HHS Public Access

Author manuscript

Atherosclerosis. Author manuscript; available in PMC 2017 June 01.

Published in final edited form as:

Atherosclerosis. 2016 June ; 249: 226–227. doi:10.1016/j.atherosclerosis.2016.04.014.

Is increased arterial stiffness a cause or consequence of atherosclerosis?

Laura Hansen[a] and **W. Robert Taylor**[a,b,c,*]

[a]Division of Cardiology, Department of Medicine, Emory University, Atlanta, GA, USA

[b]Division of Cardiology, Atlanta Veterans Affairs Medical Center, Decatur, GA, USA

[c]The Wallace H. Coulter Department of Biomedical Engineering, Georgia Institute of Technology and Emory University, Atlanta, GA, USA

Decreased vascular compliance of the large arteries manifests as increased arterial pulse pressure with both higher systolic pressures and lower diastolic pressures without a significant change in mean pressure. The clinical consequences of higher systolic pressure include an increased risk of stroke and myocardial infarction. Our understanding of changes in vascular mechanics and its effect on blood pressure has grown as technology has improved our ability to quantify vascular stiffness in man. Multiple studies have shown that arterial stiffness as determined by pulse wave velocity (PWV) can be used as a predictor for cardiovascular events [1–7]. A meta-analysis of 17 studies using pulse wave velocity as a measure of arterial stiffness found that an increase in PWV by 1 m/s corresponded to a 14% increased risk of cardiovascular events and a 15% increase in mortality [5]. Another study following the First National Health and Nutrition Examination Survey found that a pulse pressure increase of 10 mmHg was associated with an increased risk of cardiovascular death of 26% in people age 25–45 and 10% in people 46–77 years [7]. Additional studies have specifically correlated increased arterial stiffness with atherosclerosis [8–10].

The positive correlation between these mechanical parameters and disease progression, in both animal and human studies support the concept that these mechanical and physical changes play an important causal role in the progression of atherosclerosis. Thus, in their paper in this issue of *Atherosclerosis*, Maedeker et al. specifically test this hypothesis using a mouse model which has both high blood pressure and decreased compliance due to a decrease in elastin content [11]. Importantly, this model does not result in elastin fragmentation thus avoiding the potential off target effects of elastin fragments. Surprisingly and contrary to the authors' original hypothesis, these mice did not have increased plaque formation. While aortic compliance and ultrastructure differ significantly between mice and man (factors which may impact the applicability of the findings to humans) the overall negative results of the current study are nonetheless quite striking and may have very important implications for our understanding of the pathogenesis of atherosclerosis. These findings suggest that the relationship between atherosclerosis and decreased vascular compliance might not be as straightforward as previously proposed and that increased

*Corresponding author. 101 Woodruff Circle, Suite 319 WMB, Atlanta, GA 30322, USA. w.robert.taylor@emory.edu (W.R. Taylor).

stiffness is not the cause of increased atherosclerosis but rather a consequence of the pathological changes in the atherosclerotic arterial wall.

The hypothesis that increased stiffness and pulse pressure can lead to atherosclerosis is based on the concept that consequences of increased stiffness, including hemodynamic changes sensed by endothelial cells as well as strain changes that are sensed by smooth muscle cells, result in downstream signaling events that promote atherosclerosis [10,12]. Vascular cell dysfunction, specifically dysregulation of nitric oxide and smooth muscle cell phenotypic switching to a more synthetic, proliferative, migratory, and inflammatory phenotype, are important cellular changes in the development of atherosclerotic plaques [13–16]. However, the mechanisms controlling these pathological changes in phenotype and cellular signaling are not completely understood. The results of this study seem to indicate that the changes in the local mechanical environment may not be a predominant factor in driving atherogenesis, or that other changes in cell signaling, cell attachment, or the extracellular matrix may account for the different degrees of plaque development despite similar vascular mechanical changes. Indeed, the authors suggest that further insults to the vasculature such as elastin fragmentation might be necessary for plaque formation and that changes in stiffness alone are not enough to promote the development of atherosclerosis. This hypothesis is supported by comparing the current paper with a similar one by Van Herck et al. which looked at atherosclerotic plaque development in $ApoE^{-/-}C1039G^{\pm}$ which have a mutation in the *fibrillin-1* gene that causes elastin fragmentation in addition to increased aortic stiffness and increased pulse pressure [17]. The increased plaque formation in $ApoE^{-/-}$ $C1039G^{\pm}$ mice but not the $ELN^{\pm}$ $Ldlr^{-/-}$ mice in the study by Maedeker et al. suggest that the elastin fragmentation and observed increases in TGBβ are vital for the development of atherosclerosis in the first model. The paper by Van Herck et al. also demonstrated a further increase in both pulse pressure and aortic stiffness at 20 weeks versus 10 weeks on the Western diet, which also supports the hypothesis that these changes are the result of atherosclerosis development as opposed to a cause of it.

The findings in the current study by Maedeker et al. are important because they suggest a paradigm shift in the way we think about the development of atherosclerosis and strategies for better treatment. Currently, the focus on vascular stiffness as a causative factor in atherosclerosis has led to studies which attempt to modulate vascular stiffness with the expectation that it will have beneficial effects in preventing or slowing disease progression. These interventions include more global approaches including lifestyle changes (weight loss, smoking cessation, etc.), dietary supplements (fish oil, soy isoflavones, etc.), and pharmaceutical control of blood pressure [18]. Other approaches to restore vascular compliance are more specific and include using small molecules to block or break advanced glycation end products (AGEs), disrupt collagen cross-links, or inhibit metalloproteinase activity to reduce elastin fragmentation [19–23]. While these studies have shown some changes in vascular compliance, the findings in the paper by Maedeker et al. raise questions as to the effectiveness of these approaches that focus specifically on improving wall compliance as it suggests vascular stiffness alone may not be an important factor in disease progression. Indeed, increased vascular stiffness may simply be a consequence of the pathological changes that occur in the arterial wall during the progression of atherosclerosis.

Acknowledgments

Financial support

Supported in part by NHLBI F32HL 124974 (L.H.)

References

1. Mitchell GF, Hwang SJ, Vasan RS, Larson MG, Pencina MJ, Hamburg NM, Vita JA, Levy D, Benjamin EJ. Arterial stiffness and cardiovascular events: the Framingham Heart Study. Circulation. 2010; 121(4):505–511. http://dx.doi.org/10.1161/circulationaha.109.886655. Epub 2010/01/20. [PubMed: 20083680]
2. Willum-Hansen T, Staessen JA, Torp-Pedersen C, Rasmussen S, Thijs L, Ibsen H, Jeppesen J. Prognostic value of aortic pulse wave velocity as index of arterial stiffness in the general population. Circulation. 2006; 113(5):664–670. http://dx.doi.org/10.1161/circulationaha.105.579342. Epub 2006/ 02/08. [PubMed: 16461839]
3. Jankowski P, Kawecka-Jaszcz K, Czarnecka D, Brzozowska-Kiszka M, Styczkiewicz K, Loster M, Kloch-Badełek M, Wiliński J, Curyło AM, Dudek D. Pressure obotAB, Group SS. Pulsatile but not steady component of blood pressure predicts cardiovascular events in coronary patients. Hypertension. 2008; 51(4):848–855. http://dx.doi.org/10.1161/hypertensionaha.107.101725. [PubMed: 18268136]
4. Mattace-Raso FUS, Van Der Cammen TJM, Hofman A, Van Popele NM, Bos ML, Schalekamp MADH, Asmar R, Reneman RS, Hoeks APG, Breteler MMB, Witteman JCM. Arterial stiffness and risk of coronary heart disease and stroke: The Rotterdam Study. Circulation. 2006; 113(5):657–663. http://dx.doi.org/10.1161/CIRCULATIONAHA.105.555235. [PubMed: 16461838]
5. Vlachopoulos C, Aznaouridis K, Stefanadis C. Prediction of cardiovascular events and all-cause mortality with arterial stiffness: a systematic review and meta-analysis. J Am Coll Cardiol. 2010; 55(13):1318–1327. http://dx.doi.org/10.1016/j.jacc.2009.10.061. Epub 2010/03/27. [PubMed: 20338492]
6. Blacher J, Asmar R, Djane S, London GM, Safar ME. Aortic pulse wave velocity as a marker of cardiovascular risk in hypertensive patients. Hypertension. 1999; 33(5):1111–1117. http://dx.doi.org/10.1161/01.hyp.33.5.1111. [PubMed: 10334796]
7. Domanski M, Norman J, Wolz M, Mitchell G, Pfeffer M. Cardiovascular risk assessment using pulse pressure in the first national health and nutrition examination survey (NHANES I). Hypertension. 2001; 38(4):793–797. http://dx.doi.org/10.1161/hy1001.092966. [PubMed: 11641288]
8. van Popele NM, Grobbee DE, Bots ML, Asmar R, Topouchian J, Reneman RS, Hoeks AP, van der Kuip DA, Hofman A, Witteman JC. Association between arterial stiffness and atherosclerosis. The Rotterdam Study. Stroke. 2001; 32(2):454–460. [PubMed: 11157182]
9. Oberoi S, Schoepf UJ, Meyer M, Henzler T, Rowe GW, Costello P, Nance JW. Progression of arterial stiffness and coronary atherosclerosis: longitudinal evaluation by cardiac CT. AJR Am J Roentgenol. 2013; 200(4):798–804. http://dx.doi.org/10.2214/ajr.12.8653. Epub 2013/03/26. [PubMed: 23521451]
10. Palombo C, Kozakova M. Arterial stiffness, atherosclerosis and cardiovascular risk: Pathophysiologic mechanisms and emerging clinical indications. Vasc Pharmacol. 2016; 77:1–7. http://dx.doi.org/10.1016/j.vph.2015.11.083.
11. Maedeker JA, Stoka KV, Bhayani SA, Gardner WS, Bennett L, Procknow JD, Staiculescu MC, Walji TA, Craft CS, Wagenseil JE. Hypertension and decreased aortic compliance due to reduced elastin amounts do not increase atherosclerotic plaque accumulation in Ldlr−/− mice. Atherosclerosis. 2016 (in press).
12. Birukov KG. Cyclic stretch, reactive oxygen species, and vascular remodeling. Antioxidants Redox Signal. 2009; 11(7):1651–1667. http://dx.doi.org/10.1089/ars.2008.2390. Epub 2009/02/04.
13. Bennett MR, Sinha S, Owens GK. Vascular Smooth Muscle Cells in Atherosclerosis. Circulation Res. 2016; 118(4):692–702. http://dx.doi.org/10.1161/circresaha.115.306361. [PubMed: 26892967]

14. Owens GK, Kumar MS, Wamhoff BR. Molecular regulation of vascular smooth muscle cell differentiation in development and disease. Physiol Rev. 2004; 84(3):767–801. http://dx.doi.org/10.1152/physrev.00041.2003. [PubMed: 15269336]

15. Davignon J, Ganz P. Role of endothelial dysfunction in atherosclerosis. Circulation. 2004; 109(23 Suppl. 1):III-27–III-32. http://dx.doi.org/10.1161/01.CIR.0000131515.03336.f8. [PubMed: 15198963]

16. Chatzizisis YS, Coskun AU, Jonas M, Edelman ER, Feldman CL, Stone PH. Role of endothelial shear stress in the natural history of coronary atherosclerosis and vascular remodeling: molecular, cellular, and vascular behavior. J Am Coll Cardiol. 2007; 49(25):2379–2393. http://dx.doi.org/10.1016/j.jacc.2007.02.059. Epub 2007/06/30. [PubMed: 17599600]

17. Van Herck JL, De Meyer GRY, Martinet W, Van Hove CE, Foubert K, Theunis MH, Apers S, Bult H, Vrints CJ, Herman AG. Impaired fibrillin-1 function promotes features of plaque instability in apolipoprotein E–deficient mice. Circulation. 2009; 120(24):2478–2487. http://dx.doi.org/10.1161/circulationaha.109.872663. [PubMed: 19948973]

18. Wu CF, Liu PY, Wu TJ, Hung Y, Yang SP, Lin GM. Therapeutic modification of arterial stiffness: An update and comprehensive review. World J Cardiol. 2015; 7(11):742–753. http://dx.doi.org/10.4330/wjc.v7.i11.742. Epub 2015/ 12/05. [PubMed: 26635922]

19. Wolffenbuttel BH, Boulanger CM, Crijns FR, Huijberts MS, Poitevin P, Swennen GN, Vasan S, Egan JJ, Ulrich P, Cerami A, Levy BI. Breakers of advanced glycation end products restore large artery properties in experimental diabetes. Proc Natl Acad Sci U S A. 1998; 95(8):4630–4634. Epub 1998/05/16. [PubMed: 9539789]

20. Cheng G, Wang LL, Long L, Liu HY, Cui H, Qu WS, Li S. Beneficial effects of C36, a novel breaker of advanced glycation end products cross-links, on the cardiovascular system of diabetic rats. Br J Pharmacol. 2007; 152(8):1196–1206. http://dx.doi.org/10.1038/sj.bjp.0707533. Epub 2007/10/30. [PubMed: 17965740]

21. Smulyan H, Mookherjee S, Safar ME. The two faces of hypertension: role of aortic stiffness. J Am Soc Hypertens. 2016; 10(2):175–183. http://dx.doi.org/10.1016/j.jash.2015.11.012. [PubMed: 26725014]

22. Kass DA, Shapiro EP, Kawaguchi M, Capriotti AR, Scuteri A, deGroof RC, Lakatta EG. Improved arterial compliance by a novel advanced glycation end-product crosslink breaker. Circulation. 2001; 104(13):1464–1470. Epub 2001/09/26. [PubMed: 11571237]

23. Wang M, Zhang J, Telljohann R, Jiang L, Wu J, Monticone RE, Kapoor K, Talan M, Lakatta EG. Chronic matrix metalloproteinase inhibition retards age-associated arterial proinflammation and increase in blood pressure. Hypertension. 2012; 60(2):459–466. http://dx.doi.org/10.1161/hypertensionaha.112.191270. Epub 2012/06/13. [PubMed: 22689745]