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What Are the Residual Stresses Doing in Our Blood Vessels?*

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We show that the residual strain and stress in the blood vessels are not zero, and that the zero-stress state of a blood vessel consists of open-sector segments whose opening angles vary along the longitudinal axis of the vessel. When the homeostatic state of the blood vessel is changed, e.g., by a sudden hypertension, the opening angle will change. The time constant of the opening angle change is a few hours (e.g., in the pulmonary artery) or a few days (e.g., in the aorta). From a kinematic point of view, a change of opening angle is a bending of the blood vessel wall, which is caused by a nonuniformly distributed residual strain. From a mechanics point of view, changes of blood pressure and residual strain cause change of stress in the blood vessel wall. Correlating the stress with the change of residual strain yields a fundamental biological law relating the rate of growth or resorption of tissue with the stress in the tissue. Thus, residual stresses are related to the remodeling of the blood vessel wall. Our blood vessel remodels itself when stress changes. The stress-growth law provides a biomechanical foundation for tissue engineering.

Keywords—*Arteries, Residual stress, Residual strain, Blood vessels, Veins, Initial stress, Zero-stress state, Tissue engineering, Remodeling, Tissues.*

INTRODUCTION

It is an honor for me to be invited to present this ALZA lecture. I remember listening to the first ALZA lecture presented by Dr. Arthur Guyton (18) in the Johns Hopkins University Auditorium. His analog circuit of the human body is as fresh in my mind today as when I saw it that day. I have listened to many ALZA lectures through the years. To follow them is an honor and a challenge. Most of my predecessors described large programs of advanced research and showed many many-splendored scenes. Today, I'd like to go the other way, to dig a little at the foundation, to see if everything is well and sound. I would like to deal with an *ad hoc* hypothesis in biomechanics which has been so universally accepted that it has almost become an axiom. The hypothesis is that when all external loads acting on an organ are re-

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moved, there is no stress in the organ. I shall show that this is generally untrue, and that removal of this hypothesis will lead us to rethink many things.

The stress that exists in an unloaded solid body is called residual stress. The usual hypothesis in biomechanics is that the residual stress in living organs is zero. What I would like to show is that it is not. Nonvanishing residual stress exists. The residual stress affects the stress distribution in the body at its working condition under load. In a living organism, the function of its organs depends on the levels of their internal stress and strain at the working condition. For example, the force and velocity of contraction of the skeletal muscle of our limbs, the heart muscle of our heart, and the vascular smooth muscle of our blood vessels depend on the stress and strain in the muscle cells at the instant of time the muscles begin to contract. In other words, the residual stress and strain together with the external load determine the stress and strain rate of the muscles after they are stimulated to contract. The metabolic needs and the flow of oxygen, carbon dioxide, and various ions in the muscles are related to the rate of work done by the muscles, thus they depend on the stress, strain, and their residual values. The blood flow that is needed to supply or remove these materials in the muscles is related to the metabolism, hence, is related also to the residual stress. Hence, the importance of residual stress to physiological function is clear; and I will not elaborate too much on this point.

As a living organism is subjected to body forces like gravity and inertial force due to acceleration, and surface forces like pressure, shear, surface tension, and cell adhesion, internal stresses are induced in the organism's body. These internal stresses must be small enough to avoid physical injury. Below the physical injury levels, a living organism can respond to stress by growth, resorption, proliferation, death, or by remaining in a steady state. The organism not only deforms under physical forces, but can also change itself in a living manner. Our question is: How does the living tissue remodel itself? How fast? How much? How is the process controlled? What use can be made of this phenomenon? I shall discuss these questions especially in the case of the blood vessel. I would like to show that a study of the residual strain is a convenient way to study the remodeling of living tissues in a changing physical stress environment, and that the stress-growth law is a biomechanical foundation of tissue engineering.

THE ZERO-STRESS STATE OF A BLOOD VESSEL

To analyze stress and strain in a body, it is necessary to know the zero-stress state: the geometric shape assumed by the body when the stress is zero everywhere. In the literature, virtually all publications assume that the zero-stress state of a body is the state when all external loads are removed. But is it? In Fig. 1 an aorta is sketched. If we cut an aorta twice by cross-sections perpendicular to the longitudinal axis of the vessel, we obtain a ring. If we cut the ring radially, it will open up into a sector (23). By using equations of static equilibrium, we know that the stress resultants and stress moments are zero in the open sector. Whatever stress remains in the vessel wall must be locally in equilibrium. If one cut the open sector further, and can show that no additional strain results, then we can say that the sector is in zero-stress state. We did a simple experiment illustrated in Fig. 2 (from Ref. 15). Five consecutive segments (rings) 1 mm long each were cut from a rat aorta. The first four segments were then

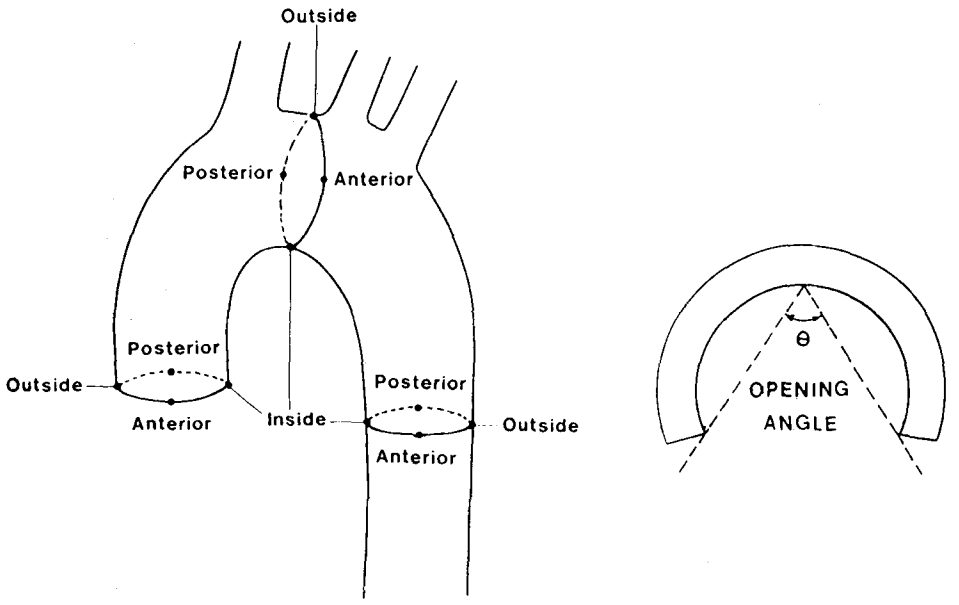

FIGURE 1. Sketch of an aorta with an indication of the cutting positions. Right: Schematic cross-section of a cut vessel segment at zero-stress, defining the opening angle θ.

cut radially and successively at the positions indicated in Fig. 1, namely, inside, outside, anterior, posterior; designated as I, O, A, P, respectively. The fifth segment was cut in all four positions, resulting in four pieces designated a, b, c, d. The open sectors of the first four rings are shown in the upper row on the right. When the four pieces of the fifth ring were reassembled in the order of abcd, bcda, cdab, bcda, with tangents matched at successive ends, we obtain four configurations shown in the lower row of Fig. 2. They resemble the shape of the four cut segments of the first row quite well. This tells us that the arterial wall is not axisymmetric, that different parts of the circumference are different, and that one cut is almost as good as four cuts in relieving the residual stress.

The rat aorta is too small for measuring the second order small differences of the strains in the specimens of the two rows shown in Fig. 2. Omens and Fung (28) did measure the residual strains in the left ventricle of the rat by first cutting a slice of the left ventricle parallel to its base (seat of mitral valve), then cutting it radially once, and radially again at a polar angle of 142° from the first cut. It was shown that the differences of strains in the slice between the first and second cuts were small quantities of the second order. Hence, we may say that one cut of the ring reduces the ring into zero-strain state within the first order of infinitesimals.

Having been assured that the open sector represents zero-stress state of a blood vessel, we conclude that the zero-stress state of an artery is not a tube. It is a series of open sectors. To characterize the open sectors, we define an *opening angle* as the angle subtended by two radii drawn from the midpoint of the inner wall (endothelium) to the tips of the inner wall of the open sections (see Fig. 1). Although a full descrip-

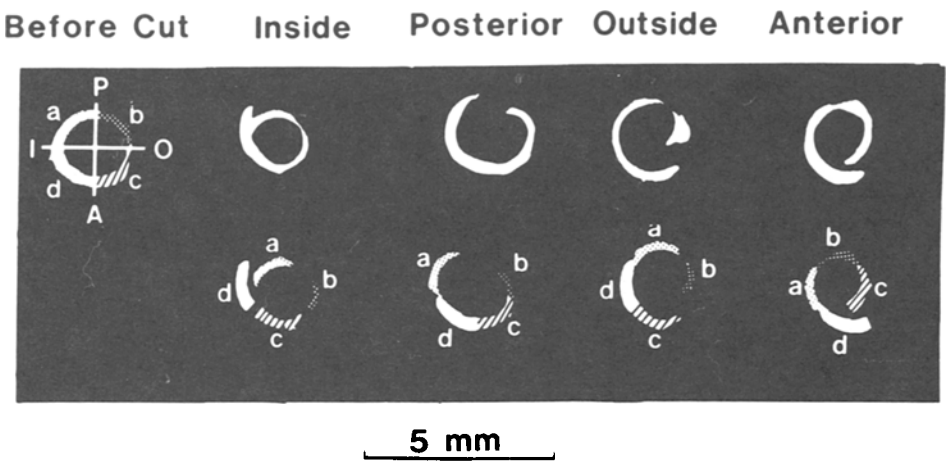

FIGURE 2. The figures in the upper row show an arterial segment of a rat before cut and after cutting at four positions. The lower row shows the same vessel cut into 4 pieces and reassembled in 4 ways. It appears that one cut is sufficient to reduce an arterial segment at no-load to the zero-stress state. From Fung and Liu (15).

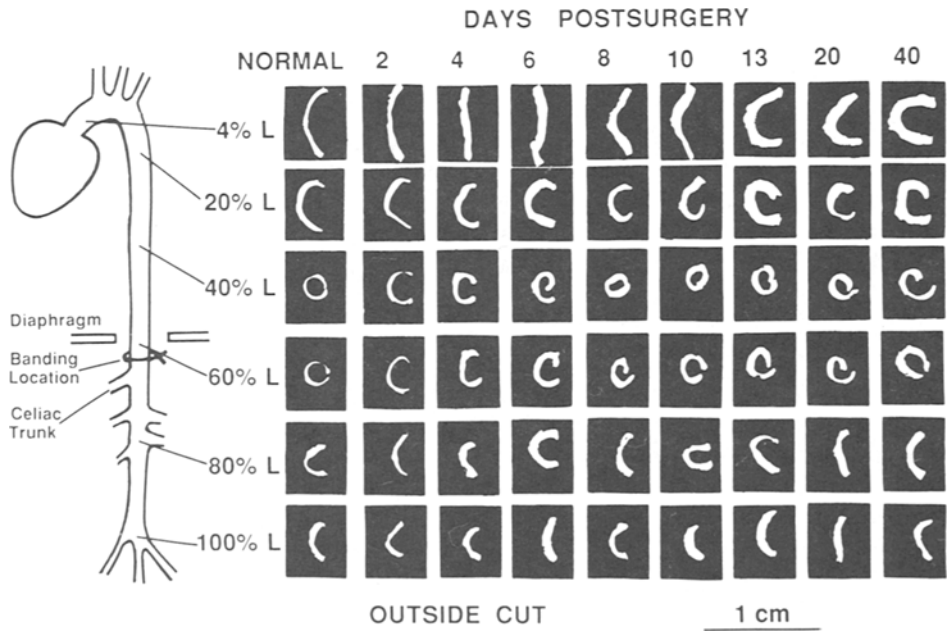

FIGURE 3. Photographs of the cross-sections of a rat aorta cut along "outside" line shown in Fig. 1. The 1st column shows zero-stress state of normal aorta. Other columns show changed zero-stress states a number of days after a sudden onset of hypertension. Successive rows correlate with locations on the aorta expressed in percentage of total length of aorta, L, from the aortic valve. The aortic cross-sectional area was clamped 97% by a metal band below the diaphragm to induce the hypertension. From Liu and Fung (15).

tion of the geometry of the sector can only be done with a photograph or its equivalent, the opening angle does provide a simple numerical index.

The photographs in the first column of Fig. 3 show a more complete picture of the zero-stress state of a normal young rat aorta (Fung and Liu, 1989, Ref. 15). The entire aorta was cut successively into many segments of approximately one diameter long. Each segment was then cut radially at the "outside" position indicated in Fig. 1. It was found that the opening angle varied along the rat aorta: it was about 160° in the ascending aorta, 90° in the arch, 60° in the thoracic region, 5° at the diaphragm level, 80° toward the iliac bifurcation point.

Following the common iliac artery down a leg of the rat, we found that the opening angle was in the 100° level in the iliac artery, dropped down in the popliteal artery region to 50°, then rose again to the 100° level in the tibial artery (17). In the medial plantar artery of the rat, the micro arterial vessel 50 μm diameter had an opening angle of the order of 100° (17).

There are similar spatial variations of opening angles in the aorta of the pig and dog (19,35), although there were quantitative differences. We also found significant opening angles in pulmonary arteries (16), systemic and pulmonary veins (37), and trachea (20). Thus we conclude that the zero-stress state of blood vessels and trachea are sectors whose opening angles vary with the locations on the vessel, and with animal species.

HYPERTENSION CAUSES CHANGE OF THE OPENING ANGLE OF AORTA

We created hypertension in rats by constricting the abdominal aorta with a metal clip placed right above the celiac trunk (15,24). The clip severely constricted the aorta locally, reduced the cross-sectional area of the lumen by 97%, with only about 3% of the normal area remaining. This caused a 20% step-increase of blood pressure in upper body, and a 55% step-decrease of blood pressure in the lower body immediately following the surgery. Later, the blood pressure increased gradually, following a course shown in Fig. 4 (from Ref. 15). It is seen that in the upper body the blood pressure rose rapidly at first, then more gradually, tending to an asymptote at about 75% above normal. In the lower body, the blood pressure rose to normal value in about 4 days, then gradually increased further to an asymptotic value of 25% above normal. Parallel with this change of blood pressure, the zero-stress state of the aorta changed. The changes are illustrated in Fig. 3 in which the location of any section on the aorta is indicated by the percentage distance of that section to the aortic valve measured along the aorta divided by the total length of the aorta (24). Successive columns of Fig. 3 show the zero-stress configurations of the rat aorta at 0,2,4,. . . ,40 days after surgery. Successive rows refer to successive locations on the aorta.

The course of change of the opening angles at various sections of the aorta is shown in Fig. 5 (from Ref. 24). The opening angles increased at first, peaked in 2 to 4 days, then decreased gradually to an asymptotic value (24). Variation with the location of the section on the aorta was great. The maximum change of the opening angle occurred in the ascending aorta, where the total swing of the opening angle was as large as 88°.

Thus we found that the blood vessel changed its opening angle in a few days following the blood pressure change. We found similar changes in pulmonary arteries

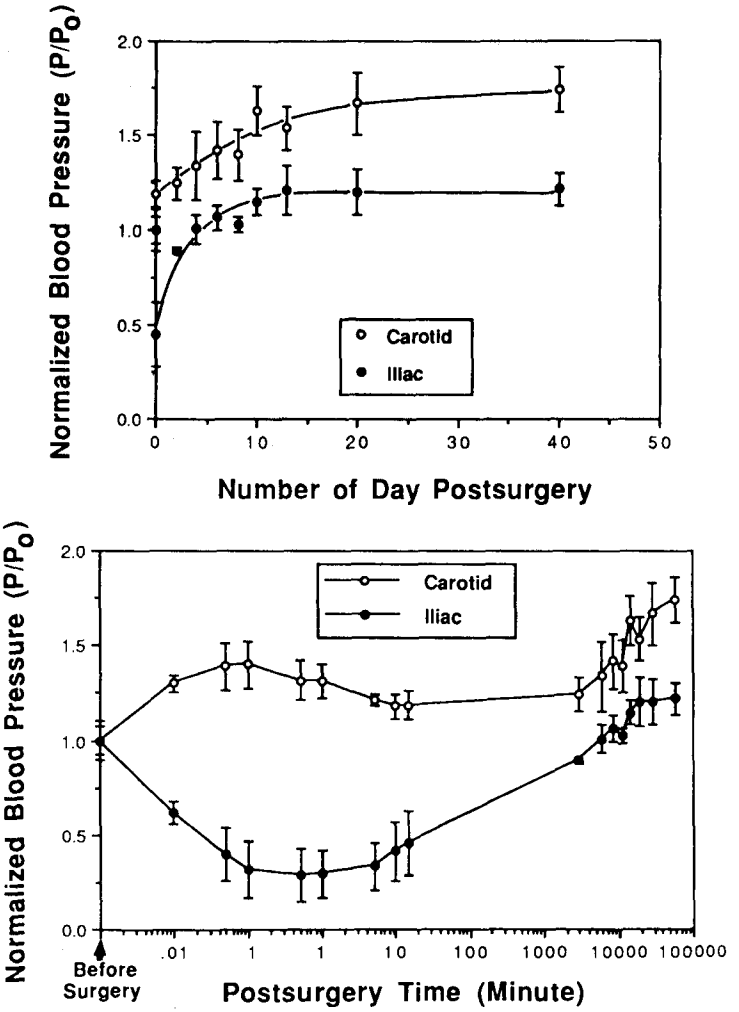

FIGURE 4. The course of change of blood pressure (normalized with respect to that before surgery) after banding the aorta. From Fung and Liu (15).

after the onset of pulmonary hypertension by exposing rats to hypoxic gas containing 10% oxygen, 90% nitrogen, at atmospheric pressure (16).

Since opening angle changes reflect structural changes, we conclude that blood vessels remodel significantly with modest blood pressure changes.

WHAT DOES THE CHANGE OF OPENING ANGLE MEAN?

The open sector configuration of an artery at zero-stress looks like a curved beam and mechanically can be analyzed as a curved beam (12). (See Fig. 1, which shows a curved beam with rectangular cross-section.) A beam can change its curvature only if one side of the beam lengthens while the other side of the beam shortens. If the opening angle increases due to tissue remodeling, then the curvature of the longitu-

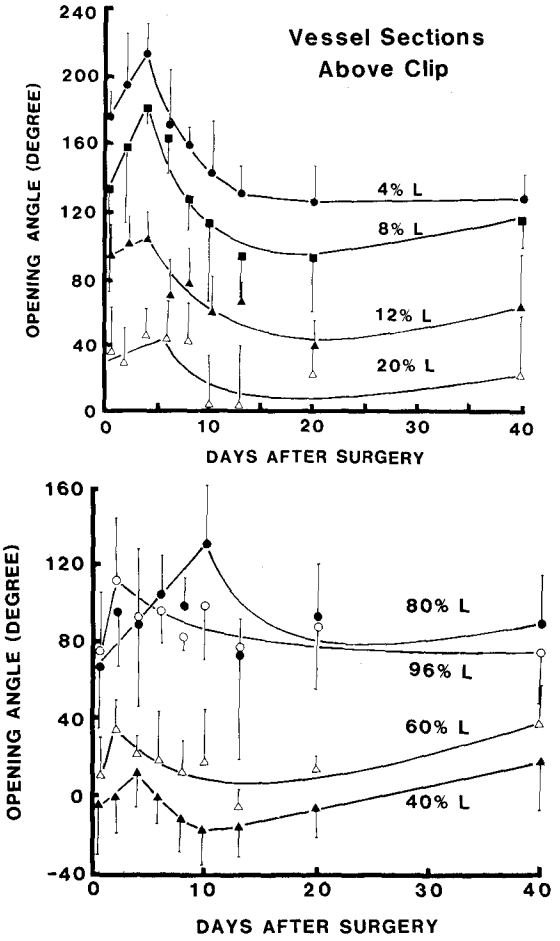

FIGURE 5. The course of change of the opening angle of the rat aorta at the zero-stress state following aortic banding to change blood pressure. L is the length of aorta. %L indicates location of section from aortic valve. (a) Locations above the constriction. (b) Locations below the constriction. From Fung and Liu (15).

dinal axis of the beam decreases. Then the endothelial side of the blood vessel wall must have an increase in circumferential strain, while the adventitial side of the blood vessel wall must have a decrease of circumferential strain, see Fig. 6 (from Ref. 12). Since these increases and decreases are not due to external loads, but are due directly to the growth and resorption of the tissue in remodeling, we can conclude without much ado that the change of opening angle of blood vessels due to change of blood pressure is due to *nonuniform* remodeling in the vessel wall.

From the point of view of studying tissue remodeling, the zero-stress state is significant because it reveals the configuration of the vessel in the most basic way, without being complicated by elastic deformation (13). If cellular or extracellular growth or resorption occurs in the blood vessel due to any physical, chemical and biological stimuli, they will be revealed by the change of zero-stress state.

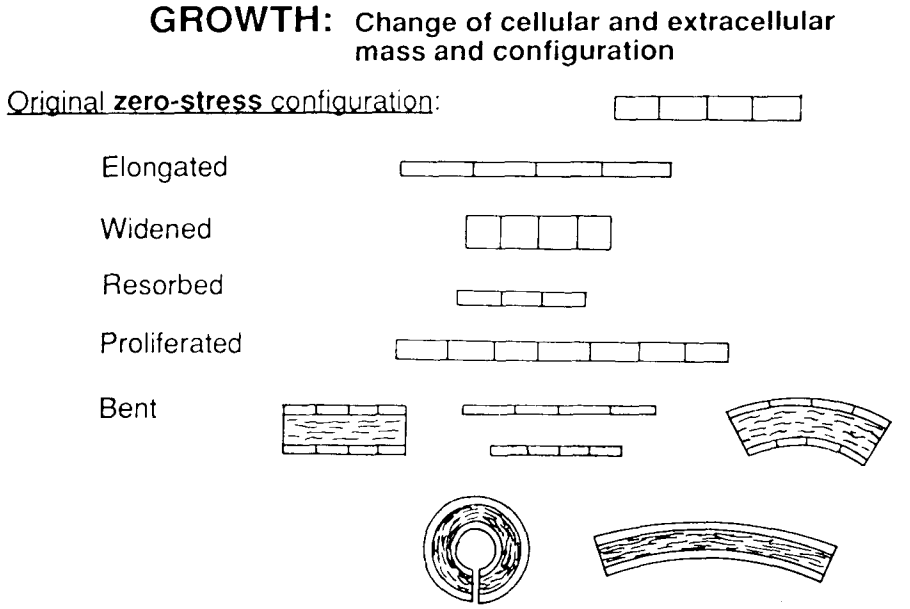

FIGURE 6. Illustration that the remodeling of a blood vessel is best described by change of its zero-stress state. From Fung (12, p. 528).

MORPHOMETRIC EVIDENCES OF NONUNIFORM REMODELING

Meyrick and Reid (26) and others have shown that pulmonary arteries subjected to hypoxic hypertension remodels rapidly and nonuniformly. Liu and I (16) used their method to study the course of morphological changes in rat pulmonary artery following the onset of pulmonary hypertension by exposing rats to a hypoxic chamber as described earlier, and also in the course of development of diabetes (25). In hypoxic pulmonary hypertension, we found intimal edema within minutes, followed by thickening of the intima and deformation of endothelial cells. Blebs appear in the intima, and disappear after 2 to 3 days (17). The media layer with smooth muscle cells thickened rapidly between 2 to 10 days following the exposure of the rat to hypoxia, then its thickening slowed in the next 10 to 30 day period (17). The adventitia thickened last: its thickness exceeded that of the intima-media after about 4 days (17). Thus the nonuniform remodeling of the vessel wall in response to the onset of hypertension can be seen morphologically.

Morphological features are difficult to quantify; and circumferential strains are especially difficult to measure by conventional morphometric means. Our opening angle measurement is a new morphometry which complements the conventional morphometry (thickness change, cell proliferation) very nicely.

WHAT DO THE RESIDUAL STRAINS IMPLY?

Why do I think it is important to know the residual strains in the arterial wall? To explain my point of view, perhaps I could be forgiven to describe a bit of personal

experience. (I was told that it is a tradition of the ALZA lectures to describe the author's personal experience and perspective.) I thought of looking for the residual stress at a BMES Annual Meeting in New Orleans in 1982. I was hoping that finding its existence would resolve a dilemma in ventricular and arterial mechanics. A large amount of theoretical work by Mirsky (27), Janz and Grimm (22), Patel and Vaishnav (29), Yin (38), Fung (8,9), and others have shown that the stress distribution in the ventricular or vascular wall at normal blood pressure is highly nonuniform, with a concentration of circumferential stress at the inner wall. At that time, Chuong and I had just finished a detailed analysis of three-dimensional stress distribution in arterial wall using a nonlinear constitutive equation which we believed in, and our theoretical results confirmed once again a very large circumferential stress concentration (2–4). In fact, we knew that the more precise the nonlinear constitutive equation is, the higher is the stress concentration (4). I didn't like this conclusion. The culprit, I suspected, was the hypothesis that the no-load state is the zero-stress state of the blood vessel or the heart.

On returning to my laboratory, Patitucci and I cut several rabbit arteries and left ventricles, and we found immediately that they readily opened up, thus contradicting the no-residual-stress hypothesis (10,11). On putting the experimental opening angle into the calculations of a thoracic aorta working under normal blood pressure, Chuong and I showed that the circumferential stress concentration is reduced (later published in Refs. 5,6).

Further theoretical analyses showed that to remove the stress concentration, a curved vessel at normal blood pressure needs a greater opening angle. I knew that the main trunk of the pulmonary artery is very curved in the neighborhood of the pulmonic valve. Liu and I examined the opening angle of the rat pulmonary arterial trunk, and we were rewarded by finding that its opening angle is usually 360° or more in this curved region (16). In other words, the main pulmonary artery would turn itself inside out when given a chance. These analyses suggest that an implication of the residual stress in arteries is to make the stress distribution more uniform in the vessel wall in normal condition.

I found out much later that almost simultaneously Vaishnav and Vossoughi (33,34,35) were investigating the same thing and were lead to a similar conclusion.

WHAT PRINCIPLE GOVERNS THE STRESS DISTRIBUTION IN LIVING ORGANS?

Questioning whether the residual stresses consist of such amounts as to make the maximum principal stress uniformly distributed in the heart and blood vessels, I presented a paper with the title "What Principle Governs the Stress Distribution in Living Organs" at the First China-Japan-United States Conference on Biomechanics held in Wuhan in June, 1983 (10), and proposed the uniform circumferential stress as a possible rule. Looking for evidences, I searched the literature on ventricular sarcomere length in diastolic heart. The data seem to support this hypothesis, i.e., the sarcomere length is fairly uniform throughout the ventricular wall when the heart is in end-diastolic condition (11, p. 61). Sidney Sobin and John Hardy then helped me to look for similar morphological evidence in blood vessels. We used rabbit mesentery, perfused and fixed it at several perfusing blood pressures, and measured the spacing of dense bodies in the circumferential direction on the vascular smooth muscle cell mem-

branes. The dense-body spacing in a smooth muscle cell is an analog of the sarcomere length of a heart muscle, and presumably the spacing of the dense bodies in the cell membrane bears a definite relationship to the dense body spacing inside of the muscle cell. We found that the dense body spacing on the cell membrane is most uniform from the inner wall of the media to the outer wall of the media in the blood vessel wall at a blood pressure of 100 mm Hg (11, pp. 62–65). If we can assume that at the zero-stress state the spacing of the dense bodies on the cell membrane of all the vascular smooth muscle cells are the same, and that all cells obey the same stress–strain relationship, then this finding implies that the stress and strain distributions are most uniform when the blood pressure is around the normal value of 100 mm Hg. By implication, the dense body spacing would be nonuniform in the smooth muscle layer at the no-load state. The strain at the no-load state is the residual strain (11). The dense body spacing is related to the strain. Hence the nonuniform spacing of dense bodies means that the residual strain is nonuniform, so that the opening angle at zero stress is non-zero as we found in experiment. Hence, the dense-body data support the hypothesis that the stress and strain distribution is uniform in the blood vessel wall at the normal (homeostatic) blood pressure.

In a series of papers since 1987, Hayashi and Takamizawa (21), Takamizawa and Hayashi (31,32) used the "uniform strain" hypothesis for blood vessels at homeostasis and computed the residual strain and zero-stress state on the basis of that hypothesis.

Such a uniform stress or uniform strain hypothesis at homeostasis would simplify the analysis of homeostatic stress and strain in blood vessels. It is very convenient. But it is a phenomenological statement. The empirical basis of this phenomenological hypothesis lies in the observations mentioned above. In 1983 I felt that the emperical basis was not sufficiently strong, and there was a need to search for a broader foundation, and a firmer empirical base. This need still exists today. This is why my students and I continue to investigate the relationship between stress and growth in detail both at the homeostatic condition and when homeostasis is disturbed. We would like to find a higher principle from which this hypothesis can be derived. I believe such a higher principle is the stress-growth law.

SPECULATION ON STRESS-GROWTH OR STRAIN-GROWTH RELATIONSHIP

Tissue growth can be affected by many factors: nutrition, growth factors, physical and chemical environment, diseases, as well as stress and strain. If other things were equal, then a stress-growth law (or a strain-growth law) may exist. Since a blood vessel is a composite material made of cells and extracellular matrix containing collagen, elastin and other substances, and each substance may have a stress-strain-growth law, there may be as many laws as there are materials.

At the present time, such a stress-growth law is unknown for blood vessels. Hence the most we can do is to speculate. I'd like to present a possible form of such a law. Referring to Fig. 7, let the solid curve represent a relationship between the rate of growth of the mass of a material, $\dot{M}$, and the stress or strain acting in the material, s. The symbol s may represent a component of the stress or strain tensor, or a stress or strain invariant: exactly what it is would have to be determined later. Let a represent a homeostatic stress, at which the tissue can maintain a steady-state. $\dot{M}$, the rate of growth of a material in a tissue, is positive when the stress or strain s exceeds a. $\dot{M}$ is negative when s is less than a. The homeostatic condition of blood vessel wall at

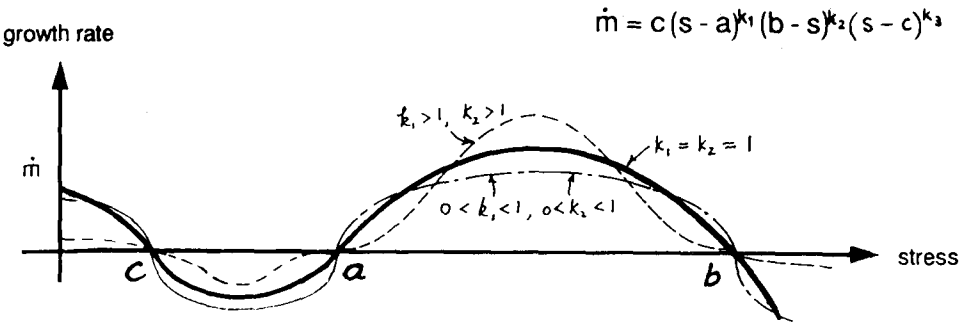

FIGURE 7. The author's proposed stress-growth law. From Fung (12, p. 530).

normal blood pressure is represented by the point a. The rate of growth $\dot{M}$, however, cannot increase indefinitely with increasing s. A well-known phenomenon of bone resorption under excessive stress or strain suggests that another homeostatic stress or strain b exists beyond which resorption occurs. Similarly, the negative rate when the stress or strain is less than a cannot be unbounded in the whole range of $s < a$. Suppose that resorption stops when $s = c$, where $c < a$; then c is another homeostatic stress or strain. If the rate of growth $\dot{M}$ is a continuous function of the stress, s, and this function has zeros at a,b,c, and if the trend of change of $\dot{M}$ at a,b,c, is as discussed above, then I would like to propose the following simple relation (12, p. 530):

$$\dot{M} = C(s-a)^{k_1}(b-s)^{k_2}(s-c)^{k_3} \tag{1}$$

in which $\dot{M}$ is the rate of increase of the volume of the tissue, s is the stress, a, b, c are constants having the units of stress (N/m^2), C is a constant with units ($m^5\ N^{-1}\ s^{-1}$), k_1,k_2,k_3, are dimensionless numbers. When $\dot{M}$ is plotted against s, Eq. (1) is illustrated in Fig. 7. When s lies between a and b or O and c, the tissue grows. When s exceeds b or falls between a and c, the tissue resorbs. As s tends to zero, I assume $\dot{M}$ to be positive as in cell culture in petrie dishes. The exponents k_1,k_2,k_3 determines how fast the growth rate changes when s deviates from the homeostatic state. If $k_1 > 1$, the slope of the growth curve is zero at $s = a$, then small deviation has little influence. The slope of the growth curves is infinite at a if $k_1 < 1$. $k_1 = 1$ signals a finite slope.

I am using this theoretical proposal as an experimental hypothesis. I hope to find out experimentally whether Eq. (1) is true or false, whether it can or cannot be modified to obtain better results.

The exact definition of s is a subject to be studied. It could be any one of the strain or stress invariants, e.g., the maximum principal stress or strain, the maximum shear stress or strain, or the von Mises or octahedral stress or strain. It is unlikely to be the first invariant (sum of the three normal stresses or strains) unless the material is compressible.

In the field of orthopedics there is the famous Wolff's law of bone transformation which says that there is a perfect mathematical correspondence between the structure of cancellous bone in the proximal end of the femur and the trajectories in Culmann's crane, and that there is a statical importance and necessity of the trajectorial struc-

ture of the bone (36, see (12), p. 500). Wolff's law has generated a huge literature, a brief review of which is presented in my Biomechanics book (12). Cowin (7) has attempted to state it in a precise tensorial form, and to emphasize that s should be strain. Carter *et al.* (1) have developed a growth-strain-energy law for the calcification of cartilage into bone, and vice versa, and demonstrated the important role of strain energy. Any formulation of growth-stress law for internal organs should refer to these papers. And there is a huge literature on physical education, athletics, sports, and sports medicine which tells people how to get strong and improve performance. Finally, there is the science and art of surgery and rehabilitation, which puts growth-stress relationship to daily practice. Thus there exists a large stock of knowledge which, however, has not been distilled into a mathematical form. The reason for this lack of mathematization is probably because of a lack of suitable means for controlled experimentation. I hope that the simple and convenient ways shown here for blood vessels may help.

RELEVANCE TO TISSUE ENGINEERING

Tissue engineering is a field dedicated to the engineering of living tissues (13,14,30). The field of tissue engineering lies between the field of genes and cells and molecular biology on the one hand, and that of organ physiology and holistic medicine on the other hand. To master tissue engineering one must know how the health of tissues is maintained, improved, or degenerated. To understand artificial tissues containing live cells, one must know more about the behavior of natural cells in association with artificial materials. If we talk about tissue engineering of arteries, we should at least know how natural arteries behave. What we discussed above is elementary and fundamental for tissue engineering. To create and control a tissue, we must know all the relevant stress-growth laws. We have much to learn. The task is a large one. That's why I offer the speculative Eq. (1) as a starter, to invite further thinking and experimentation.

In conclusion, I must say that I am amazed at the way our arteries remodel themselves in response to changing blood pressure. I believe that these modes of change would offer us a handle on controlling our blood vessels if we understood their behavior fully.

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