both models, estimations of $\text{WA}\text{E}_{\text{col}}$ had the order of magnitude; e.g., using the SE model with an exponential fit, the ratio of $\text{WA}\text{E}_{\text{col}}/D_e$ of ~4 kPa follows from the wall-to-lumen ratio (0.057) and elastin content (12.4%) as observed by TEM in combination with an elastin stiffness of 560 kPa. For the HO model, initial predictions of $\text{WA}\text{E}_{\text{col}}$ were unrealistically low: collagen fibers are known to be ~1,000-fold more stiff than elastin fibers (8). Yet, the product of content and elastic modulus ($A_{\text{f}} \cdot E_c$, in Table 1) was less than 1000-fold higher for collagen. This would indicate that these vessels contain ~10-fold less collagen compared with elastin, which seems unreasonable based on histological studies (6). In fact, the current electron microscopy work (Fig. 4) reveals 3.4 times as much collagen as elastin. When we fixed $\text{WA}\text{E}_{\text{col}}$ to 10-fold higher values, appropriate fits were still obtained. However, in this case, mean collagen hook-on strain became much higher, indicating that under normal conditions the vast majority of fibers remains slack (see also the dotted line in Fig. 5C). It seems difficult to understand why a vessel would need all this slack collagen that is, based on the HO model, not contributing to vascular mechanics.

The main effect of collagenase treatment on the vessels was a quite substantial increase in strain at physiological equivalent pressures. As an extreme example, the vessel in Fig. 3D had a control passive diameter of 228 μm at 100-mmHg equivalent pressure, which rose to 515 μm after the second round of collagenase digestion. Importantly, this large increase in diameter was still associated with a high stiffness in this range. Consequently, a clear intercept exists between the strain-tension curve and physiologically relevant isobars (e.g., the 100-mmHg line in Fig. 3). The digested vessels would therefore still be mechanically stable under pressurized rather than isometric conditions. We tried to test this directly on cannulated, pressurized vessels but found that leakage occurring during digestion prevented adequate control of intraluminal pressure.

The substantial rightward shift of the strain-tension curve after digestion seems fully incompatible with the HO model. According to this model (Fig. 7), digestion would result in pivoting of the steep part of the strain-tension curve around the point where collagen recruitment starts rather than in a rightward shift. This is a consequence of the shape of the collagen recruitment function (Fig. 7C) and the presence of substantial “spare” collagen with recruitment strains only marginally larger than the highest strains in the control runs.

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According to this model, such spare fibers would take over after digestion and still greatly limit distension. While we could have considered more complex collagen recruitment distributions, both our HO model and previous analyses (5, 30) indicate that in passive vessels at \( \sim 100 \) mmHg, recruitment of collagen fibers would be low and still in the steep upward slope phase of the density function. Substantial distension could, according to the HO model, occur suddenly if the vast majority of collagen fibers were digested (bottom curve in Fig. 7A). However, the strain-tension relation would then be dominated by the linear elastin and no longer be steep, resulting in mechanical instability. Moreover, in two periods of digestion, we observed a more or less regular increase in maximal strain (Fig. 3), indicating a gradual effect of digestion on maximal strain that is not predicted by the HO model. We did not consider the possibility that “short” collagen fibers are preferentially digested, but there seems to be no evidence for this view.

The large reduction in tension at submaximal strain after collagenase digestion was inconsistent with both models. This reduction could be explained by a possible uneven digestion along the length of the vessel, where the stop length of the whole vessel depends on the least digested part of it, while tensions at lower strains represent averages over the vessel length (Fig. 9). Alternatively, the elastin stiffness could have been affected. While it is unlikely that collagenase had directly digested elastin fibers (17, 12), our electron microscopy images did reveal changes in the internal elastic lamina. These could have been caused by the removal of surrounding collagen or by the severe distension of the vessel after digestion.

The models were fitted to data on wire-mounted rather than pressurized vessels, and implications for pressure-diameter relations were simply based on Laplace’s law. The geometric distortion of the vessel passed around the wires may have influenced the results. Thus, upon the initiation of distension, an extra force will be needed to deform the vessel from its round circumference. However, we believe that this force is negligible, because these same vessels readily flatten and collapse when cannulated and subjected to very slight (<1 mmHg) negative pressures.

Comparison with earlier collagenase experiments. Effects of collagenase digestion on mechanical properties have been studied before in large vessels and lung tissue strips. Dobrin et al. (9) found a modest, parallel shift of the pressure-diameter relation above \( \sim 50 \) mmHg in human external iliac arteries, resembling our data and the prediction of the SE model for low degrees of digestion (Fig. 8D). Internal iliac arteries had a more substantial shift. In both vessels, some compliance remained up to 300 mmHg in both undigested and digested vessels. This aspect is inconsistent with the SE model, where compliance would fall to zero once all collagen is straight. It is also inconsistent with the HO model because extreme extension of collagen would be required. Therefore, more complex, two-dimensional models may be needed for description of the behavior of large vessels under such high pressures. Kitoh et al. (13) observed an upward shift of pressure-volume curves in the dog external jugular vein after collagenase digestion, again resembling the data of Fig. 8A. Yuan et al. (31) found a substantial rightward shift of the stress-strain relation and a reduction in stress at all strains in lung tissue strips, resembling the changes that we found in the small arteries and the prediction by the SE model (Fig. 8A). These authors indeed indicate that SE models, as previously suggested for lung tissue by Maksym and Bates (15), form probable explanations for such behavior.

Importance for vascular physiology. Vascular structure continuously adapts to local pressure and flow (14), among other factors. Thus increasing flow is known to induce outward remodeling in large (23, 25) and small vessels (26). Such remodeling requires removal of collagen fibers or cross-links by matrix metalloproteinases. According to the SE model but not the HO model, a gradual relation exists between the degree of outward remodeling and amount of collagen removal. This gradual relation would allow for regulation of caliber without massive removal of collagen fibers or losing mechanical stability under pressurized conditions. As an example, according to the fits to the experimental data, a 20% at random removal of collagen would cause a 2.1% and 22.8% increase, respectively, in the passive diameter at 100 mmHg in the HO and SE models (Figs. 7 and 8). The relation between formation of new collagen fibers and inward remodeling in both models is more difficult to predict. Here, the length of the newly formed fibers is a critical parameter. In analogy to the effect of removing collagen, depositing collagen according to the existing distribution would cause little effect in the classic model and a gradual inward remodeling in the SE model. Depositing short collagen, on the other hand, would cause a rapid inward remodeling (3) according to both models.

In the presence of SMC tone, there seems relatively little contribution of the collagen and elastin to the wall stress. However, collagen turnover during remodeling may well be linked to not only the passive but also the active diameter. Thus there is a clear relation between the diameter where active force is maximal and the passive diameter. In general, peak active tension is found a diameters \( \sim 90\% \) of the passive diameter at 100 mmHg. Indeed, this common relation is being used to set the distension for vessels during wire myography (20). It seems that either the structural regulation of active and passive elements is closely coordinated or the relation between active and passive stress-strain curves is a direct consequence of the extensive and continuous connection of elastic and contractile fibers in the wall. In either case, remodeling of the matrix is very likely to be linked to a shift of also
the active properties and thus the diameter of the active vessel.

In summary, we have presented a new concept for static passive properties of blood vessels. Compared with the classic HO model, this SE model seems the more realistic choice as a starting point for the modeling of vascular mechanics for several reasons: 1) no extensive strain of individual collagen fibers; 2) no extremely low collagen recruitment fractions, low content, or low stiffness; 3) no assumptions on collagen stiffness, other than that it needs to be orders of magnitudes higher than elastin stiffness; 4) a better prediction of collagenase effects; and 5) adequacy in describing strain-tension relations with as few as three or (in the case of exponential tightening distributions) even two parameters. The SE model may therefore prove a useful basis for the understanding of the relation between collagen turnover and vascular remodeling.

APPENDIX: COLLAGEN STRAIN VERSUS VESSEL STRAIN IN THE HO MODEL

In the HO model, collagen strain ($\varepsilon_c$) is less than strain of the whole vessel ($\varepsilon_v$). Their relation can be derived as follows: vessel strain is defined as

$$\varepsilon_v = (L - L_0)/L_0, \quad L = L_0 \cdot (1 + \varepsilon)$$

(A1)

where $L$ and $L_0$ are the actual and resting lengths of the vessel. Likewise, strain of a collagen fiber is defined as

$$\varepsilon_c = (L_c - L_{c0})/L_{c0}, \quad L_c = L_{c0} \cdot (1 + \varepsilon)$$

(A2)

where $L_c$ and $L_{c0}$ are the actual and resting lengths of the fiber. The collagen recruitment strain is defined as the vessel strain where collagen is just tight

$$\varepsilon_c = \varepsilon_L = L_{c0}$$

(A3)

Combining Eqs. A1 and A3

$$\varepsilon_c = (L - L_{c0})/L_{c0}, \quad L = L_{c0} \cdot (1 + \varepsilon)$$

(A4)

If the collagen has hooked on, the collagen fiber and vessel have the same length

$$L = L_{c0}, \quad \varepsilon > \varepsilon_c$$

(A5)

Combining Eqs. A2 and A5

$$\varepsilon_c = (L - L_{c0})/L_{c0}, \quad L = L_{c0} \cdot (1 + \varepsilon)$$

(A6)

Combining Eqs. A1 and A4

$$\varepsilon_c = (\varepsilon - \varepsilon_c)/(\varepsilon_c + 1), \quad \varepsilon > \varepsilon_c$$

(A7)

The expertise technical assistance of Titia Rolf in performing the electron microscopy is highly appreciated.

REFERENCES


