Effect of Calcification on In Vivo Mechanical Response of Rabbit Arteries to Balloon Dilation

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Background. Atherosclerosis has been associated with loss of artery wall distensibility in human cadavers and in experimental animal models, giving it the lay term “hardening of the arteries.”

Methods and Results. To assess the effect of calcification on arterial distensibility, balloon pressure and volume were recorded during dilation of calcified aortas in Watanabe heritable hyperlipidemic (WHHL) rabbits in vivo. Calcification was induced by dietary supplements of cholesterol, vitamin D3, and calcium. Balloon pressure, volume, and time signals were acquired at high frequency with controls for temperature and balloon inflation rate.

Resistance to balloon dilation was minimal in control rabbit aortas (ΔVmax=5.0±3.5 μl) and in excised nonatherosclerotic human coronary arteries, and it was small in aortas from cholesterol-fed rabbits (12.3±8 μl), even when lipid levels were markedly elevated by a high cholesterol diet (611±347 mg/dl). With dietary cholesterol, vitamin D3, and calcium supplements, WHHL rabbits developed mild hypercalcemia (15±1.9 mg/dl), hypercholesterolemia (1,100±633 mg/dl), moderate-to-marked aortic calcification, and high resistance to balloon dilation (38±27) comparable to that seen in angioplasty patients.

Conclusions. It is concluded that experimentally induced calcification decreases the distensibility of the rabbit aorta in vivo and that it yields to balloon dilation by plastic deformation closely resembling that seen in balloon angioplasty of human coronary arteries. These findings suggest that calcification contributes to arterial “hardening” associated with atherosclerosis. (Circulation 1991;83:2083–2093)

Loss of arterial distensibility may be a central element in the transition from coronary atherosclerosis to clinical ischemic heart disease. Without the shock-absorbing capacity of a normal artery, the atherosclerotic wall may be subjected to greater shear and intramural stresses on impact of pulsatile pressure waves, exposing the intima and plaque to greater injury. Arterial “hardening” also may limit both conservation of lumen area by compensatory enlargement1 and enlargement of lumen area by balloon angioplasty. Both increased and decreased distensibility, early and late in atherosclerosis, respectively, have been measured in atherosclerotic arteries of experimental animal models and in postmortem humans.2–7

In previous studies, we described a method for recording pressure and volume signals from atherosclerotic human coronary arteries in vivo during balloon dilation through the angioplasty catheter.8,9 Preliminary results suggest a relation between pressure–volume patterns and clinical outcome.9

The purpose of the present study was to assess the effect of artery wall calcification on mechanical response of atherosclerotic arteries to balloon dilation in an experimental animal model. Almost no resistance to balloon distension was found in normal and atheromatous aortas from cholesterol-fed and control Watanabe heritable hyperlipidemic (WHHL) rabbits. However, with dietary supplements of cholesterol, calcium, and vitamin D3, the rabbit aortas developed calcification and a mechanical response to dilation similar to that seen in human coronary arteries. These results suggest that calcification is important in the arterial “hardening” associated with atherosclerosis.
Methods

Homozygous WHHL rabbits\textsuperscript{10} were obtained from the Atherosclerosis Research Unit of the UCLA School of Medicine and treated in conformity with the guiding principles of the American Physiological Society. All received standard rabbit chow (Purina 5322) until the time of the study.

Six control WHHL rabbits continued to receive standard chow during the 6-week study period (control group). Seven WHHL rabbits were given a 1% cholesterol diet (Purina 5731C-6) for the 6-week study period (cholesterol-fed group). One rabbit died spontaneously after 5 weeks. Seven WHHL rabbits were administered oral supplements of calcium carbonate, 250 mg/day (5 days/wk), and vitamin D\textsubscript{2} (Ergocalciferol, Eli Lilly, Indianapolis, Ind.), 50,000 units 3 days each week, in addition to the 1% cholesterol diet (calcium/cholesterol-fed group). One rabbit in this group died spontaneously after 4 weeks. Two other rabbits were included in the control group to check for an age effect. Serum cholesterol and calcium levels were obtained within 24 hours of catheterization. Serum calcium was also obtained midway through the diet period in all but one (not obtainable) of the calcium/cholesterol-fed rabbits and in two cholesterol-fed rabbits with unexpected hypercalcemia.

An electronic pressure transducer (model P51-2, Konigsberg, Pasadena, Calif.) and a linear variable differential transformer (model 1002 XS-D, Schaevitz, Pennsauken, N.J.) were incorporated by custom machining (Buchi AG, Uster, Switzerland) into a stainless steel inflation syringe (USCI, Billerica, Mass.) to measure balloon pressure and volume.

Signals were conditioned (model SMSGPM-108A, Schaevitz) and amplified with transformer-coupled isolation, electromagnetic shielding, and battery power to ensure safety. Pressure and volume were monitored on a 20-MHz storage oscilloscope (model COS-5020-ST, Kikusui, Torrance, Calif.), digitized at 10 Hz (LabVIEW NB-MI016, National Instruments, Austin, Tex.), and displayed on a computer monitor (Figure 1). The frequency response and linearity of the pressure transducer and volume transducer were greater than 20 kHz and ±0.04 atm and 3 kHz and ±0.80\% of full range, respectively.

At the end of the diet period, rabbits were anesthetized with 8 mg/kg xylazine (20 mg/ml) (Rompun, Mobay Corp., Shawnee, Kan.) and 45 mg/kg ketamine (50 mg/ml) (Ketalar, Parke-Davis, Morris-town, N.J.) intramuscularly. A right femoral arteriography was performed. A 3.0-mm angioplasty balloon on a custom-manufactured, 13-cm-long catheter (Advanced Cardiovascular Systems, Mountain View, Calif.) was primed with water, was inserted into the arteriotomy site over an angioplasty wire, and was advanced into the distal aorta just proximal to the iliac bifurcation. Position was checked by fluoroscopy (Philips Super, 100 R/S; L/9 image intensifier) and by length markers on the catheter. Angiography (roll film changer, Franklin) was performed in two rabbits of each group with iopamidol contrast material (Isovue) injected through a 3F Sones catheter or through the balloon angioplasty catheter. Roentgenographic magnification was determined by including a 1 cm external radio-opaque marker or by the 2-cm radio-opaque markers on the balloon catheter. Pressure–volume curves were obtained during inflation of the balloon to 8–12 atm at a rate of 1/8 turn/sec (25 \textmu l/sec). Balloon inflation was repeated at the same site of the aorta until no further changes occurred in the pressure–volume curve, approximately three or four inflations for most aortas.

After the balloon was withdrawn, an anesthetic overdose was given, and the aorta was surgically exposed. Abdominal aortic segments measuring 2 cm in situ were excised immediately distal to the renal arteries. They were washed free of blood and dissected free of adventitia. To measure luminal surface area, they were cut lengthwise and opened flat so that the shape could be traced onto filter paper of highly uniform thickness and density. Area was then calculated from the weight of the traced section of filter paper relative to the weight of a 1-cm\textsuperscript{2} section of the same paper: lumen surface area is equal to weight of

![Diagram of the device used to measure inflation pressure and volume during balloon angioplasty. An electronic pressure transducer and a linear variable differential transformer were incorporated into a stainless steel inflation syringe. Pressure and volume signals were amplified, digitized, and displayed on a computer.](http://circ.ahajournals.org/...
traced section of filter paper divided by weight per unit area of filter paper.

Specimens were individually dried for 12 hours in a warming oven at 100°C, then ashed in a high-temperature oven (Tempco, Hershaw Scientific) at approximately 700°F during 24 hours. The ash was dissolved in 1.25 ml of 1N HCl, then neutralized with 1.25 ml of 1N NaOH. Calcium concentration was determined by atomic absorption spectrophotometry. Total calcium content was calculated, and wall calcium content was normalized for the luminal surface area.

Segments of the abdominal aorta, from the iliac bifurcation to 3 cm proximally, were cut into 3-mm sections and preserved in 10% neutral-buffered formalin for 48 hours, were rinsed in double-distilled water, and were sequentially dehydrated with 80%, 95%, and 100% ethyl alcohol each for 60 minutes. Specimens were infiltrated with a solution of glycol methacylate and benzoperoxide and molded in polymerizing solution (Polysciences, Warrington, Penn.) overnight before sectioning and staining.

Serum calcium concentration was measured with atomic absorption spectrophotometry. Total free cholesterol was determined with enzymatic colorimetry (Sclavo Inc., Wayne, N.J.).

To determine whether the three groups of rabbits had comparable aortic diameters in vivo, intravascular ultrasonic imaging was performed in vivo with a prototype 20-MHz (50% bandwidth) intravascular ultrasound imaging system (InterTherapy, Costa Mesa, Calif.) with a 25-cm-long, 1.5-mm-diameter flexible shaft and a 1-mm diameter transducer tip. Cross-sectional images were obtained by manual rotation of the catheter. The device was internally calibrated with a crystal oscillator and assumed a nominal velocity for sound in blood and tissue. Aortic diameter was measured at a position 2.5 cm proximal to the aortic bifurcation. The size of the shaft relative to the size of the aorta minimized potential misregistration.

Pressure–volume curves were also recorded during in vitro dilation of human coronary arteries obtained from two explanted cardiomyopathic hearts lacking grossly evident atherosclerosis.

To describe the rate of change in stenosis severity, the difference at each pressure between the unopposed balloon volume and that measured within the stenosis (ΔV) was plotted as a function of time. To describe resistance to balloon dilation, ΔV_max was defined as the maximal volume difference between the initial and control pressure–volume curves.

Statistical Analysis

Values of all parameters are given as mean±SD. Mean values of ΔV_max, wall calcium concentration, serum calcium concentration, and cholesterol concentration for the three groups of rabbits were compared by use of the Student’s t test. Level of significance was considered at a p value less than 0.05.

Reproducibility was assessed by inflating the balloon catheters repeatedly in the absence of external constraint. At a constant temperature of 37°C and a constant inflation rate of 25 μl/sec, pressure–volume curves were superimposed (Figure 2). Reproducibility was lost by change in temperature or inflation rate or by addition or removal of fluid or air from the syringe-catheter system.

Frequency response of the contrast-filled, balloon catheter pressure measurement system to square-wave input was measured at 70 Hz. The pressure response was a first order decay with a time constant of 0.06 seconds.

Intimal and medial calcifications (Figures 3A and 3B), as well as intimal proliferation and foam cell lesions (Figures 4A and 4B), were seen in the aortas of calcium/cholesterol-fed WHHL rabbits. Aortic sections from cholesterol-fed and control rabbits showed mild-to-moderate intimal proliferation and rare or no calcification. In the calcium/cholesterol-fed rabbits, intimal proliferation and calcification were more severe in the thoracic than in the abdominal aorta, especially in the arch.

At the site of balloon dilation, disruption of medial calcification was observed in three calcium/cholesterol-fed rabbits (Figure 5) but not in the remaining calcium/cholesterol-fed rabbits or in the cholesterol-fed and control rabbits. Although this medial disruption cannot be distinguished with certainty from processing artifact, the presence of erythrocytes within the intimal and medial discon-
FIGURE 3. Histology from aorta of Watanabe heritable hyperlipidemic (WHHL) rabbits fed supplemental cholesterol, calcium, and vitamin D$_2$. Panel A: Aortic section of calcium/cholesterol-fed WHHL rabbit showing circumferential midwall calcification (von Kossa stain; original magnification, ×4). Panel B: Same as panel A (original magnification, ×10).

Continuity in the example shown suggests that the fracture occurred in vivo rather than during tissue processing.

Pressure–volume curves obtained during balloon inflation of the distal abdominal aorta of calcium/cholesterol-fed rabbits showed plastic deformation...
FIGURE 4. Histology from aorta of calcium/cholesterol-fed Watanabe heritable hyperlipidemic rabbit showing (panel A) focal calcification and intimal proliferation (hematoxylin and eosin stain; original magnification, ×4) and (panel B) calcification and intimal proliferation (hematoxylin and eosin stain; original magnification, ×4). In the lower left corner is the lumen of the adjacent pulmonary artery, also showing medial calcification.
similar to that of human coronary arteries (Figures 6A–6C). Almost no resistance to dilation was seen in the cholesterol-fed and control rabbits (Figure 7). Similar results (data not shown) were seen in normal human coronary arteries from explanted hearts.

In the three calcium/cholesterol-fed rabbits with fracture patterns, ΔV changed abruptly in steps at rates of 20–130 μl/sec. The value of ΔV_{max} was significantly greater for calcium/cholesterol-fed (38±27 μl) than for cholesterol-fed (12.3±8 μl) and control (5.0±3.5 μl) rabbits (p<0.05). There was a trend toward higher values of ΔV_{max} in cholesterol-fed compared with control rabbits, but the difference was not significant (p>0.05).

According to intravascular ultrasonic imaging and angiography, mean aortic diameters were 2.1 mm for calcium/cholesterol-fed, 2.2 mm for cholesterol-fed, and 2.0 mm for control rabbits. These differences were within measurement error for both methods.

Aortograms failed to reveal discrete stenoses, regardless of diet (Figure 8). The minor, symmetric irregularities near the diaphragm were attributed to indentation by vertebral disks. Changes in aortic diameter could not be detected during repeated aortography after balloon dilation.

Mean final body weights were 3.0±0.3 kg in the control, 2.9±0.4 in the cholesterol-fed, and 2.2±0.4 in the calcium/cholesterol-fed rabbits. The low body weight of the calcium/cholesterol-fed rabbits was most likely due to anorexia of hypercalcemia; initial weights were the same. Serum calcium concentration (Table 1) was significantly greater in the calcium/cholesterol-fed rabbits (15.0±1.9 mg/dl) than in the cholesterol-fed (11.4±2.4 mg/dl) rabbits (p<0.01). The moderately elevated serum calcium (11.8±2.9 mg/dl) in the control WHHL rabbits was unexpected and may relate to advanced age, stress, or inactivity. Serum cholesterol concentration was greater in the calcium/cholesterol-fed (1.100±633 mg/dl) than in the cholesterol-fed (611±347 mg/dl) and control (343±146 mg/dl) rabbits, but the differences were not significant. These levels are all far above the normal range of 27±13 mg/dl. Wall calcium concentration per square centimeter of luminal surface area (measured after excision) was significantly greater (p<0.025) in the calcium/cholesterol-fed (0.73±0.59 mg/cm²) than in the cholesterol-fed (0.042±0.020 mg/cm²) and control (0.052±0.035 mg/cm²) rabbits (Figure 9).

**Discussion**

The earliest descriptions of advanced atherosclerosis referred to "ossification" and "degeneration of arteries into bone." As reflected in the lay term "hardening of the arteries," atherosclerosis is generally accepted to impart irreversible changes in the mechanical properties of the artery wall. The nature of these changes becomes particularly important with widespread clinical use of mechanical means, such as balloon angioplasty, rotary atherectomy, and ultrasonic ablation, to treat coronary artery disease.
Human cadaver atherosclerotic artery segments resist longitudinal stretch with greater force at increasing ages, yet direct mechanical measurements have shown a paradoxical increase in distensibility in cholesterol-fed animals, even when atherosclerosis occupies up to 50% of the aortic surface. To assess the effects of calcification on mechanical behavior of arteries in vivo, calcific atheromatous lesions were induced in aortas of WHHL rabbits, and the in vivo mechanical responses of these aortas to balloon distension were compared with those responses of aortas from control WHHL rabbits. It was found that aortas of control rabbits offered little resistance to balloon distension but that calcified aortas from calcium/cholesterol-fed rabbits resist and yield to balloon distension in a manner comparable to that of human atherosclerotic coronary arteries.

Arterial distensibility has been measured previously in normal and WHHL rabbits, after but not during balloon angioplasty, and in diabetic human arteries in vitro. The relative contribution of plaque components to hardening may be different in human cadaver arteries, which lack in situ tethering and undergo autolysis, altered smooth muscle tone, and temperature-related change in state of lipid elements. The role of fibrosis is not addressed in the present study, but normal distensibility has been observed in cerebral arteries with pure fibrosclerotic disease.

**Figure 6.** Pressure-volume recordings during balloon dilation of aorta of calcium/cholesterol-fed Watanabe heritable hyperlipidemic rabbits. Abrupt pressure drops occurred at 6 atm (panel A), at 8 and 9 atm (panel B), and at 5 and 6 atm (panel C).
The average increase of 38 $\mu$l in $\Delta V_{\text{max}}$ in the rabbit calcified aortas corresponds to lumen enlargement of approximately one third of the volume of a 3-mm angioplasty balloon or to the volume of a 2-mm-diameter channel in a 7-mm-long arterial segment. This degree of change and the fracture patterns are also seen in patients undergoing coronary balloon angioplasty (Figure 10). Stress-relieving fracture occurred after 10 seconds of inflation, with $\Delta V$ decreasing at 12 $\mu$l/sec (Figure 11), corresponding with the sudden loss of balloon “waist” on fluoroscopy. These patterns suggest disruption of solid lesion components supporting stresses on the order of $10^6$ dynes/cm$^2$. Small fractures may be difficult to detect, and the pattern may resemble stretching when multiple small fractures occur sequentially, as is known to occur in connective tissue elements.\textsuperscript{19}

The minimal resistance of normal artery wall to balloon dilation is consistent with previous studies. The working diameter change of angioplasty balloons is approximately 0.2 mm\textsuperscript{8} or 10% or less strain. For a normal human cadaver artery, this degree of strain requires less than 0.10 atm distending pressure.\textsuperscript{3} Similarly, rabbit\textsuperscript{8} and canine arteries undergo 50% stretch with pressures less than 0.3 atm.\textsuperscript{6} The normal artery wall also does not retain the dilated shape until stretched beyond its elastic limit, which is approximately 30% strain.\textsuperscript{4}

Potential artifacts in pressure and volume measurements were considered and addressed as follows:

1. Surface tension. The energy required to overcome the surface tension developing between inner surfaces of the balloon at high-negative pressures may cause a pressure artifact in the early portion of a rapid inflation. Such artifacts were excluded by slow initial filling, which allows the inner surfaces to separate gradually at low pressure.

2. Viscosity. Resistance to flow of viscous contrast material through the narrow catheter lumen may result in a reversible, rate-dependent pressure artifact throughout the inflation. This effect was minimized by use of a short catheter and slow and constant inflation rates.

3. Damping. The narrow catheter lumen tends to dampen the pressure signal, as described earlier. The result is “smoothing” of high-frequency events so that the fracture phenomena may be even more abrupt than they appear in Figures 6, 7, 10, and 11. Greater sensitivity may be possible by incorporating a miniature pressure transducer (Millar Instruments, Houston, Tex.) into the balloon itself.

4. Air compression. False increases in compliance could be introduced by compression of air in the syringe-catheter system. These effects were minimized by 1) removal of as much air as possible at the time of filling and by 2) comparison with the control...
TABLE 1. Effect of Diet on the Mechanical Response of Rabbit Aorta to Balloon Dilation In Vivo

<table>
<thead>
<tr>
<th>Rabbit</th>
<th>Age (mo)</th>
<th>Serum calcium (mg/dl)</th>
<th>Cholesterol (mg/dl)</th>
<th>Aortic [Ca²⁺] (mg/cm² surface area)</th>
<th>ΔVₘₐₓ (μl)</th>
</tr>
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<tr>
<td>Calcium/cholesterol diet</td>
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<td>ND</td>
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<tr>
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<td>12.8</td>
<td>354</td>
<td>0.686</td>
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<td>12.8</td>
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<td>1.800</td>
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<td>Mean±SD</td>
<td>13.9±0.9</td>
<td>15.0±1.9†</td>
<td>1,100±633†</td>
<td>0.73±0.59</td>
<td>38±27</td>
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<td>611±347†</td>
<td>0.042±0.020</td>
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<td>Control diet</td>
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<td>11.2</td>
<td>257</td>
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<tr>
<td>Mean±SD</td>
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<td>11.8±2.9</td>
<td>343±146</td>
<td>0.052±0.035</td>
<td>5.0±3.5</td>
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</table>

Calcification is normalized for luminal surface area. In some cases, blood drawings for calcium and cholesterol levels were repeated. Both values are included.

Diets are as follows: calcium/cholesterol diet: 250 mg/day calcium carbonate, 50,000 IU/alternate day vitamin D₂, and 1% cholesterol chow; cholesterol diet: 1% cholesterol chow. ΔVₘₐₓ is an index of aortic wall stiffness, defined as the maximum difference in volume between initial and control pressure-volume curves recorded during balloon inflation within the aorta. ND, not done.

*Expired at 5 weeks.
†Mean of second values (obtained later during course of diet).

Curve, which is equally affected by the added compliance, thus canceling the artifact.

5. Dissolution of microbubbles. Dissolution and reformation of microbubbles under high-negative and high-positive pressures may result in a gradual apparent decrease in volume during maintained high pressures. This effect was too slow to alter the inflation curves but may mimic the phenomenon of "creep" in recordings of volume as a function of time during held inflations.

6. Cardiac motion and pulse pressure. Inertial effects from flow pulsations may introduce pressure artifacts. Direct arterial pressure would be limited to the proximal end of the balloon and would correspond to approximately 0.1–0.2 atm. Cardiac motion artifact would be absent in the distal rabbit aorta, but the pressure artifact may occur 30–50 times per 20-second inflation. These factors may explain the baseline irregularity seen in the ΔV data and its greater magnitude in the human coronary artery than in the rabbit aorta.
tracings. Another possible source of baseline artifact is spontaneous contractile activity of the arterial wall.10

In general, the pressure experienced by the artery wall (P') is not the same as the pressure inside the angioplasty balloon. Unlike the low-pressure balloons used to study ventricular mechanics, angioplasty balloons are highly noncompliant in the working pressure range so that pressure acting on the balloon wall may not be fully transmitted to the artery, depending on whether the balloon’s small working range of size is on the high- or low-slope portion of the artery’s compliance curve. P' is the excess pressure at a given volume, that is, the difference between balloon pressure at a given volume during artery dilation and balloon pressure at that same volume during unopposed inflation. If the artery is too flaccid to resist balloon inflation or too large relative to the balloon, it experiences little or no pressure from the balloon, and little or no pressure excess (P') is observed. If the artery is tense and small relative to the balloon, then it experiences more distending pressure, and more pressure excess (P') is observed. This concept is important for clinical selection of balloon size.

Circumferential wall stress (S) may be estimated from pressure–volume data, assuming the artery to be an elastic circular cylinder with a thickness of 0.25–2 times the lumen radius:11

\[
S(x) = \frac{P'[(r+x)^2+(r+h)^2]}{(r+x)^2[(r+h)^2-r^2]}
\]

where \(r\) is depth from the inner radius, \(h\) is thickness, and \(r\) is inner radius. Such a stress estimate is necessarily an average because focal indentation of the balloon by a stenosis leads to stress concentration. The normally circumferential balloon wall tension gains an outward component when the balloon is distorted from its desired cylindrical shape. Pressure–volume relations are also affected by catheter shaft compliance, which may be estimated by measuring the pressure–diameter relation of the balloon and calculating balloon volume from diameter assuming cylindrical geometry. However, cylindrical geometry is unlikely at low pressures and in eccentric stenoses.
The calcium concentration in the aorta of WHHL rabbits fed calcium, vitamin D₂, and cholesterol was approximately 20 times the normal level. Similar arterial calcification has been achieved in a rat model using larger doses of calcium and vitamin D₂. Whether the calcification in this rabbit model is a form of metastatic calcification, due to high levels of serum calcium, or dystrophic calcification, as occurs in human atherosclerosis, is not clear. However, its preferential location in the intima and media rather than adventitia of the artery wall suggests that the process involved more than a generalized precipitation of calcium into tissue.

Arterial calcification has been linked to atherogenesis for more than half a century. With increasing age, calcium gradually accumulates in the aortic media in normal humans and in laboratory animals. It follows patterns of distribution similar to those of atherosclerosis, has a role independent of hyperlipidemia, and is induced by mechanical factors. The present results suggest that decreased arterial flexibility associated with atherosclerosis is mediated by wall calcification. It is possible that “hardening” by a shell of calcium mineral limits compensatory lumen enlargement. If so, balloon dilation may be most effective when the shell is disrupted. Whether prevention of arterial calcification can alter the course of atherosclerosis may be worthy of investigation.

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References


KEY WORDS: pressure–volume relation • balloon angioplasty • distensibility • atherosclerosis • coronary artery disease
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