Review Article

http://dx.doi.org/10.3349/ymj.2012.53.2.258
pISSN: 0513-5796, eISSN: 1976-2437

Yonsei Med J 53(2):258-261, 2012

YMJ

Role of Inflammation in the Pathogenesis of Arterial Stiffness

Sungha Park[1] and Edward G. Lakatta[2]

[1]Division of Cardiology, Cardiovascular Center, Yonsei University College of Medicine, Seoul, Korea.
[2]Laboratory of Cardiovascular Science, Gerontology Research Center, National Institute on Aging, Baltimore, Maryland, USA.

Received: December 26, 2011
Corresponding author: Dr. Edward G. Lakatta, Laboratory of Cardiovascular Science, Gerontology Research Center, Intramural Research Program, National Institute on Aging, NIH, 5600 Nathan Shock Dr., Baltimore, MD 21224-6825, USA.
Tel: 1-410-558-8202, Fax: 1-410-558-8150
E-mail: LakattaE@grc.nia.nih.gov

· The authors have no financial conflicts of interest.

Increased arterial stiffness is an independent predictor of cardiovascular disease independent from blood pressure. Recent studies have shed new light on the importance of inflammation on the pathogenesis of arterial stiffness. Arterial stiffness is associated with the increased activity of angiotensin II, which results in increased NADPH oxidase activity, reduced NO bioavailability and increased production of reactive oxygen species. Angiotensin II signaling activates matrix metalloproteinases (MMPs) which degrade TGFβ precursors to produce active TGFβ, which then results in increased arterial fibrosis. Angiotensin II signaling also activates cytokines, including monocyte chemoattractant protein-1, TNF-α, interleukin-1, interleukin-17 and interleukin-6. There is also ample clinical evidence that demonstrates the association of inflammation with increased arterial stiffness. Recent studies have shown that reductions in inflammation can reduce arterial stiffness. In patients with rheumatoid arthritis, increased aortic pulse wave velocity in patients was significantly reduced by anti tumor necrosis factor-α therapy. Among the major classes of anti hypertensive drugs, drugs that block the activation of the RAS system may be more effective in reducing the progression of arterial stiffness. Thus, there is rationale for targeting specific inflammatory pathways involved in arterial stiffness in the development of future drugs. Understanding the role of inflammation in the pathogenesis of arterial stiffness is important to understanding the complex puzzle that is the pathophysiology of arterial stiffening and may be important for future development of novel treatments.

Key Words: Arterial stiffness, inflammation, angiotensin II

INTRODUCTION

Increase in arterial stiffness is a consequence of vascular fibrosis and elastic fiber degradation of the large arteries, with resulting in decreased in the arterial compliance. Increased arterial stiffness is the major underlying cause for the increase in systolic blood pressure that is associated with aging. The increase in systolic blood pressure is an important reason for the adverse prognosis associated with increased arterial stiffness. However, arterial stiffness has been demonstrated to be a predictor for increased risk for stroke, coronary artery disease and heart failure independent from blood pressure.[1-6] Although increased arterial stiffness is highly correlated with the aging process, it acts in concert with extrinsic factors such as hypertension,

high sodium intake, diabetes, dyslipidemia, obesity, neurohormonal system activation interact with structural elements of the vasculature to accelerate this aging process.[5-10] These factors result in endothelial dysfunction, vascular inflammation, vascular smooth muscle cell hyperplasia, increased collagen, and elastin degradation.[7,11,12] Recent studies have shed new light on the importance of inflammation in the pathogenesis of arterial stiffness. This review will discuss the role of inflammation in the pathogenesis of arterial stiffness.

MECHANISMS OF ARTERIAL STIFFNESS: CHANGES IN THE STRUCTURAL, CELLULAR COMPONENTS

Arterial stiffness is characterized by thickening of the intima-media, accompanied by an increase in the central arterial lumen,[13] endothelial dysfunction, vascular smooth muscle cell hyperplasia, increased collagen, and elastin degradation. The increased fragmentation of elastin molecules that is characteristic of arterial stiffness is mediated by activation of various types of matrix metalloproteinases (MMP) and serine proteinases.[7,14] The activity of MMP is increased in intima media of aged aortic tissues and is accompanied by decreased activity of TIMP-2, an endogenous inhibitor of MMP. The relative imbalance between MMP/TIMP-2 activity is important in ECM remodeling and subsequent arterial stiffening.[15,16] In addition to elastin degradation, the collagenolytic activity of MMP results in creation of uncoiled, stiffer collagen.[7] Also, degradation of basement membrane ECM by activated MMPs and stimulation of chemotaxis may result in increased smooth muscle migration and proliferation in the intima.[16,17]

The increased MMP activity may be mediated by increased activity of the renin angiotensin system, oxidative stress, endothelial dysfunction, AGE stimulated activation of RAGE, and increased activity of proinflammatory cytokines or cell adhesion molecules.[18-20]

THE ROLE OF INFLAMMATION IN ARTERIAL STIFFNESS: THE BASIC MECHANISM

Arterial stiffness is associated with increased activity of angiotensin II, which results in increased NADPH oxidase activity, reduced NO bioavailability and increased production of reactive oxygen species[20-22] AngII signaling activates MMPs which degrade the TGFβ precursor to produce active TGFβ. AngII signaling also activates cytokines including monocyte chemoattractant protein-1 (MCP-1), TNF-α, Interleukin-1, Interleukin-17 and interleukin-6.[20,23-26] Necropsy studies performed in aged human thoracic aorta demonstrated increased levels of angiotensin converting enzyme, angiotensin II, angiotensin receptor type 1 MMPs and MCP-1, compared to young aorta, suggesting the likelihood for the significant role of inflammation in the pathogenesis of arterial stiffening.[20] The activation of the MCP-1/CCR2 pathway, which has been demonstrated to play a significant role in mediating arterial inflammation and remodeling, further stimulates arterial inflammation, increases expression of cell adhesion molecules, increases secretion of MMP, amplifies the activity of other cytokines and increases vascular smooth muscle cell migration.[19,27-29] Inflammatory cytokines stimulate the local production of C-reactive protein (CRP) by vascular smooth muscle cells. CRP has an active role in promoting vascular inflammation and reducing endothelial function.[30-32] Recent studies have demonstrated a significant association of high-sensitivity (hs) CRP and arterial stiffness.[33-35] Although hsCRP is a surrogate marker of vascular inflammation, CRP itself may play an active role in mediating arterial stiffness. For example, CRP may have a direct role in inducing endothelial dysfunction. As a consequence, endothelial dysfunction may result in increased expression of proinflammatory cytokines and cell adhesion molecules. The increased vascular inflammation will increase vascular fibrosis, smooth muscle cell proliferation, and impair endothelial mediated vasodilation, which will subsequently lead to increase in arterial stiffness.[32,36,37] Oxidative stress appears to play a role in the pathogenesis of arterial stiffness, as oxidative injury may result in increased vascular inflammation and increased cellular proliferation, which may subsequently lead to impaired arterial elasticity.[38]

CLINICAL EVIDENCE OF THE ASSOCIATION OF INFLAMMATION AND ARTERIAL STIFFNESS

hsCRP is an inflammatory biomarker that is widely used to determine the degree of low grade systemic inflammation. Numerous studies have demonstrated that hsCRP is an inde-

pendent predictor of adverse cardiovascular events.[38] A study done in a normotensive population demonstrated that increase in systemic inflammation, as demonstrated by increase in hsCRP, is an independent predictor of future development of hypertension in normotensive population. The results demonstrate that systemic inflammation may have a role in the pathogenesis of vascular remodeling that leads to the development of hypertension.[39] In individuals without any traditional cardiovascular risk factors, high cysteine level, which is a marker of increased extracellular oxidative stress, was associated with pulse wave velocity (PWV) and augmentation index, independent of age, gender, arterial pressure, height, weight, heart rate and CRP.[38] A 20-year follow-up from the Caerphilly Prospective Study, a predominantly Caucasian cohort of 825 men who underwent baseline and follow-up PWV measurement, demonstrated that the only independent predictors of the PWV at follow-up was pulse pressure, CRP, glucose and waist circumference. Among the clinical variables, cumulative exposure to CRP was the variable with the strongest association, demonstrating the importance of chronic low grade inflammation in the progression of arterial stiffness.[39]

TARGETING INFLAMMATION FOR THE TREATMENT OF ARTERIAL STIFFNESS

Recent studies have shown that reduction of inflammation can reduce arterial stiffness. In patients with rheumatoid arthritis, increased aortic pulse wave velocity in patients was significantly reduced by anti tumor necrosis factor-α therapy.[40] Drugs that block the activation of the RAS system may also effectively reduced the progression of arterial stiffness. In one study, hypertensive males over 65 years of age received either angiotensin receptor blocker (Valsartan), ACE inhibitor (Tenocapril), L,N type calcium channel blocker (cilnidipine) or L type calcium channel blocker (nifedipine CR) for 3 months and were assessed for baseline and follow-up brachial ankle PWV (baPWV). Angiotensin receptor blockers yielded the largest reduction in baPWV followed by ACE inhibitors, whereas L type calcium channel blockers showed no significant improvement.[41] A similar study in patients with essential hypertension randomized to either valsartan or nifedipine demonstrated the superiority of Valsartan in reducing PWV, despite a similar reduction in blood pressure.[42] Thus, there is rationale for targeting specific inflammatory pathways involved in arterial stiffness in the development of future drugs.

CONCLUSION

The importance of inflammation in the pathogenesis of arterial stiffness has been amply demonstrated. Understanding the role of inflammation in the pathogenesis of arterial stiffness is important in understanding the complex puzzle that is the pathophysiology of arterial stiffening and is important for future development of novel treatments.

ACKNOWLEDGEMENTS

This research was supported in part by the Intramural Research Program of the NIH, National Institute on Aging and by a grant 2011-0020950 from the Public welfare & Safety research program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education, Science and Technology, Republic of Korea.

REFERENCES

1. Franklin SS, Gustin W 4th, Wong ND, Larson MG, Weber MA, Kannel WB, et al. Hemodynamic patterns of age-related changes in blood pressure. The Framingham Heart Study. Circulation 1997;96:308-15.
2. Laurent S, Katsahian S, Fassot C, Tropeano AI, Gautier I, Laloux B, et al. Aortic stiffness is an independent predictor of fatal stroke in essential hypertension. Stroke 2003;34:1203-6.
3. Domanski MJ, Mitchell GF, Norman JE, Exner DV, Pitt B, Pfeffer MA. Independent prognostic information provided by sphygmomanometrically determined pulse pressure and mean arterial pressure in patients with left ventricular dysfunction. J Am Coll Cardiol 1999;33:951-8.
4. Abramson JL, Weintraub WS, Vaccarino V. Association between pulse pressure and C-reactive protein among apparently healthy US adults. Hypertension 2002;39:197-202.
5. Boutouyrie P, Tropeano AI, Asmar R, Gautier I, Benetos A, Lacolley P, et al. Aortic stiffness is an independent predictor of primary coronary events in hypertensive patients: a longitudinal study. Hypertension 2002;39:10-5.
6. Sutton-Tyrrell K, Najjar SS, Boudreau RM, Venkitachalam L, Kupelian V, Simonsick EM, et al. Elevated aortic pulse wave velocity, a marker of arterial stiffness, predicts cardiovascular events in well-functioning older adults. Circulation 2005;111:3384-90.
7. Zieman SJ, Melenovsky V, Kass DA. Mechanisms, pathophysiology, and therapy of arterial stiffness. Arterioscler Thromb Vasc Biol 2005;25:932-43.
8. Scuteri A, Najjar SS, Muller DC, Andres R, Hougaku H, Metter

EJ, et al. Metabolic syndrome amplifies the age-associated increases in vascular thickness and stiffness. J Am Coll Cardiol 2004;43:1388-95.
9. Dart AM, Kingwell BA. Pulse pressure--a review of mechanisms and clinical relevance. J Am Coll Cardiol 2001;37:975-84.
10. Xu C, Zarins CK, Pannaraj PS, Bassiouny HS, Glagov S. Hypercholesterolemia superimposed by experimental hypertension induces differential distribution of collagen and elastin. Arterioscler Thromb Vasc Biol 2000;20:2566-72.
11. Lakatta EG, Levy D. Arterial and cardiac aging: major shareholders in cardiovascular disease enterprises: Part I: aging arteries: a "set up" for vascular disease. Circulation 2003;107:139-46.
12. Lakatta EG. Arterial and cardiac aging: major shareholders in cardiovascular disease enterprises: Part III: cellular and molecular clues to heart and arterial aging. Circulation 2003;107:490-7.
13. Virmani R, Avolio AP, Mergner WJ, Robinowitz M, Herderick EE, Cornhill JF, et al. Effect of aging on aortic morphology in populations with high and low prevalence of hypertension and atherosclerosis. Comparison between occidental and Chinese communities. Am J Pathol 1991;139:1119-29.
14. Jacob MP. Extracellular matrix remodeling and matrix metalloproteinases in the vascular wall during aging and in pathological conditions. Biomed Pharmacother 2003;57:195-202.
15. Li Z, Froehlich J, Galis ZS, Lakatta EG. Increased expression of matrix metalloproteinase-2 in the thickened intima of aged rats. Hypertension 1999;33:116-23.
16. Wang M, Lakatta EG. Altered regulation of matrix metalloproteinase-2 in aortic remodeling during aging. Hypertension 2002;39: 865-73.
17. Pauly RR, Passaniti A, Bilato C, Monticone R, Cheng L, Papadopoulos N, et al. Migration of cultured vascular smooth muscle cells through a basement membrane barrier requires type IV collagenase activity and is inhibited by cellular differentiation. Circ Res 1994;75:41-54.
18. Wendt T, Bucciarelli L, Qu W, Lu Y, Yan SF, Stern DM, et al. Receptor for advanced glycation endproducts (RAGE) and vascular inflammation: insights into the pathogenesis of macrovascular complications in diabetes. Curr Atheroscler Rep 2002;4:228-37.
19. Galis ZS, Khatri JJ. Matrix metalloproteinases in vascular remodeling and atherogenesis: the good, the bad, and the ugly. Circ Res 2002;90:251-62.
20. Wang M, Zhang J, Jiang LQ, Spinetti G, Pintus G, Monticone R, et al. Proinflammatory profile within the grossly normal aged human aortic wall. Hypertension 2007;50:219-27.
21. van der Loo B, Labugger R, Skepper JN, Bachschmid M, Kilo J, Powell JM, et al. Enhanced peroxynitrite formation is associated with vascular aging. J Exp Med 2000;192:1731-44.
22. Csiszar A, Ungvari Z, Edwards JG, Kaminski P, Wolin MS, Koller A, et al. Aging-induced phenotypic changes and oxidative stress impair coronary arteriolar function. Circ Res 2002;90:1159-66.
23. Spinetti G, Wang M, Monticone R, Zhang J, Zhao D, Lakatta EG. Rat aortic MCP-1 and its receptor CCR2 increase with age and alter vascular smooth muscle cell function. Arterioscler Thromb Vasc Biol 2004;24:1397-402.
24. Csiszar A, Ungvari Z, Koller A, Edwards JG, Kaley G. Aging-induced proinflammatory shift in cytokine expression profile in coronary arteries. FASEB J 2003;17:1183-5.
25. Gerli R, Monti D, Bistoni O, Mazzone AM, Peri G, Cossarizza A, et al. Chemokines, sTNF-Rs and sCD30 serum levels in healthy aged people and centenarians. Mech Ageing Dev 2000;121:37-46.
26. Belmin J, Bernard C, Corman B, Merval R, Esposito B, Tedgui A. Increased production of tumor necrosis factor and interleukin-6 by arterial wall of aged rats. Am J Physiol 1995;268:H2288-93.
27. Ishibashi M, Hiasa K, Zhao Q, Inoue S, Ohtani K, Kitamoto S, et al. Critical role of monocyte chemoattractant protein-1 receptor CCR2 on monocytes in hypertension-induced vascular inflammation and remodeling. Circ Res 2004;94:1203-10.
28. Jiang Y, Beller DI, Frendl G, Graves DT. Monocyte chemoattractant protein-1 regulates adhesion molecule expression and cytokine production in human monocytes. J Immunol 1992;148:2423-8.
29. Viedt C, Vogel J, Athanasiou T, Shen W, Orth SR, Kübler W, et al. Monocyte chemoattractant protein-1 induces proliferation and interleukin-6 production in human smooth muscle cells by differential activation of nuclear factor-kappaB and activator protein-1. Arterioscler Thromb Vasc Biol 2002;22:914-20.
30. Venugopal SK, Devaraj S, Yuhanna I, Shaul P, Jialal I. Demonstration that C-reactive protein decreases eNOS expression and bioactivity in human aortic endothelial cells. Circulation 2002;106:1439-41.
31. Torzewski M, Rist C, Mortensen RF, Zwaka TP, Bienek M, Waltenberger J, et al. C-reactive protein in the arterial intima: role of C-reactive protein receptor-dependent monocyte recruitment in atherogenesis. Arterioscler Thromb Vasc Biol 2000;20:2094-9.
32. Pasceri V, Willerson JT, Yeh ET. Direct proinflammatory effect of C-reactive protein on human endothelial cells. Circulation 2000; 102:2165-8.
33. Mahmud A, Feely J. Arterial stiffness is related to systemic inflammation in essential hypertension. Hypertension 2005;46:1118-22.
34. Nagano M, Nakamura M, Sato K, Tanaka F, Segawa T, Hiramori K. Association between serum C-reactive protein levels and pulse wave velocity: a population-based cross-sectional study in a general population. Atherosclerosis 2005;180:189-95.
35. Mattace-Raso FU, van der Cammen TJ, van der Meer IM, Schalekamp MA, Asmar R, Hofman A, et al. C-reactive protein and arterial stiffness in older adults: the Rotterdam Study. Atherosclerosis 2004;176:111-6.
36. Pasceri V, Cheng JS, Willerson JT, Yeh ET. Modulation of C-reactive protein-mediated monocyte chemoattractant protein-1 induction in human endothelial cells by anti-atherosclerosis drugs. Circulation 2001;103:2531-4.
37. Boos CJ, Lip GY. Elevated high-sensitive C-reactive protein, large arterial stiffness and atherosclerosis: a relationship between inflammation and hypertension? J Hum Hypertens 2005;19:511-3.
38. Patel RS, Al Mheid I, Morris AA, Ahmed Y, Kavtaradze N, Ali S, et al. Oxidative stress is associated with impaired arterial elasticity. Atherosclerosis 2011;218:90-5.
39. McEniery CM, Spratt M, Munnery M, Yarnell J, Lowe GD, Rumley A, et al. An analysis of prospective risk factors for aortic stiffness in men: 20-year follow-up from the Caerphilly prospective study. Hypertension 2010;56:36-43.
40. Mäki-Petäjä KM, Hall FC, Booth AD, Wallace SM, Yasmin, Bearcroft PW, et al. Rheumatoid arthritis is associated with increased aortic pulse-wave velocity, which is reduced by anti-tumor necrosis factor-alpha therapy. Circulation 2006;114:1185-92.
41. Takami T, Shigemasa M. Efficacy of various antihypertensive agents as evaluated by indices of vascular stiffness in elderly hypertensive patients. Hypertens Res 2003;26:609-14.
42. Munakata M, Nagasaki A, Nunokawa T, Sakuma T, Kato H, Yoshinaga K, et al. Effects of valsartan and nifedipine coat-core on systemic arterial stiffness in hypertensive patients. Am J Hypertens 2004;17(11 Pt 1):1050-5.