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Arterial calcification and its physiological consequences: Ideas from animal models

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Introduction

In man age-linked aortic wall calcification occurs at two main levels: intimal plaques and the medial elastic fibre network (medial elastocalcinosis^{37,48}). Several recent reviews deal with the subjects of arterial ageing and elastocalcinosis.^{1,3,10,11,19,23,25,35,36,45}

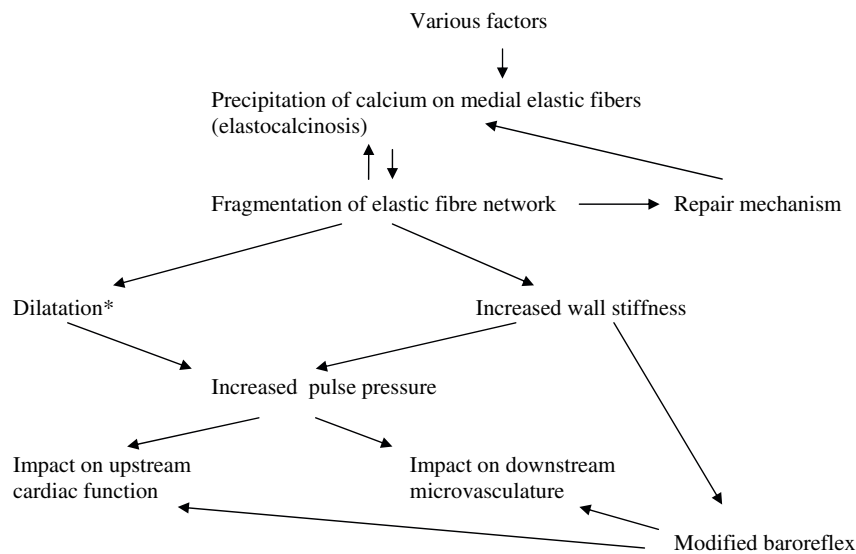
Although vascular calcification was described at the beginning of the 20th century³⁷ it was not until the 1940s that research on this subject intensified. After finding that vascular wall calcification was less marked in syphilitic aortitis in which the elastic elements of the media are destroyed, Blumenthal et al.⁵ suggested that medial calcification is primarily associated with elastic fibres. In the age range of 81–103 years, the aortic wall elastin content fell and the calcium content rose concomitantly.²⁷ Furthermore, in coronary arteries, calcification was accompanied by elastic fibre fragmentation.²⁷ All of these observations suggest that medial calcification involves destruction of elastic fibres.⁴

As elastin plays a major role in aortic wall elasticity, it is possible that the development of elastocalcinosis with age is involved in age-linked stiffening of the aortic wall as described by Wilens in 1937⁴⁹. However, although elastocalcinosis and wall stiffening were described over 60–70 years ago, evidence of the way in which the two are linked is still lacking. This short review is an attempt to provide evidence from animal models of these possible links (Fig. 1).

Animal models of aortic elastocalcinosis: Spontaneous age-linked vascular calcification

Rat arteries contain up to 5 times more calcium than other soft tissues and calcify with age (2- to 3-fold) whereas other soft tissues do not.^{9,26} The old rat suffers from mild medial elastocalcinosis: calcium bound to vascular elastin increases with age in the rat.^{34,40} Studies on age-related changes in vascular mechanics show that although the elastic modulus of the aortic wall increases there is no rise in central aortic pulse pressure.⁹ Furthermore there is no correlation between elastic fibre calcification and increased arterial stiffness upon ageing in normotensive

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Various factors acting in polar and apolar environments by acellular and cellular mechanisms, involving osteogenesis regulation precipitate calcium apatite onto elastic fibres. This elastocalcinosis disrupts the elastic fibre 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.

Figure 1 Mechanisms and consequences of arterial medial elastocalcinosis.

rats.³⁴ Thus although elastocalcinosis occurs with ageing in the rat it is relatively mild and associated with but minor changes in wall mechanics.

Hypervitaminosis D plus nicotine (VDN model)

Possible correlations between elastocalcinosis and increased wall stiffness were evaluated in the hypervitaminosis D plus nicotine (VDN) model that suffers from a far more intense degree of medial elastocalcinosis (Table 1). Hass and co-workers²⁰ and several laboratories used hypervitaminosis D, alone^{14,43} or in combination with nicotine^{2,13,50} or cholesterol⁴⁴ to produce arterial calcification. Although arteries such as the aorta are most susceptible, hypervitaminosis D treatment also leads to calcification of the heart, kidneys and other organs^{21,22,26}. Hypervitaminosis D with or without nicotine produces aortic elastocalcinosis with calcification localised on elastic fibres.^{12,38,39}

We studied the links between elastocalcinosis, arterial stiffening and the consequences of the latter in the VDN rat (one day’s treatment with vitamin D and nicotine followed by several months of recovery). VDN treatment does not modify aortic wall thickness, wall thickness to lumen ratio, or wall stress; central aortic mean blood pressure does not increase.^{38,39} VDN rats show increased arterial wall rigidity (increased elastic modulus, increased isobaric elasticity, and decreased pulse amplification) with increased central aortic pulse pressure (with no statistically significant change in stroke volume) (Table 1). There is an increase in diameter.²⁴ It should be remembered that induction of arterial calcification is also used in animal models of

aneurysm.¹⁷ Albeit, in the VDN model, aortic impedance increases and systemic arterial compliance decreases.^{2,38,39,47}

The VDN model is interesting in that 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 fibre network,¹⁸ (Table 1 and Fig. 2) and there is an inverse relationship between the calcium and desmosine contents of the aortic wall.³⁹ Desmosines are cross-linking amino acids specific to elastin. Thus elastocalcinosis involves both elastic fibre fragmentation and a loss of elastin cross-linking. Factors involved in osteogenetic vascular calcification such as S-100 calcium-binding proteins^{6,7} are found in the medial calcium deposits.^{38,39}

Regarding the upstream cardiac consequences of increased aortic wall stiffening there is little global change in cardiac performance at base and under volume overload.²⁸ A number of compensatory mechanisms presumably maintain cardiac performance. Left ventricular hypertrophy occurs and ventricular mass is positively correlated to aortic wall isobaric elasticity.³⁹ There is mild ventricular fibrosis and a shift in myosin isoforms to the beta form²⁸ (Table 1). 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 so increases efficiency.²⁴ The VDN model may prove useful for the study of cardiac adaptation to increased pulse pressure following increased arterial stiffening.

Regarding the downstream impact of increased pulse pressure we have studied renal function in the VDN model.

Table 1 Cardiovascular features of the hypervitaminosis D plus nicotine (VDN) model of aortic elastocalcinosi and increased wall stiffness.

	Control	VDN	P
Aorta and aortic wall			
Calcium content (micromol/g) ^a	24 ± 2 (14)	318 ± 85 (21)	<0.05
Desmosines (microg/g) ^a	1243 ± 83 (14)	555 ± 36 (21)	<0.05
Elastic fibre fragmentation ^b	0.95 ± 0.03 (10)	0.61 ± 0.04 (12)	<0.05
Elastic modulus (10 ⁶ dynes/cm ²) ^a	6.7 ± 0.5 (14)	13.2 ± 1.4 (21)	<0.05
Central pulse pressure (mmHg) ^a	39 ± 2 (14)	66 ± 6 (21)	<0.05
Heart			
Baseline stroke volume (microl) ^c	223 ± 18 (8)	211 ± 13 (10)	>0.05
Left ventricle weight/body weight (g/kg) ^c	1.54 ± 0.07 (8)	1.73 ± 0.05 (10)	<0.05
Collagen (microg/g) ^c	31 ± 4 (8)	52 ± 4 (10)	<0.05
Beta myosin isoform (%) ^c	18 ± 2 (8)	31 ± 3 (10)	<0.05

Results are means ± SEM with number of rats in brackets.

^a Niederhoffer, et al.,^{38,39}

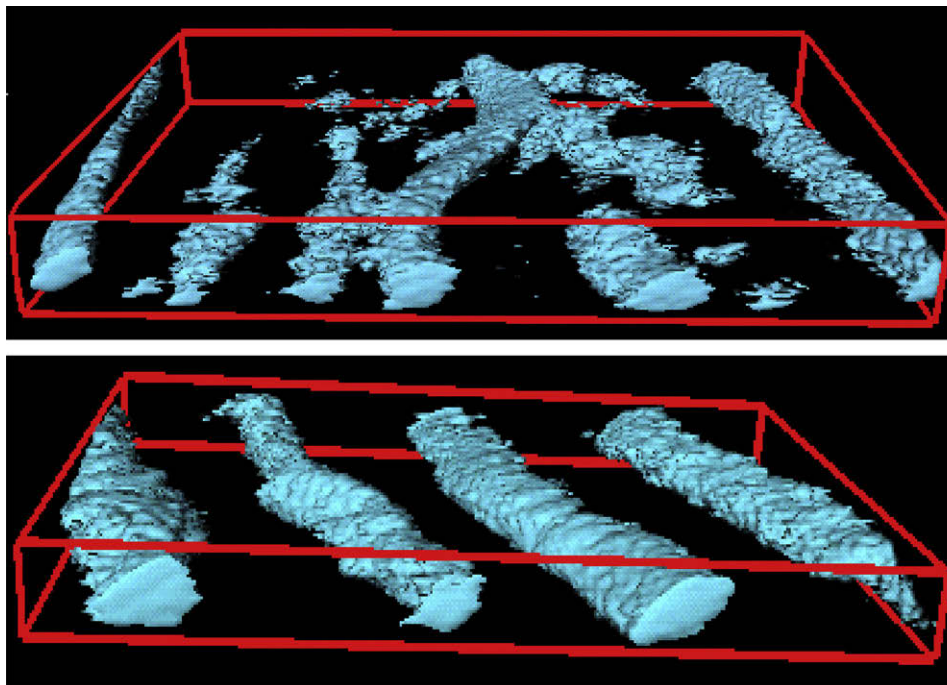
^b ratio of the length of elastic fibres to the length of the medial area section. Gaillard, et al.,^{15,16}

^c Lartaud-Idjouadiene, et al.,²⁸

Clinical studies suggest a strong link between chronic renal failure and vascular calcification, the latter leading to arterial wall stiffening and hyperpulsatility. An increase in pulse pressure in the renal circulation could increase pulsatile wall stress and so damage endothelial and smooth muscle cells.^{8,42} The kidneys of 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.¹⁶ These preliminary results suggest a link between

increased central aortic pressure pulsatility and downstream microvascular function (in the kidney).

In summary, vascular calcification may be species-specific to man. As laboratory animals such as the rat grow old they suffer from only 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 aetiology is difficult, such models could be useful in the non clinical study of the pathophysiological consequences of vascular calcification. Thus the VDN model



Images are computerized voxel reconstructions of confocal fluorescence microscopy pictures. Elastic lamella are in blue. (Giummelly, McGrath and Atkinson, unpublished).

Figure 2 Rupture of the elastic lamellar network in the aortic wall of the VDN model (upper) compared to control (lower panel).

reproduces the structural and functional aspects of medial elastocalcinosis of arteries seen with ageing in man. A proviso has to be added. All surgical or pharmacological "injury" models involve an acute challenge to a relatively young animal. Does this mimic what happens during senescence of the human aortic wall elastic fibre over decades? The fibre is subject to slowly developing mechanical failure following the cumulative effect, over a very long time, of repetitive systolic shocks to the wall⁴¹ and this in an environment that may include hypertension, atheroma, diabetes and other cardiovascular complications.

What is the evidence in man that aortic calcification is linked to increased wall stiffness? Asymptomatic hypertensive patients with aortic pulse wave velocity values above normal show abdominal aortic calcification.^{32,46} The calcium antagonist, nitrendipine, lowers pulse wave velocity in patients with aortic calcification but has no effect in those with non-calcified vessels.³³ An increase in aortic pulse wave velocity is related to aortic calcification in patients suffering from end-stage renal failure^{30,31} and arterial medial calcification is a strong prognostic marker for cardiovascular mortality in haemodialysis patients.³¹ In diabetic patients also, arterial medial calcification is related to cardiovascular mortality, coronary heart disease and stroke.²⁹

Finally, the VDN model may provide a useful tool to evaluate potential anticalcinotic therapy with drugs such as calcium entry blockers²² or angiotensin I converting enzyme inhibitors.^{21,47} Recent evidence suggests that anti-inflammatory PPAR-gamma ligands such as the thiazolidinediones (glitazones) are anticalcinotic.¹⁵ Other potential molecular candidates are compounds that compete with calcium for binding sites on the elastic fibre or those that chelate calcium.

References

1. Abedin M, Tintut Y, Demer LL. Vascular calcification; mechanisms and clinical ramifications. *Arterioscler Thromb Vasc Biol* 2004;**24**:1161–70.
2. Atkinson J, Poitevin P, Chillon JM, Lartaud I, Levy B. Vascular Ca overload produced by vitamin D₃ plus nicotine diminishes arterial distensibility in rats. *Am J Physiol* 1994;**266**:H540–7.
3. Atkinson J. Age-related medial elastocalcinosis in arteries: mechanisms, animal models and physiological consequences. *J Appl Physiol* 2008;**105**:1643–51.
4. Basalyga DM, Simionescu DT, Xiong W, Baxer BT, Starcher BC, Vyavahare NR. Elastin degradation and calcification in an abdominal aorta injury model: role of matrix metalloproteinases. *Circulation* 2004;**110**:3480–7.
5. Blumenthal HT, Lansing AI, Wheeler PA. Calcification of the media of the human aorta and its relation to intimal arteriosclerosis, ageing and disease. *Am J Pathol* 1944;**20**:665–79.
6. Bobryshev YV, Lord RSA. Detection of vascular dendritic cells and extracellular calcium-binding protein S-100 in foci of calcification in human arteries. *Acta Histochem Cytochem* 1995;**28**:371–80.
7. Bobryshev YV, Lord RSA. S-100 positive cells in human arterial intima and in atherosclerotic lesions. *Cardiovasc Res* 1995;**29**:689–96.
8. Byrom FD, Dodson LF. The causation of acute arterial necrosis in hypertensive disease. *J Pathol Bacteriol* 1948;**60**:357–68.
9. Cantini C, Kieffer P, Corman B, Liminana P, Atkinson J, Lartaud-Idjouadiene I. Aminoguanidine and aortic wall mechanics, structure, and composition in aged rats. *Hypertension* 2001;**38**:943–8.
10. Dao HH, Essalihi R, Bouvet C, Moreau P. Evolution and modulation of age-related medial elastocalcinosis: impact on large artery stiffness and isolated systolic hypertension. *Cardiovasc Res* 2005;**66**:307–17.
11. Doherty TM, Fitzpatrick LA, Inoue D, Qiao JH, Fishbein MC, Detrano RC, et al. Molecular, endocrine and genetic mechanisms of arterial calcification. *Endocr Rev* 2004;**25**:629–72.
12. Eisenstein R, Zeruolis L. Vitamin D-induced aortic calcification. *Arch Pathol* 1964;**77**:27–35.
13. Fleckenstein A, Frey M, Zorn J, Fleckenstein G. Calcium, a neglected key factor in hypertension and arteriosclerosis. In: Laragh JH, Brenner BM, editors. *Hypertension: pathophysiology, diagnosis and management*. New York: Raven Press; 1990. p. 471–509.
14. Fleisch H, Russell RG, Bisaz S, Muhlbauer R, Williams DA. The inhibitory effect of phosphonates on the formation of calcium phosphate crystals in vitro and on aortic and kidney calcification in vivo. *Eur J Clin Invest* 1970;**1**:12–8.
15. Gaillard V, Casellas D, Seguin-Devaux C, Schohn H, Dauca M, Atkinson J, et al. Pioglitazone improves aortic wall elasticity in a rat model of elastocalcinotic arteriosclerosis. *Hypertension* 2005;**46**:1–8.
16. Gaillard V, Jover B, Casellas D, Cordaillat M, Atkinson J, Lartaud I. Renal function and structure in a rat model of arterial calcification and increased pulse pressure. *Am J Physiol* 2008;**295**:222–9.
17. Gertz SD, Kurgan A, Eisenberg D. Aneurysm of the rabbit common carotid artery induced by periarterial application of calcium chloride in vivo. *J Clin Invest* 1998;**81**:649–56.
18. Giummelly P, Colas T, Atkinson J, Robert A, Daly C, Luo D, et al. Fluorescence of the medial aortic elastic lamella in elastocalcinotic rats. *N.S. Arch Pharmacol* 1998;**358**:R218 (abstract).
19. Greenwald SE. Ageing of the conduit arteries. *J Pathol* 2007;**211**:157–72.
20. Hass GM, Trueheart RE, Taylor CB, Stumpe M. An experimental histologic study of hypervitaminosis D. *Am J Pathol* 1958;**34**:395–431.
21. Henrion D, Chillon JM, Capdeville-Atkinson C, Vinceneux-Feugier M, Atkinson J. Chronic treatment with the angiotensin I converting enzyme inhibitor, perindopril, protects *in vitro* carbachol-induced vasorelaxation in a rat model of vascular calcium overload. *Br J Pharmacol* 1991;**104**:966–72.
22. Henrion D, Chillon JM, Capdeville-Atkinson C, Atkinson J. Effect of chronic treatment with the calcium entry blocker, isradipine, on vascular calcium overload produced by vitamin D₃ and nicotine in rats. *J Pharmacol Exp Ther* 1992;**260**:1–8.
23. Jayalath RW, Mangan SH, Gollledge J. Aortic calcification. *Eur J Endovasc Surg* 2005;**30**:476–88.
24. Jegger D, de Silva R, Jeanrenaud X, Nasratullah M, Tevæarai H, van Segesser LK, et al. Ventricular-arterial coupling in a rat model of reduced arterial compliance provoked by hypervitaminosis D and nicotine. *Am J Physiol* 2006;**291**:H1942–51.
25. Johnson RC, Leopold JA, Loscalzo J. Vascular calcification. Pathobiological mechanisms and clinical implications. *Circ Res* 2006;**99**:1044–59.
26. Kieffer P, Robert A, Capdeville-Atkinson C, Atkinson J, Lartaud-Idjouadiene I. Age-related arterial calcification in rats. *Life Sci* 2000;**66**:2371–81.
27. Lansing AI, Ales M, Rosenthal TB. Calcium and elastin in human arteriosclerosis. *J Gerontol* 1949;**5**:12–9.
28. Lartaud-Idjouadiene I, Lompré AM, Kieffer P, Colas T, Atkinson J. Cardiac consequences of prolonged exposure to an isolated increase in aortic stiffness. *Hypertension* 1999;**34**:63–9.
29. Lehto S, Nuskanen L, Suhonen M, Ronnema T, Laakso M. Medial artery calcification. *Arterioscler Thromb Vasc Biol* 1996;**16**:978–83.

30. London GM, Marchais SJ, Safar ME, Genest AF, Guerin AP, Metivier F, et al. Aortic and large artery compliance in end-stage renal failure. *Kidney Int* 1990;**37**:137–42.
31. London GM, Guerin AP, Marchais SJ, Metivier F, Pannier B, Adda H. Arterial media calcification in end-stage renal disease: impact on all-cause and cardiovascular mortality. *Nephrol Dial Transplant* 2003;**18**:1731–40.
32. Maarek BC, Simon AC, Levenson J, Pithois-Merli I, Bouthier JD. Heterogeneity of the atherosclerotic process in systemic hypertension poorly controlled by drug treatment. *Am J Cardiol* 1987;**2**:1111–20.
33. Marchais SJ, Boussac I, Guerin AP, Delavaux G, Metivier F, London GM. Arteriosclerosis and antihypertensive response to calcium antagonists in end-stage renal failure. *J Cardiovasc Pharmacol* 1991;**18**(Suppl.):S14–8.
34. Michel JB, Heudes D, Michel O, Poitevin P, Philippe M, Scalbert E, et al. Effect of chronic ANG I-converting enzyme inhibition on aging processes. II. Large arteries. *Am J Physiol* 1994;**267**:R124–35.
35. Moe SM, Chen NX. Pathophysiology of vascular calcification in chronic kidney disease. *Circ Res* 2004;**95**:560–7.
36. Moe SM, Chen NX. Inflammation and vascular calcification. *Blood Purif* 2005;**23**:64–71.
37. Mönckeberg JG. Über die reine mediaverkalkung der extremitätenarterien und ihr verhalten zür arteriosklerose. *Virchows Arch (Pathol Anat)* 1903;**171**:141–67.
38. Niederhoffer N, Bobryshev YV, Lartaud-Idjouadiene I, Giummelly P, Atkinson J. Aortic calcification produced by vitamin D₃ plus nicotine. *J Vasc Res* 1997;**34**:386–98.
39. Niederhoffer N, Lartaud-Idjouadiene I, Giummelly P, Duvivier C, Peslin R, Atkinson J. Calcification of medial elastic fibres and aortic elasticity. *Hypertension* 1997;**29**:999–1006.
40. Orimo H, Tershita K, Nakamura T, Ohshima J. Ca and atherosclerosis. *J Nutr Sci Vitaminol* 1985;**31**(Suppl.):S33–6.
41. O'Rourke MF. Pulsatile arterial hemodynamics in hypertension. *Aust N Z J Med* 1976;**6**:40–8.
42. O'Rourke MF, Safar M. Relationship between aortic stiffening and microvascular disease in brain and kidney. *Hypertension* 2005;**46**:200–4.
43. Potokar M, Schmidt-Dunker M. The inhibitory effect of new diphosphonic acids on aortic and kidney calcification in vivo. *Atherosclerosis* 1978;**30**:313–20.
44. Rosenblum IY, Flora L, Eisenstein R. The effect of disodium ethane-1-hydroxy-1,1-diphosphonate (EHDP) on a rabbit model of athero-arteriosclerosis. *Atherosclerosis* 1975;**22**:411–24.
45. Shao JS, Cai J, Towler DA. Molecular mechanisms of vascular calcification – lessons learned from the aorta. *Arterioscler Thromb Vasc Biol* 2006;**26**:1423–30.
46. Simon A, Levenson J. Early detection of subclinical atherosclerosis in asymptomatic subjects at high risk for cardiovascular disease. *Clin Exp Hypertens* 1993;**15**:1069–76.
47. Tatchum-Talom R, Niederhoffer N, Amin F, Makki T, Tankosic P, Atkinson J. Aortic stiffness and left ventricular mass in a rat model of isolated systolic hypertension. *Hypertension* 1995;**26**:963–70.
48. Virchow R. Cellular pathology. As based upon physiological and pathological histology. Lecture XVI – atheromatous affection of arteries. 1989. *Nutr Rev* 1858;**47**:23–5.
49. Wilens SL. The post mortem elasticity of the adult aorta. Its relation to age and to distribution of intimal atheromas. *Am J Pathol* 1937;**13**:811–34.
50. Yamauchi-Takahara K, Azuma J, Kishimoto S. Taurine protects against experimental calcinosis in mice. *Biochem Biophys Res Commun* 1986;**140**:679–83.