Physical Factors in the Progression of Stenotic Vascular Lesions

By Simon Robbards, M.D., Ph.D.

An explanation of the progression of stenotic lesions was sought in animal experiments. After surgical decrease of the lumen of arteries, progressive ingrowth of fibrous connective tissue led to the development of stenosis with changes in the artery that resembled those of coarctation. These changes are explained by the action of local blood pressures. Phenomena such as progressive stenosis, valvulogenesis, patterns of lipid infiltration, medial hypertrophy, thinning, and cystic change are discussed in terms of the concepts derived from these studies.

The high pressure cardioid to stenotic arterial lesions, as for example in coarctation of the aorta and in closure of vital vessels such as the coronary arteries, is often sufficient to cause vascular injury with the production of aneurysms and rupture of the vessel wall. Paradoxically, these continuously high arterial pressures never dilate the constricted arterial ring and relieve the stenosis.

The same paradox holds for stenotic lesions of the cardiac valves. Thus, in aortic or pulmonic valvular stenosis, the hypertrophied ventricle generates high pressures that beat recurrently against the contracted outlet; yet the stenosis is inexorably progressive, leading ultimately to cardiac failure.

These anomalous situations have been highlighted recently by repeated demonstrations that gentle digital dilation of stenotic mitral valves is sometimes sufficient to free the agglutinated leaflets and lead to clinical relief from the symptoms of obstructed blood flow. It is remarkable that the continuous action of the relatively high atrial pressure never achieves the same dilating effect as the momentary insertion of the surgeon's finger.

The mechanisms responsible for the development, persistence, and progression of these stenotic lesions have been ascribed to "congenital" or "inflammatory" processes. Unfortunately neither of these etiologic mechanisms is subject to adequate experimental analysis.

Other factors, such as mechanical forces, may also participate in the initiation and progression of stenosis. These forces can be analyzed relatively easily to determine their potential influences on elastic or deformable vessels. Thus, flow can generate forces that cause the walls of elastic channels to be drawn together, producing a sharply reduced flow. In other experiments the flowing stream regularly induced stenosis of channels lined with silicone sometimes forming valves, coartations, stenoses, dissections, and other arrangements strikingly similar to those of the cardiovascular system. These structural modifications have been shown to result from the pressure effects produced by high velocities of flow at a given point in the channel.

In the present study on animals, deviations of the blood streamlines are shown to induce the progression of stenotic lesions, with the production of valve-like structures and other modifications of the blood vessel wall. These

From the University of Buffalo, Chronic Disease Research Institute, Buffalo, New York, and the Cardiovascular Department, Medical Research Institute, Michael Reese Hospital, Chicago, Ill. The Chronic Disease Research Institute is supported in part by a grant-in-aid from the New York State Department of Health. The Cardiovascular Department is supported in part by the Michael Reese Research Foundation.

Aided by grants H-690 and H-2271 from the National Heart Institute of the U. S. Public Health Service.

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![Image of aorta](http://circ.ahajournals.org/)

**Fig. 1.** Technic of placement of tuck in the wall of aorta, permitting a portion of the circumference of the vessel to be free of manipulation. In some instances the tuck was placed on the subclavian artery.

effects appear to result from the response of the structures of the vessel to the local pressure acting on its walls.

**METHODS**

In preliminary experiments an encircling silk or linen ligature was used to constrict the thoracic aorta in 6 dogs. A slight proliferation of the intima with the production of a ring-like thickening was observed at the site of narrowing. Similar findings leading to nearly complete obstruction were described nearly 50 years ago by Halsted. Since these changes could be attributed to injury of the vessel wall by the circumferential ligature, the procedure was modified to reduce the element of direct local injury.

In the experiments reported below, the cross section of the lumen was diminished by placing a mattress suture of linen or catgut in an arc of the vessel wall. Care was taken not to injure the portion of the wall not involved by the suture material (fig. 1). Sutures were placed in the descending thoracic aorta of 70 chicks and in the subclavian artery of 10 dogs. After periods of time up to 1 year, the animals were sacrificed and the heart and blood vessels were examined.

**RESULTS**

*Effect of Slight Reduction in Lumen.* In 15 experiments a suture was placed through a small arc of the blood vessel wall involving less than 25 per cent of the cross-section area. Examination at necropsy in periods up to 4 months revealed a small scar at the suture site as expected, but no significant changes were present in the remainder of the vessel wall.

These studies showed that the simple placement of the foreign material caused no significant change in the general structure of the vessel except for the local distortion, injury, and reaction.

*Greater Degrees of Narrowing.* In 55 chicks the cross section of the aorta was reduced by approximately half or more. Examination within a day or 2 after surgery in 4 chicks showed no notable changes in the vessels, beyond those directly due to the surgery itself.

Autopsy at periods of 1 week to several months after surgery revealed in most of the specimens that the suture had resulted in an isolated, nonproliferative scar, similar to those seen when only a small arc of the vessel was pinched off, as noted above.

However, in 17 chicks striking changes were seen at the site of the surgical narrowing. In general these consisted of a grossly visible ingrowth of tissue into the lumen of the vessel, immediately distal to the site of the placement of the suture. In some animals the vessel lumen was almost completely occluded by a diaphragm-like structure (figs. 2 and 3).

Gross examination revealed that the apparent diaphragm in some specimens was so thin as to be nearly translucent. In others a thick wall was present with only a tiny lumen remaining, usually in the center of the ingrowth. The growth varied from specimen to specimen and was not uniform, except for the generally marked tendency to proliferation into the lumen of the vessel.
Microscopic examination of specimens taken at sacrifice 2 to 6 weeks after placement of the tuck revealed that the obstructing diaphragm consisted of young connective tissue with little or no collagen. The intima was not uniformly developed but consisted of relatively loose connective tissue, sometimes in large masses, and in other sites consisting of tag-like excrescences. The growth was definitely present in sites away from the suture material (figs. 4 and 5). There was no evidence that these structures were due to a previous local thrombosis, since blood pigment was not present. In no instance was the lumen completely

FIG. 2 Top. Subclavian artery of a dog, partially constricted by a tuck 2 months before sacrifice. Cardiac side of the specimen (left); cross section at the level of greatest narrowing of the artery (right).

FIG. 3 Bottom. Subclavian artery of a dog partially constricted 4 months prior to sacrifice. Cardiac portion of the artery showing a coarctation-like stenosis (right). Cephalad end of the same specimen (left). The small central lumen is seen.

FIG. 4 Top. A chick aorta after partial narrowing by a tuck of catgut 3 weeks previously (Weigert stain). The catgut, with a marked inflammatory reaction, is still seen at lower portion of figure. The remaining lumen contains an ingrowth of intimal connective tissue. This comprises a central mass as well as small tags that have their origin on the portion of the wall not directly involved by the suture.

FIG. 5 Bottom. Microscopic section of a segment of the wall adjacent to section shown in figure 4. Finger-like projections of hyperplastic intima consisting of oval to spindle-shaped fibroblasts are seen. The surface is lined by endothelial cells. An occasional mononuclear cell is seen. Large cells with vacuolated cytoplasm are present. Hematoxylin and eosin. × 430.
closed; a small orifice could always be seen.

At the site of the suture an inflammatory round-cell infiltration and organization was present around the suture material, particularly within the first week or 2. In other specimens, the local inflammatory reaction had subsided.

The media in the regions not involved by the suture also showed changes. In some aortas there was an apparent change in the alignment of the elastic and muscular elements of the media. Upstream to the region of constriction the media had a well-developed muscularis and elastica. Beyond the constricting diaphragm the arterial wall was considerably thinned and the muscularis and elastica were of lesser thickness. A specimen demonstrating these differences in thickness of the vessel wall as well as showing a valve-like structure is illustrated in fig. 6.

A thick-walled chick aorta above the region of narrowing, with reorganization of the elastic components of the media, and cystic change, is shown in figure 7.

In 5 of 8 dogs in which a subclavian artery had been partially constricted by the method described for chicks, a marked narrowing was present at the site of suture placement. A diaphragm occluded the lumen except for a small orifice which remained in all specimens. Histologic examination revealed a pattern of intimal ingrowth into the vessel, generally similar to that described above for the chick.

Growth around a Linen Suture. In 6 chicks a linen suture was pulled through the aortic lumen, leaving a "violin string" bridge across it. The linen became completely covered by intima. The upstream face of the suture was covered by a thin layer of endothelial cells and a small amount of subendothelial connective tissue. By contrast, the downstream face of the suture was covered by a relatively thick layer of connective tissue, sometimes with frond-like trailers (fig. 8).

Blood Pressures. Evidence for dynamic effects of the narrowing was seen in blood pressure measurements. The intraarterial blood pressure above and below the constriction was measured with a Sanborn electromanometer in 19 chicks. The arterial pressure above the stenosis was significantly higher than the usual levels for chicks of comparable age in 4 of the test animals. The blood pressure below the site of constriction was markedly reduced. A marked pressure drop across the constriction was observed in 7 of 8 chicks in which pressures above and below the constriction were measured simultaneously.

Discussion

The present experiments demonstrate that partial narrowing of the lumen of a blood vessel may be followed by an ingrowth of connective tissue and the development of a
Intima. The normal intima of blood vessels is ordinarily very thin, consisting primarily of flattened endothelial cells and a thin subendothelial layer. It is suggested that the flattening of the endothelial cells and their functional specialization may result from their continuous compression by the lateral blood pressure.

The endothelium, like other connective tissue, has a great potential for growth. Ordinarily this potential becomes apparent only after injury to the vessel wall, when the endothelial cells proliferate rapidly and reline the injured area. This growth potential can also manifest itself in the proliferation of the intimal cells into the lumen, with an ultimate complete obstruction to flow. Such a sequence occurs when blood is stripped from a segment of artery that is then tied at both ends. A rich intimal proliferation of young connective tissue quickly fills the lumen under these circumstances. It is here suggested that this potential growth is usually inhibited by the distending pressure normally present in arteries and veins, presumably by a process akin to pressure atrophy.

In the present experiments, narrowing of the vessel lumen by placement of a tuck probably increased the velocity of the bloodstream at this site. A marked pressure drop would result locally, in accord with the principle of conservation of energy (Bernoulli*). As the velocity increases to a critical value the distending pressure may fall to or even below the level of the surrounding tissue pressure. The normal distending pressures are thus eliminated and the intimal layer, freed from the atrophic influences of pressure, can grow into the lumen.

As growth proceeds the narrowing of the lumen becomes more severe; the velocity of the stream is further increased and the distending pressure at the site falls still more. Stenosis thereby tends to become progressive.

*The total energy at any point in a stream is equal to that expended as lateral or distending pressure, plus that expended as velocity. An increase in velocity at a site will therefore necessarily result in a local fall in the distending pressure.
This interpretation provides an explanation for the paradox that the high upstream pressure never dilates and "cures" a stenotic vascular ring. Similarly, restenosis of a surgically dilated mitral ring might be expected when a high velocity flow through it persists because of inadequate dilatation or because of the generation of an insufficiency at the site.

This hypothesis is supported by the experiments in which a suture bridging the lumen became covered by endothelium and connective tissue. The thinly covered upstream side was constantly subjected to the pressure of the stream, presumably inhibiting proliferation at this site. The downstream side of the suture was thickly covered with connective tissue and endothelium; it is this portion that would have the lowest pressures acting on it. The distribution of growth along the suture therefore conforms with growth patterns expected on the basis of the hydrodynamic interpretation given above.

In other studies we have illustrated some of these streamline patterns by use of "wall-mapping" technics demonstrating the development of valves and stenoses of similar appearance.

Further support for the hydraulic concept may be derived from unpublished data in cholesterol-fed chicks that show fatty infiltrations of the arterial wall above and below the site of narrowing, but not at the constriction itself. The high velocity at the narrowing results in a low local pressure, which would be associated with a reduced infiltration at this site.

Orifice. The process of progressive stenosis reaches an ultimate end point, at which a small probe patency remains. As the lumen becomes progressively narrowed, the resistance to flow through it rises sharply (Poiseuille's law) and the velocity is reduced. The resulting local increase in lateral pressure may then act to halt intimal ingrowth. An equilibrium is thus achieved between lumen...
Fig. 9. An interpretation of the sequence of events after placement of a tuck in a blood vessel. In A, radial and longitudinal section of the vessel are shown, the arrow giving the direction of flow. In B, sutures (x) are placed in an arc of the vessel wall, reducing the lumen. In C, ingrowth into the lumen is indicated in the region near the sutures. In D, concentric intimal ingrowth narrows the lumen producing a coarctation-like obstruction. Thickening of the wall above and thinning of the wall beyond the narrowing are related to the pressures present in the various portions of the vessel.

size and velocity, resulting in the maintenance of anatomic but "nonfunctional" patency. Probe patency of this type is common in stenotic processes such as in coarctation of the aorta, as well as in patent foramen ovale and ductus arteriosus without significant shunts.17, 18

Media. The response of the media is determined primarily by the tension on the blood vessel wall. If either the pressure or the diameter is increased, the tension is increased proportionately.19 The medial elements then increase in amount and become compact. At sites of reduced pressure these elements of the media are diminished. The same mechanisms may account for the pattern of medial development in our specimens in the segments of the arteries where the pressure was normal or raised. Above the stenotic site, the medial wall was markedly thickened. Beyond the site of constriction, where the arterial pressure was diminished, the elastic elements of the vessel were reduced and the wall was notably thinned. These findings accord with the concept that the degree of development of the media is an adaptive response to the distending force it must meet. Such a concept would explain the medial thinning at atheromatous plaques,20 since the "lift" of the bloodstream would actually reduce the tension acting on the media under the plaque. A "lifting" force of this type may also account for the presence of "cystic" spaces in the media at a site of partial obstruction (fig. 7).21, 22

These studies suggest that the structure of blood vessels may depend to a significant extent upon the action of physical forces on the intimal and medial elements of the vessel wall.

SUMMARY

The lumen in blood vessels of chicks and dogs was reduced by placing a mattress suture in an arc of the wall. A small reduction in the cross section area produced a localized inflammatory response; at autopsy the cross section was of the preoperative size. Placement of the suture to produce a marked reduction in cross section area was followed by intimal proliferation at the site, with the development of valve-like or progressive, coarctation-like stenoses. The intimal proliferation appears to result from hydrodynamic factors lowering the pressure locally.

The medial changes were related to the tension acting on the vessel wall. Above the constriction, where the pressure was high, the media tended to be thickened. Medial cystic spaces were present near the constriction. At the constriction, the lines of the elastic fibers were reorganized in patterns that may relate to the stress forces in this region. Below the narrowing, the medial wall was thin.

ACKNOWLEDGMENT

I am indebted to Chizuko Kakita, B.S., Christine B. Williams, B.A., and Walter Stone, M.D., for assistance in the surgical preparations; and to Francis Williams, M.A., for the blood pressure determinations. T. T. Bronk, M.D., of the Department of Pathology gave assistance in the description of the microscopic specimens. Dr. L. N. Katz, Director of the Cardiovascular Department, Michael Reese Hospital, contributed to many discussions during the development of the study.
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SUMMARIO IN INTERLINGUA

Le lumine de vasos de sanguine de gallinas e canes esseva reduce per effectuar un sutura de matrassero in un areo parietal. Un micre reduction in le area del section transverse produciva un responsa de inflammation localisate. Al necropsia le section transverse habeva le magnitude preoperatori. Quando le sutura esseva placiata da manera que un marcate reduction esseva effectuate in le area del section transverse, le consequentia esseva un proliferation intimal al sito del operatione con le disveloppamento de stenoses progressive de character coarctatori e valvuloide. Il pare que le proliferation intimal resulta de factores hydrodynamic que effectua un reduction local del pression.

Le alterations medical esseva relationate al tension que ageva super le pariete del vaso. Supra le constrictione, ubi le pression esseva alte, le media exhibiva le tendentia de spissificare se. Cystic spatiis medial esseva presente in le vicinitate del constrictione. Al sito del constrictione, le linea del fibras elastic esseva reorganisate in configurationes que es possibilemente relationate al fortias de tension in iste region. Infra le constrictione le pariete medial esseva tenue.

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SIMON RODBARD

_Circulation_. 1958;17:410-417
doi: 10.1161/01.CIR.17.3.410

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1958 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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