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HIGHLIGHTED TOPIC | *Physiology of the Aging Vasculature*

Age-related medial elastocalcinosis in arteries: mechanisms, animal models, and physiological consequences

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Atkinson J. Age-related medial elastocalcinosis in arteries: mechanisms, animal models, and physiological consequences. *J Appl Physiol* 105: 1643–1651, 2008. First published September 4, 2008; doi:10.1152/japplphysiol.90476.2008.—With age, the calcium content of the arterial wall increases. Calcification occurs at two main levels: intimal plaques and the medial elastic fiber network. The latter has been referred to as medial elastocalcinosis and is the subject of this review. The mechanisms involved in elastocalcinosis are complex and involve polar, apolar, and active processes. Vascular calcification may be species specific to humans. As laboratory animals, such as the rat, grow old, they suffer from only very mild arterial calcification. Different animal models of induction of massive arterial calcification by pharmacological and other means exist. Although extrapolation from such models to the clinical situation in terms of etiology is difficult, such models could be useful in the nonclinical study of the pathophysiological consequences of vascular calcification. Vascular calcification modifies arterial wall stiffness, and this could have clinically significant consequences on cardiac function and downstream circulatory control.

artery; calcium; wall stiffness; aging

Development of the Concept of Elastocalcinosis

Several recent reviews deal with the subject of elastocalcinosis (1, 21, 25, 41, 54, 56, 82, 108).

Age-linked vascular calcification has been known since the nineteenth century (85, 122). It appears to be "specific" in that vascular wall calcium and phosphorus contents increase with age, whereas there are no significant increases in the aortic content of most other elements, such as sodium, potassium, and magnesium (128). Vascular calcification linked to age is also specific for arteries and does not involve other soft tissues, such as veins (57, 60, 117). Vascular calcification is associated with hypertension. Blumenthal et al. (9) showed that the onset of arterial calcification occurs at an earlier age in hypertensive subjects. The association in humans between arterial calcification and hypertension has since been reported by many investigators (75). The etiology of the complex multifactorial interactions, however, between hypertension (and associated changes in vascular wall mechanics) and amplification of calcification remains obscure.

Vascular calcification can occur in localized intimal plaques and in a diffuse fashion in the media (53), and often there is no indication in published reports of where samples were taken. Méndez and Tejada (76) reported that the calcium content of plaques is 10-fold higher than that of "plaque-free" artery. Thus "contamination" of samples with plaque material could mask medial, diffuse elastocalcinosis. It is to be noted that the calcium content of "normal" intima (i.e., free of plaques and fatty streaks) is low and shows only a slight increase with age (6, 29). Medial elastocalcinosis independent of atheroma-associated calcification has been demonstrated by Elliot and McGrath (29), who selected specimens that were free of plaques and showed that calcium content increased 30- to 40-fold from the age of 20–90 yr. It should also be noted that, as histologists and pathologists often routinely decalcify arterial specimens before examination, much vital information is lost on the localization and extent of calcification. With the above provisos in mind, the rest of this review is on medial elastocalcinosis.

Calcification of Medial Elastic Fibers: Elastocalcinosis

As vascular wall calcification was less marked and sometimes absent in syphilitic aortitis in which the elastic elements of the media are destroyed, Blumenthal et al. (9) suggested that medial calcification is primarily associated with elastic fibers. The Blumenthal group also showed that, in any given age group, the calcium and phosphorus contents of aortic elastic tissue were always substantially higher than those of the whole aorta (128). Furthermore, over the age range of 81–103 yr, the aortic wall elastin content fell, and the calcium content rose concomitantly (63). Likewise, in coronary arteries, calcification was accompanied by elastic fiber fragmentation (63). These observations suggest that medial calcification involves destruction of elastin (5).

In animal models of vascular calcification with calcification of very different etiologies [vitamin D plus nicotine (VDN)

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administration (88); warfarin plus vitamin K administration (30)], calcium accumulates on elastic fibers. Furthermore, in the rat, arteries that calcify the most with age are those (e.g., aorta) with the highest elastin content (60).

Mechanisms of Elastocalcinosis

Calcium deposition in a polar environment. The polar nature of calcification is suggested by the fact that most molecules involved in the initiation and regulation of biological mineral formation are anionic and that this property is essential to their ability to facilitate the interactions between minerals and matrix elements (12). Lansing et al. (63) showed that, as the calcium content of elastin increased, so did that of the acidic groups (glutamic and aspartic acids) and suggested that the latter modification increased the base-binding capacity, thus promoting calcium binding, and that vascular calcification was of a polar, mineral nature. This view was challenged by Yu and Blumenthal (128, 129), who claimed that a change in the primary structure of elastin (or in any other mature protein) is difficult to conceive. An explanation was provided by Hall (42), who showed that a protein with a higher proportion of polar amino acids ("pseudo-elastin") could be separated from elastin by urea. This protein has an amino acid composition different from elastin, is closely associated with elastin, and accumulates and calcifies with age (59). Other nonprotein components associated with the elastic fiber, such as acid mucopolysaccharides, may also be involved in elastocalcinosis (130).

Calcium and cholesterol: calcification in an apolar environment. Kanabrocki et al. (57) showed that, in the aorta, calcium rose some 12-fold from childhood to the age of 70 yr, and cholesterol content showed a similar evolution. They drew the conclusion that there may be some relationship between calcification and cholesterol accumulation and that calcification can occur in an apolar environment. Many groups have shown that cholesterol feeding in animals produces fatty streaks in the vascular wall, which accumulate calcium; for example, cholesterol feeding induces arterial calcification in rabbits (61) and in monkeys (62). It may be that calcification precedes lipid accumulation. Molinari-Tosatti and coworkers (84) and Hornbeck and Partridge (48) suggested that the configurational changes produced by calcium binding to elastin produce a structure presenting a larger number of hydrophobic amino acid side chains at water interfaces, giving rise to increased interaction with predominantly hydrophobic molecules, such as cholesterol.

Inflammation and oxidant stress. Inflammation and oxidant stress are powerful mechanisms that promote matrix remodeling, compromise anti-calcification defense mechanisms, and promote vascular calcification by cellular and noncellular processes (56, 108). See Fig. 1.

C-reactive protein (CRP), an indicator of inflammation, was shown to be highly associated with the extent and progression of carotid plaques, but its association with aortic calcification (measured by radiography) was less pronounced (28). One explanation for this is that, while inflammation is a key element

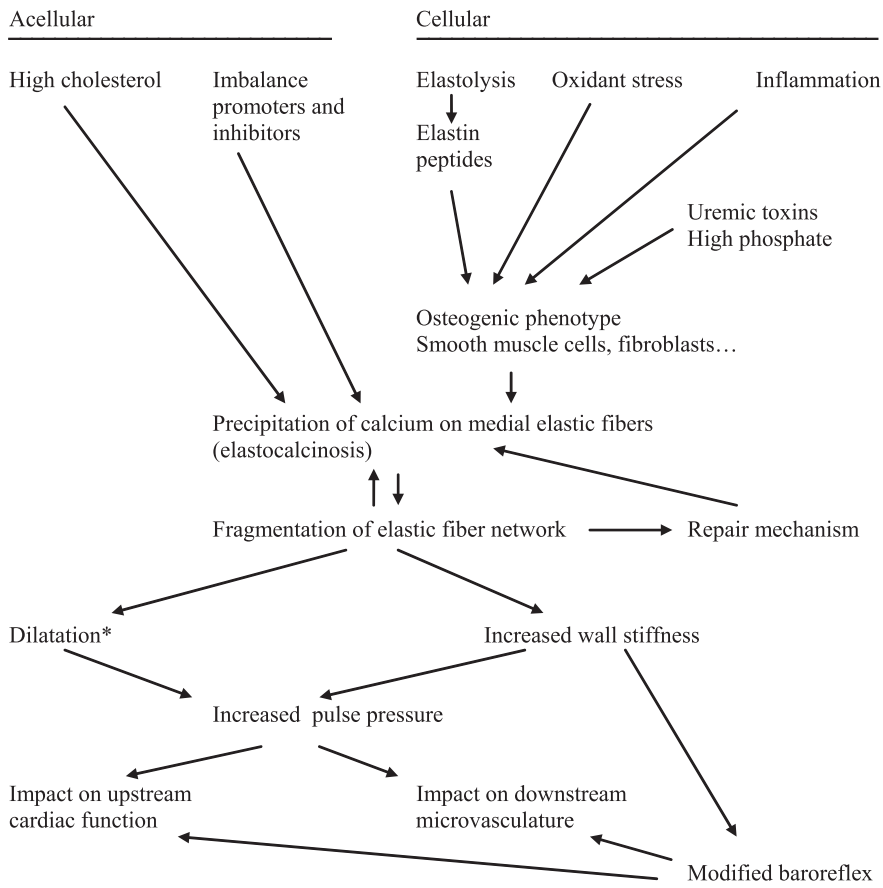

Fig. 1. Various factors acting by acellular and cellular mechanisms, involving osteogenesis regulation, precipitate calcium apatite onto elastic fibers. This elastocalcinosis disrupts the elastic fiber network, producing increased wall stiffness. The latter leads to an increase pulse pressure with impact on upstream cardiac function and the downstream microvasculature. *Dilatation would be expected to increase compliance and so decrease pulse pressure. This "compensatory" mechanism is presumably unable to hold pulse pressure at a "normal" level in the long term.

in atheroma and plaque calcification, it may be less important in medial calcification.

Oxidant stress can modulate the activity of several processes in vascular calcification. Bone morphogenetic proteins (BMPs) play crucial roles in vascular calcification (56), and oxidant stress is an important modulator of BMP activity (79). Oxidant stress may also stimulate an osteogenetic transition in calcifying vascular cells, a subpopulation of smooth muscle cells in the vascular wall (94).

Inflammation and oxidant/carbonyl stress may be linked to vascular calcification via advanced glycation products. Kitauchi et al. (60a) showed an association between pentoside levels and aortic calcification score (computed tomography scan). It is uncertain whether this association reflects the fact that advanced glycation products are indicative of calcification related to inflammation and/or oxidant/carbonyl stress, or whether advanced glycation products have a direct effect on the biophysical properties of vascular elastin (66, 126) and that such changes promote calcification. This could be important in diabetes.

Metabolic dysfunction and vascular calcification: renal failure. Patients with end-stage renal disease have arterial calcification, which is secondary to metabolic dysfunction (50). In such cases, it appears that diffuse medial calcification and plaque calcification both occur (80). Furthermore, in arterial calcification linked to end-stage renal disease, bone matrix proteins, such as osteopontin, colocalize with calcium deposits (80). Several factors are involved (81). Uremic toxins and high phosphate increase expression of core binding factor-α1 (Cbfa-1), osteopontin, and alkaline phosphatase in cultured vascular smooth muscle cells. Uremic serum also increases inflammatory procalcification factors, such as CRP (90). Furthermore, dialysis patients have low levels of fetuin-A, which inhibits mineralization in the same culture system (81, 82).

Concerning the consequences of vascular calcification in kidney disease, in end-stage renal disease patients, arterial wall stiffening appears to be related to wall calcification (see Refs. 67 and 68 and below). Increased pulse pressure following stiffening of the arterial wall may provoke microvascular damage (see below). In hemodialysis patients, a reduction in baroreflex sensitivity is often observed, and it has been proposed that this is linked to reduced carotid artery compliance following wall calcification (18). This interesting impact of wall stiffening (following age-linked medial elastocalcinosis) merits further investigation, as such changes in baroreflex sensitivity will alter cardiac and microvascular function.

Metabolic dysfunction and vascular calcification: diabetes. Hyperglycemia is a strong, independent risk factor for vascular calcification (99). Arterial calcification is also strongly associated with the metabolic dysfunction of diabetes, but, although diabetic polyneuropathy may be involved, the mechanism is unclear (109), and a genetic determinant independent of diabetes may be present (for review, see Ref. 25). It has been suggested (26, 108) that vascular dysfunction found in diabetes may be related to calcification-induced arterial stiffening and increased pulse pressure. The potentially damaging effect of increased pulse pressure on the microvasculature will be dealt with later in relation to renal failure as a consequence of elastocalcinosis.

Balance Between Promoters and Inhibitors of Calcification

Calcium and phosphate in biological fluids are at concentrations close to which the precipitation of mineral salts will occur. There exists, therefore, a number of proteins that chelate or sequester these ions (essentially calcium), thus lessening their availability and the possibility of precipitation (38, 105). The use of mutated mouse models has revealed the existence of a number of inhibitors of calcification: matrix Gla proteins, osteopontin, pyrophosphate, β-glucosidase, carbonic anhydrase II, fetuin-A, desmin, osteoprotegerin (OPG), and Smad 6 (37). While some of these, for example, osteopontin (35, 36, 103), have been shown to be involved in inflammatory plaque calcification, their role in medial elastocalcinosis is less well known.

In surgical specimens from pathology, Schurgers et al. (106) showed that, in Mönckeberg's medial sclerosis, uncarboxylated matrix Gla protein were associated with calcification. In aging rats, calcification of the vasculature was also associated with impaired carboxylation of matrix Gla protein (114).

The balance between inducers, such as high phosphate, and inhibitors, such as matrix Gla proteins or osteopontin, determines whether or not calcification occurs (37). Hyperphosphatemia, common in end-stage renal disease, is a major risk factor for arterial calcification and cardiovascular mortality in such patients (8). Raised phosphate levels in the culture medium (levels similar to those observed in hyperphosphatemic patients) cause vascular smooth muscle cells to change phenotype, develop osteochondrogenic markers such as Cbfa-1/Runx2, and mineralize (113).

Oxidant stress may be involved in the balance between induction and inhibition of mineralization. The inhibitory activity of matrix Gla proteins is dependent on the presence of Gla residues, and vitamin KH2 is essential for the carboxylation of target glutamic acid residues. Vitamin KH2 is an antioxidant that is the target of several oxidants (121).

Elastolysis, elastin peptides, and calcification. Several lines of evidence suggest a direct correlation between elastin degradation and calcification. While it is probable that calcification of the elastic fiber leads to its destruction, evidence is accumulating that breakdown of elastin may be a signal for calcification.

Following subdermal implantation of purified elastin in the rat, elastolysis involving matrix metalloproteinases (MMPs) occurs, producing elastin peptides that fix onto the elastin-laminin receptor (3, 4). Activation of this receptor could then lead to development of an osteoblast-like phenotype of smooth muscle cells and fibroblasts with upregulation of bone proteins (e.g., Cbfa-1, osteocalcin) and hence to elastin calcification (110, 111). This process has also been demonstrated in vascular injury models and occurs following injury to the aortic wall by short-term peri-adventitial treatment of rodent abdominal aorta with low concentrations of calcium chloride (5). Again, it involves transforming growth factor-β_1, which is a major determinant of the response of the arterial wall to injury (102).

As elastin peptides upregulate MMP expression in vascular smooth muscle cells (110), the above process could be self-amplifying. Finally, treatment of elastin with aluminum chloride leads to binding of aluminum to elastin, thus preventing elastolysis and elastin-oriented calcification (3, 5). It is uncertain as to whether, for example, peri-arterial application of

nontoxic concentrations of aluminum salts could be useful in the development of a treatment capable of slowing down age-related medial elastocalcinosis. Another possibility is the application of phenolic tannins, such as pentagalloyl glucose (52). Interestingly, in this case, the application of tannin appeared to "protect" the elastin and stop the development of aneurysm, but without inhibiting calcification of elastin.

Cellular processes. The involvement of a cellular process in calcification of the medial elastic fiber network was shown by several authors, for example, Tanimura et al. (115). They demonstrated the presence of matrix vesicles of a structure similar to those seen in the initial foci of calcification of cartilage, bone, and dentin, and they suggested that such vesicles were extruded from the cytoplasm of arterial smooth muscle cells. In medial calcification, the source of the many bone proteins, such as alkaline phosphatase and Gla protein, is the smooth muscle cell (107). The latter authors also showed that primary cultures of smooth muscle cells from the wall of Mönckeberg's sclerosis expressed osteoblast-specific genes.

Smooth muscle cell vesicles are thought to arise by apoptosis and to serve as mineral nucleation sites (98). Vascular smooth muscle cells can release tissue factor-rich microparticles of the same size as vesicles (104), and these may be the site of calcification.

Besides smooth muscle cells, fibroblasts may play a role in arterial calcification (111). The latter authors treated rat dermal fibroblasts in vitro with elastin degradation products and transforming growth factor-β_1. They showed osteogenic differentiation of fibroblasts with expression of Cbfa-1, osteocalcin, alkaline phosphatase, and OPG.

Another factor involved in smooth muscle transformation may be oxidant stress, and it has been proposed that lipid oxidation products, such as oxidized low-density lipoprotein, induce a subpopulation of smooth muscle cells (calcifying vascular cells) to calcify (93). It is possible that calcifying vascular cells arise from local progenitors in response to vascular injury (19); whether injury can be represented by the mechanical stress of cumulative systolic shocks to a stiffened arterial wall (see below) is less certain.

Vascular calcification and bone formation. The possibility of bone marrow formation in plaques was observed in the mid-19th century (122). More recently, Demer and colleagues (13, 22) have put forward a major hypothesis in this area: that vascular calcification is a consequence of active bone formation by osteoblast-type cells.

Regulated ossification with both osteogenic and chondrogenic differentiation is thought to be the mechanism behind vascular calcification, primarily that of plaques (1). Vascular calcification depends on factors involved in bone formation (23, 120), and several of these factors, BMP-2a (13), osteopontin (35), osteocalcin (39), matrix Gla protein (97), and collagen I (58), have been found in plaques. It is difficult to separate mechanisms of diffuse calcification of medial elastic fibers from those of calcification associated with localized intimal atheroma plaques, and either process is not totally dependent on one single mechanism (54), although the role of the factors involved in bone formation in medial calcification independent of plaque formation is less well known (49). For example, in sections free of atheroma and calcification, Fitzpatrick et al. (31) could find no evidence of osteopontin staining.

Osteoporosis and vascular calcification. There may be a link between senile osteoporosis and arterial calcification in humans (43, 47) [but not apparently in animals (86)]. After noting that senile osteoporosis is more common in aged women than in men, Blankenhorn (7) suggested that specific factors control body calcium distribution between bone and soft tissue and that these were more active in women than in men. There is also a link between osteoporosis and coronary artery calcification in situations of marked vascular calcification, such as adult end-stage renal disease patients (83).

Many epidemiological studies indicate that coronary heart disease is low in premenopausal women and that this gender protection is lost following menopause (25). Many factors are involved, one of which may be vascular calcification (87). It would be interesting to test the impact of hormonal replacement therapy postmenopause on vascular calcification.

The paradox of vascular calcification associated with osteoporosis may be explained by the fact that the accumulation of oxidized lipids in the vasculature of bone inhibits differentiation of osteoblasts, whereas accumulation in the arterial wall induces differentiation and mineralization (93, 94). Another possibility concerns the RANKL/RANK/OPG osteoclast regulatory system (20). According to this theory, the receptor activator of nuclear factor-κβ (RANK) and its ligand (RANKL) promote, while OPG protects against vascular calcification. This is based on several lines of evidence. For example, OPG knockout mice suffer from early onset osteoporosis and arterial medial calcification (15, 78). Furthermore, OPG prevents arterial calcification in animal models of vascular calcification (96).

Animal models of arterial calcification: spontaneous age-linked vascular calcification. Marked vascular calcification may be species specific and restricted to humans, although some degree of vascular calcification is known to occur in several species, for example, the elephant (74). Waugh et al. (124) observed a twofold increase in vascular calcium in the rabbit between 3 and 46 mo. Data for most other mammalian species are, however, lacking.

In the rat, arteries contain up to five times more calcium than other soft tissues and calcify with age (2- to 3-fold), whereas other soft tissues do not (60, 17). Calcium bound to vascular elastin increases with age in the rat (91, 77), so the old rat suffers from medial elastocalcinosis, albeit of a much less intense degree than in humans. Kieffer et al. (60) and Cantini et al. (17) reported that neither strain nor hypertension has any effect on age-related arterial calcification. Others (e.g., Ref. 32), however, showed more intense arterial calcification in hypertensive (spontaneously hypertensive rats) compared with normotensive controls (Wistar-Kyoto rats).

Rats do not become hypercalcemic with age, although accumulation of calcium in the arterial wall with age is essentially extracellular. In our laboratory's experiments on the rat, intracellular calcium is some 100,000 lower than total arterial calcium content (calculated from data in Refs. 17, 60, 100, 119). Furthermore, it is uncertain whether changes in vascular wall intracellular calcium with age could be physiologically relevant. The curve relating vasoconstriction to intracellular calcium is very steep (119). However, although arterial intracellular calcium levels approximately double with age, as the sensitivity of the contractile apparatus to calcium decreases with age, the final result in terms of contractility is of minor importance (100).

Parallel studies on age-related changes in vascular mechanics are generally not carried out, except for rare cases such as that by Michel et al. (77), but, in the latter, the authors did not show any correlation between elastic fiber calcification and increased arterial stiffness upon aging in normotensive rats. Such a correlation is seen in the hypervitaminosis D plus nicotine (VDN model, see below), which, however, suffers from a far more intense degree of medial elastocalcinosis.

Pharmacological induction of vascular calcification in animals: blockade of matrix Gla protein inhibition of calcification. An interesting model is provided by the use of warfarin, which blocks the vitamin K-dependent enzyme γ-glutamate carboxylase, thus preventing the formation of carboxyglutamic acids residues. The latter bind ions and so prevent the precipitation of calcium phosphate (21, 30). In this model, medial elastocalcinosis develops over the first few weeks. Pulse wave velocity increases, suggesting that elastic fiber calcification stiffens the arterial wall. Stiffening of the wall is accompanied by isolated systolic hypertension, a phenomenon observed in elderly hypertensive subjects.

Stimulation of elastolysis. Bailey et al. (3) have described a model of subdermal implantation of elastin purified from bovine neck ligament. This has an amino acid composition similar to that of aortic wall elastin and has no lipids or collagen. Implants are removed several days or weeks following implantation, and mineral content is determined, together with zymography and DNA analysis. This system has the advantage that only elastin is involved.

Local insult to the elastic fiber network followed by aneurysm can be provoked by periadventitial application of calcium chloride (34, 51). Such changes are accompanied by massive wall calcification. The model was altered by Basalyga et al. (5), who used lower concentrations of calcium chloride and showed clear elastocalcinosis, with elastolysis (decrease in desmosine content) and apoptosis. MMP-2 and MMP-9 knockout mice were resistant to calcium chloride insult, showing a clear link between elastolysis and calcification and suggesting that macrophage MMP-9 and mesenchymal MMP-2 act in concert (69).

Periarterial application of calcium chloride was originally developed as a model of aneurysm and shows a clear link between wall calcification and aneurysm. This link is seen in other models, such as the fibrillin hypomorph mouse model of Marfan (72), but not in others, such as the VDN rat model below (64, 73).

Hypervitaminosis D plus nicotine (VDN model). Serum levels of 1,25-$(0H)_2D_3$ are inversely related to coronary calcification intensity, but the mechanism behind why the osteoregulatory steroid, vitamin D, is a negative determinant of coronary calcium mass is unclear (24, 123).

Several studies show that calcitrophic hormones (parathyroid hormone and vitamin D) are involved in vascular calcification. Toxic levels of vitamin D induce arterial calcification, and this may involve the stimulation of matrix vesicles, which then act as mineral nucleation sites (118). This effect of hypervitaminosis D is exploited in the VDN model.

Hass and coworkers (44) and several laboratories, including our own, have used hypervitaminosis D alone (33, 95) or in combination with nicotine (2, 32, 127) or cholesterol (101). Although arteries such as the aorta are most susceptible, hypervitaminosis D treatment also leads to calcification of the heart, kidneys, and other organs (45, 46, 60). Hypervitaminosis D produces aortic elastocalcinosis with calcification localized on elastic fibers (27, 88, 89).

Potential Physiological Consequences of Elastocalcinosis

Arterial stiffening. Medial calcification may be implicated in the age-related decrease in arterial elasticity. Blumenthal et al. (9) noted that the time course of the decrease of elasticity with age shown by Wilens (125) closely paralleled that of the evolution of medial calcification with age and speculated that calcification of medial elastic fibers contributes to the age-linked decrease in arterial elasticity.

Later studies suggest a link between arterial calcification and stiffness; asymptomatic hypertensive patients with aortic pulse wave velocity values above normal show abdominal aortic calcification (70, 112). Furthermore, the calcium antagonist, nitrendipine, lowers pulse wave velocity in patients with aortic calcification but has no such effect in those with noncalcified vessels (71). In patients suffering from end-stage renal failure, an increase in aortic pulse wave velocity is related to aortic calcification (67, 68), and arterial medial calcification is a strong prognostic marker for cardiovascular mortality in hemodialysis patients (68). In diabetic patients also, arterial medial calcification is related to cardiovascular mortality, coronary heart disease, and stroke (65). The importance of increased wall stiffness in this latter situation is uncertain.

VDN model: arterial stiffening. We studied the links between elastocalcinosis, arterial stiffening, and the consequences of the latter in the VDN rat. The model involves 1 day's treatment with VDN, followed by several weeks or months of recovery.

VDN treatment does not modify aortic wall thickness, wall thickness-to-lumen ratio, or wall stress; mean blood pressure remains normotensive (88, 89). VDN rats show increased arterial wall rigidity, increased pulse pressure (with no change in stroke volume), increased aortic impedance, decreased systemic arterial compliance, decreased in situ and in vitro carotid artery compliance, increased elastic modulus, increased isobaric elasticity, and decreased pulse amplification (2, 14, 88, 89, 116).

In the VDN rat, a change in wall composition, elastocalcinosis, independent of any change in geometry, determines the mechanical properties of the wall. VDN treatment produces widespread fragmentation of the medial elastic fiber network (40), and there is an inverse relationship between the calcium and desmosine contents of the aortic wall (89). These observations suggest that elastocalcinosis involves both elastic fiber fragmentation and a loss of elastin cross-linking. A factor involved in osteogenetic vascular calcification, S-100 calcium-binding protein (10, 11), is found in the medial calcium deposits (88, 89).

VDN model: cardiac changes. Regarding the upstream consequences of increased arterial wall stiffening, we have shown that left ventricular mass is positively related to aortic wall isobaric elasticity in VDN rats with calcified aortas (89). This result can be interpreted as adaptation of the heart to the increased work load following the increase in pulse pressure and in telesystolic arterial blood pressure. Pulse pressure is also characterized by decreased diastolic arterial blood pressure, and, given the unique physiology of the coronary circulation

(flow mainly in diastole), this could have a negative effect on cardiac performance.

Preload recruitable stroke work and end-systolic elastance are both elevated in VDN, and this lowers the ratio of arterial elastance over end-systolic elastance and increases efficiency (55). Wave reflection is augmented in VDN rats, as shown by the increase in the wave reflection coefficient, Γ, and the amplitude of the reflected pressure wave. The VDN treatment provoked alterations in cardiac function, arterial impedance, arterial function, and ventricular-arterial interaction, which, in many aspects, are similar to effects of an aged and stiffened arterial tree. The VDN model may thus prove to be a useful model to study the pathophysiological effects of increased arterial stiffness on cardiac structure and function.

Arterial calcification and renal failure. Vascular calcification occurs frequently in patients with chronic kidney and end-stage renal disease, and the increased medial arteriosclerotic calcification and plaque calcification in patients on dialysis is linked to increased morbidity and mortality (82).

Mönckeberg's arteriosclerosis refers to sclerosis of the media of an artery and is not limited to the aorta but, as described in the original 1903 publication, involves other arteries, such as those supplying the head, thyroid, breast, and extremities. It has been reported that young adults with chronic renal failure have a high prevalence of arteriopathy, vascular calcification, and indicators of inflammation such as CRP (90).

VDN model: renal function. As stated above, clinical studies suggest a strong link between chronic renal failure and vascular calcification, with the latter leading to arterial wall stiffening and hyperpulsatility, especially in end-stage renal disease patients. An increase in pulse pressure in the renal circulation could increase pulsatile wall stress and so damage endothelial and smooth muscle cells (16). It has been suggested that this occurs following medial calcification in humans, and that a similar phenomenon is involved in peripheral arteriopathy in diabetes (65), but evidence is lacking.

As the mechanisms responsible are complex and difficult to explore in humans, we evaluated renal function and structure in the VDN model. VDN rats show extensive damage to glomeruli and vasa recta. Glomerular filtration rate decreases, and albuminuria increases. There are significant linear relationships between albuminuria or glomerular filtration rate and central aortic pulse pressure. This unpublished study provides the first evidence, in an experimental model of renal dysfunction, the VDN, of a link between increased central aortic pulsatility and renal dysfunction.

In summary, the VDN model reproduces the structural and functional aspects of medial elastocalcinosis of arteries seen with ageing in humans and the consequences of such elastocalcinosis. It may provide a useful tool to test potential anticalcinotic drugs (45, 46, 116).

A final proviso has to be added. All surgical or pharmacological "injury" models involve an acute challenge to the arterial wall. Whether this parallels what happens in the case of senescence of the aortic wall elastic fiber, which is subject to slowly developing mechanical failure following the cumulative effect over a very long time of repetitive systolic shocks to the wall (92), is uncertain. Certain investigators have suggested that the change in smooth muscle cell phenotype to an osteochondrogenic state with subsequent calcification may be a tissue repair mechanism (37). Teleologically, elastocalcinosis may be a mechanism that "repairs" elastic fibers damaged by cumulative systolic shocks.

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