초청 강연 I

Basis of arterial stiffness and clinical meanings

- 좌장 | 동국의대 이명묵

- 동국의대 이무용

Basis of Arterial Stiffness and Clinical Meanings

Moo-Yong Rhee, Assoc. Prof. PD Dr. med.
Cardiovascular center
Department of Internal Medicine
DongGuk University International Hospital, Goyang, Korea

Introduction

To maintain life of human being, blood should carry oxygen and nutrient to the organs and waste products from the organs. Blood travel blood vessels, arteries and veins. Heart propels blood to the aorta, arteries and arterioles. To travel blood through aorta and arteries, appropriate blood pressure should be maintained. Normal range of blood pressure is below 120 mmHg of systolic pressure and 80 mmHg of diastolic pressure. The wall property of aorta and arteries is important. The wall of aorta and arteries composed with three layers. From the inner lumen, the first layer is intima, the second layer is media, and the last layer is adventitia. The major component of media is smooth muscle cells. Normally arterial wall has elastic property. During systolic period, heart ejects stroke volume of blood into the aorta. Approximately 50% of the stroke volume is directly forwarded to the peripheral circulation. Remained 50% of stroke volume is stored in the peripheral resistance and elastic expansion of the aortic wall.[1] With a fall in aortic pressure, the elastic property of aortic wall propels blood to the peripheral circulation. During diastolic phase, pressure and blood flow are maintained. A nearly continuous peripheral blood flow maintained in spite of rhythmic ejection of blood by heart. Maintenance of blood flow during diastolic phase is by the elastic property of aorta which is called "Windkessel function".[2] Another mechanism to maintain blood pressure during diastole, is the reflected wave from the peripheral circulation. Reflected wave from peripheral circulation returns to the ascending aorta during early diastole.[3] The Windkessel function largely depends on the elasticity of the aorta. The elasticity of aorta and arteries changes with increasing age and blood pressure. Various disease conditions, such as diabetes and hypercholesterolemia causing atherosclerosis, also can change the elasticity. The elastic property of artery is exerted by media, containing elastin fibers, collagen fibers and smooth muscle. Changes of elastic property of arterial wall, especially media leads to increase in arterial stiffness. Aging process induces increase in arterial stiffness. With increasing age, progression of atherosclerosis, degenerative changes in arteries cause arterial dilatation and thickening of arterial wall, and this change leads to increase in arterial

stiffness. High arterial distending pressure increases arterial stiffness.[4] Chronic rise in blood pressure cause recruitment and accumulation of less extendible collagenous fibers in arterial media, and makes arteries stiffer. In addition to high blood pressure, endothelial dysfunction causes increased arterial stiffness. Diabetes, chronic renal failure and other disorders causing rapid progression of atherosclerosis increase arterial stiffness. Atherosclerosis decreases arterial elasticity or increase stiffness. Increase in arterial stiffness causes deterioration of Windkessel function and increase in pulse wave velocity. Stiffening of large arteries increases the amplitude of the pressure wave and enhances the propagation velocity of the pressure wave. This leads to earlier return of reflected pressure waves to the central aorta, where they augment central pulse pressure. This increased load of central pulse pressure may promote ventricular and vascular hypertrophy and fibrosis.

Arterial stiffness can be measured by various methods. Among the methods, pulse wave velocity (PWV) is widely and easily used. PWV is derived from the measurement of pulse transit time (t) and the distance (L) traveled by the pulse between two pulse recording sites, using the formula: PWV (cm or m/sec) = L/t. First measurement of PWV was done by Bramwell et al.[5] in 1922. PWV increases as arterial wall stiffened and diameter of artery decreased. Pulse transit time is determined from the time delay between the foot of the two corresponding waves, proximal and distal, for example carotid and femoral artery. Traditionally, the distance traveled by pulse is obtained from superficial measurement of the distance between the two sensors by tape. Recently, easy and comfortable devices which can measure PWV is developed and widely used.

Clinical implications of arterial stiffening

Increased arterial stiffness is a hallmark of the aging process and the consequence of various diseases, and has been recognized as a strong independent predictor of cardiovascular event, such as myocardial infarction, heart failure and stroke, in several cardiovascular disease and chronic renal failure.[6-12]

Age and arterial stiffness

Arterial stiffness increases with age. Age-dependent increase in central arterial stiffness is independent of mean blood pressure or the presence of other risk factors.[13] Age is the major clinical determinant of aortic stiffness.[14,15] The effects of aging are different on proximal, predominantly elastic arteries, compared to distal, muscular arteries.[16-18] A number of clinical studies analyzed the effects of age on aortic stiffness by measurement of PWV. Central arteries stiffen progressively with age, whereas stiffness

of muscular arteries changes little with age.[16] Aortic stiffness increases gradually and continuously with age, similarly for men and women.[19] Aortic stiffness increases with age independently of other cardiovascular risk factors or other associated conditions. In the past, vascular stiffening and increase in systolic and pulse pressure have been considered as a part of normal aging and no treatment for these changes have been proposed. However, it has now been confirmed that older subjects with increased arterial stiffness and elevated systolic and pulse pressure have higher cardiovascular morbidity and mortality.[20-24] Thus increased arterial stiffness should be considered as a major risk factor for cardiovascular event.

Hypertension and arterial stiffness

In subjects with hypertension, the principle structural change in arterial wall is medial hypertrophy and intimal thickening.[17,25] Elevation of blood pressure induce reduced carotid and central arterial compliance in spite of increase in arterial diameter.[4] In elderly hypertensive patients, high blood pressure induces thickening of arterial wall leading to atherosclerosis. This change is associated with reduced compliance and distensibilty independent of blood pressure level.[26]

Ejection of blood from heart into aorta generates a pressure wave propagating to other arteries. Forward traveling pressure wave is reflected at where structural and functional discontinuity of arterial tree exists, generating a reflected wave traveling backward toward the descending aorta.[17] Forward and reflected waves are summed up, and summed wave determines final amplitude and shape of pulse pressure. The timing of forward and reflected pressure wave depends on PWV, the traveling distance of pressure waves, the level of reflection coefficients, and the duration of ventricular ejection. Increased PWV induces earlier return of reflected waves and makes returning of reflected wave more closely to the phase of forward wave. The earlier return of reflected wave close to the forward wave means that reflected wave amplify aortic pressure during systole and reduce aortic pressure during diastole.[17,25] This alteration of systolic and diastolic blood pressure results in increased pulse pressure. And also earlier return of reflected wave during systolic phase results in increased afterload of left ventricle. Increased afterload induces left ventricular hypertrophy and is associated with cardiovascular event and mortality. Thus increased aortic PWV may be a major determinant of cardiovascular risk in hypertensive subjects. A number of antihypertensive drugs, such as calcium channel blockers, angiotensin converting enzyme inhibitors and angiotensin receptor blockers can reduce stiffened arteries.

Diabetes and arterial stiffness

Hyperglycemic diabetics have increased arterial stiffness. Diabetic patients have diffuse arterial thickening and stiffening. The duration of diabetes related to the degree of atherosclerosis. A number of studies have reported that type I and II diabetic patients have stiffer arteries than normal subjects.[27-34] Fasting blood glucose and insulin level also showed positive correlation with increased arterial stiffness. Recently close relationship of metabolic syndrome to the increased arterial stiffness have reported.[35]

End-stage renal disease (ESRD) and arterial stiffness

ESRD has high prevalence of isolated systolic hypertension. Increased aortic stiffness with increased PWV and wave reflection, augmentation index is the principle factor responsible for isolated systolic hypertension.[36,37] Increased aortic stiffness is independent risk factor for total mortality and cardiovascular morbidity and mortality in ESRD patients. The consequence of increased arterial stiffness in ESRD patients is an early return of wave reflections to the aorta and disappearance of aortic-to-peripheral pressure amplification.[38] This phenomenon, which normally appears after the sixth decade, appears already during the fourth decade in ESRD patients. When compared to non-ESRD subjects with similar brachial blood pressure, the aortic systolic blood pressure is higher in ESRD patients.

Hyperlipidemia and arterial stiffness

The influence of hyperlipidemia on arterial stiffness is controversial. Research with animal showed increase in aortic distensibility in animals exposed to grossly elevated plasma cholesterol levels with severe experimental atherosclerosis at an early stage, and subsequently decreased as atheroma progressed at the later stage of disease.[39,40] Young patients with familial hypercholesterolemia have significantly more distensible aortas than the control subjects.[41] Contrary to young hypercholesterolemic subjects, adults with familial hypercholesterolemia had significantly less distensible aortas than normocholesterolemics.[42,43] However, studies from different populations showed no demonstrable association between aortic stiffness and total plasma cholesterol.[44,45]

Summary

Various diseases induce changes in arterial wall. These changes in arterial wall are not the only consequence of disease. Arterial wall changes and increase in arterial stiffness will aggravate cardiovascular disease and eventually lead to mortality. Increased arterial stiffness is an independent risk factor for total mortality and cardiovascular

morbidity.

References

1. Bader H. Importance of the gerontology of elastic arteries in the development of essential hypertension. Clin Physiol Biochem. 1983;1:36-56.
2. Wiggers CJ. The circulation and circulation research in perspective. In: Hamilton WF, ed. Handbook of Physiology, Section 2, Circulation, Volume 1. American Society of Physiology, Washington, D.C.;1962:1-10.
3. O'Rourke M. Arterial stiffness, systolic blood pressure, and logical treatment of arterial hypertension. Hypertension. 1990;15:339-47.
4. Laurent S, Caviezel B, Beck L, Girerd X, Billaud E, Boutouyrie P, Hoeks A, Safar M. Carotid artery distensibility and distending pressure in hypertensive humans. Hypertension. 1994;23(6 Pt 2):878-83.
5. Bramwell JC, Hill AV. Velocity of transmission of the pulse wave: and elasticity of arteries. Lancet 1922;199:891-892.
6. Chae CU, Pfeffer MA, Glynn RJ, Mitchell GF, Taylor JO, Hennekens CH. Increased pulse pressure and risk of heart failure in the elderly. JAMA. 1999;281:634-9.
7. Franklin SS, Larson MG, Khan SA, Wong ND, Leip EP, Kannel WB, Levy D.Does the relation of blood pressure to coronary heart disease risk change with aging? The Framingham Heart Study. Circulation. 2001;103:1245-9.
8. Mitchell GF, Moye LA, Braunwald E, Rouleau JL, Bernstein V, Geltman EM, Flaker GC, Pfeffer MA. Sphygmomanometrically determined pulse pressure is a powerful independent predictor of recurrent events after myocardial infarction in patients with impaired left ventricular function. SAVE investigators. Survival and Ventricular Enlargement. Circulation. 1997;96:4254-60.
9. Vaccarino V, Berger AK, Abramson J, Black HR, Setaro JF, Davey JA, Krumholz HM. Pulse pressure and risk of cardiovascular events in the systolic hypertension in the elderly program. Am J Cardiol. 2001;88:980-6.
10. Kostis JB, Lawrence-Nelson J, Ranjan R, Wilson AC, Kostis WJ, Lacy CR. Association of increased pulse pressure with the development of heart failure in SHEP. Systolic Hypertension in the Elderly (SHEP) Cooperative Research Group. Am J Hypertens. 2001;14(8 Pt 1):798-803.
11. Blacher J, Guerin AP, Pannier B, Marchais SJ, Safar ME, London GM. Impact of aortic stiffness on survival in end-stage renal disease. Circulation. 1999;99:2434-9.
12. Benetos A, Safar M, Rudnichi A, Smulyan H, Richard JL, Ducimetieere P, Guize L. Pulse pressure: a predictor of long-term cardiovascular mortality in a French male

population. Hypertension. 1997;30:1410-5.

13. Relf IR, Lo CS, Myers KA, Wahlqvist ML. Risk factors for changes in aorto-iliac arterial compliance in healthy men. Arteriosclerosis. 1986;6:105-8.
14. Asmar R, Benetos A, London G, Hugue C, Weiss Y, Topouchian J, Laloux B, Safar M. Aortic distensibility in normotensive, untreated and treated hypertensive patients. Blood Press. 1995;4:48-54.
15. Laogun AA, Gosling RG. In vivo arterial compliance in man. Clin Phys Physiol Meas. 1982;3:201-12.
16. Nichols WV, O'Rourke MF: McDonald's blood flow in arteries, in Arnold E. (ed): Theoretical, Experimental and Principles, 3 ed. London, Melbourne, Auckland, 1990, pp 77–142, 216–269, 283–269, 398–437.
17. Benetos A, Laurent S, Hoeks AP, Boutouyrie P, Safar M. Arterial alterations with aging and high blood pressure. A noninvasive study of carotid and femoral arteries. *Arterioscler Thromb* 1993;13:90–97.
18. Laurent S, Hayoz D, Trazzi S, Boutouyrie P, Waeber B, Omboni S, Brunner HR, Mancia G, Safar MJ: Isobaric compliance of the radial artery is increased in patients with essential hypertension. J Hypertens 1993;11:89–98.
19. Van der-Heijden-Spek JJ, Staessen JA, Fagard RH, Hoeks AP, Struijker-Boudier HA, Van Bortel LM. The effect of age on brachial artery wall properties differs from the aorta and is gender dependent: a population study. *Hypertension* 2000;35:637–642.
20. Benetos A, Safar M, Rudnichi A, Smulyan H, Richard JL, Ducimetiere P, Guize L. Pulse pressure: a predictor of long term cardiovascular mortality in a French male population. Hypertension 1997;30:1410–1415.
21. Mitchell F, Moye LA, Braunwald E, Rouleau JL, Bernstein V, Geltman EM, Flaker GC, SAVE Investigators and Pfeffer M. Sphygmomanometric determined pulse pressure is a powerful independent predictor of recurrent events after myocardial infarction in patients with impaired left ventricular function. Circulation 1997;96:4254–4260.
22. Franklin S, Khan SA, Wong ND, Larson MG, Levy D. Is pulse pressure useful in predicting risk for coronary heart disease? The Framingham Heart Study. Circulation 1999;100:354–360.
23. Benetos, M. Zureik, J. Morcet, F. Thomas, K. Bean, P. Ducimetière, M. Safar and L. Guize , A decrease in diastolic blood pressure combined with an increase in systolic blood pressure is associated with a higher cardiovascular mortality in men. J Am Coll Cardiol 2000;35:673–680.
24. Laurent S, Boutouyrie P, Asmar R Gautier I, Laloux B, Guize L, Ducimetiere P, Benetos A: Aortic stiffness is an independent predictor of all-cause and

cardiovascular mortality in hypertensive patients. Hypertension 2001;37:1236–1241.
25. Safar ME, London GM. The arterial system in human hypertension. In: J.D. Swales, Editor, *Textbook of Hypertension*, Blackwell Scientific, London (1994), pp. 85–102.
26. Blacher J, London GM, Safar ME, Mourad JJ. Influence of age and end-stage renal disease on the stiffness of carotid wall material in hypertension. *J Hypertens* 1999;17:237–244.
27. Woolam GL, Schnur PL, Vallbona C, Hoff HE. The pulse wave velocity as an early indicator of atherosclerosis in diabetic subjects. Circulation 1962;25:533–539.
28. Okada M, Matsuto T, Satoh S, Igarashi S, Baba M, Sugita O, Okada M. Role of pulse wave velocity for assessing autonomic nervous system activities in reference to heart rate variability. Med Inform (Lond) 1996;21(Suppl 1):81–90.
29. Lehmann ED, Gosling RG, Sonksen PH. Arterial wall compliance in diabetes. Diabet Med. 1992;9:114-9.
30. Kool MJ, Lambert J, Stehouwer CD, Hoeks AP, Struijker Boudier HA, Van Bortel LM. Vessel wall properties of large arteries in uncomplicated IDDM. Diabetes Care. 1995;18:618-24.
31. Ahlgren AR, Lane T, Wollmer P, Sonesson B, Hansen F, Sundkvist G. Increased arterial stiffness in women, but not in men, with IDDM. Diabetologia 1995;38:1082–1089.
32. Tanokuchi S, Okada S, Ota Z. Factors related to aortic pulse-wave velocity in patients with non-insulin-dependent diabetes mellitus. J Int Med Res. 1995;23:423-30.
33. Hopkins KD, Lehmann ED, Jones RL, Turay RC, Gosling RG. A family history of NIDDM is associated with decreased aortic distensibility in normal healthy young adult subjects. Diabetes Care. 1996;19:501-3.
34. Emoto M, Nishizawa Y, Kawagishi T, Maekawa K, Hiura Y, Kanda H, Izumotani K, Shoji T, Ishimura E, Inaba M, Okuno Y, Morii H. Stiffness indexes beta of the common carotid and femoral arteries are associated with insulin resistance in NIDDM. Diabetes Care. 1998;21:1178-82.
35. Nakanishi N, Suzuki K, Tatara K. Clustered features of the metabolic syndrome and the risk for increased aortic pulse wave velocity in middle-aged Japanese men. Angiology. 2003;54:551-9.
36. London GM, Guerin AP, Pannier B, Marchais SJ. A. Benetos and M.E. Safar , Arterial wave reflections and increased systolic and pulse pressure in chronic uremia: study using noninvasive carotid pulse waveform registration. Hypertension 1992;20:10-19.
37. London GM, Marchais SJ, Safar ME, Genest AF, Guerin AP, Metivier F, Chedid K,

London AM. Aortic and large artery compliance in end-stage renal failure. Kidney Int. 1990;37:137-42.

38. Marchais SJ, Guerin AP, Pannier BM, Levy BI, Safar ME, London GM. Wave reflections and cardiac hypertrophy in chronic uremia. Hypertension. 1993;22:876-83.
39. Gosling RG, Hayes JA, Segre-Mackay W. Induction of atheroma in cockerels as a model for studying alterations in blood flow. J Atheroscler Res. 1969;9:47-56.
40. D Newman DL, Gosling RG, Bowden NL. Changes in aortic distensibility and area ratio with the development of atherosclerosis. Atherosclerosis. 1971;14:231-40.
41. Lehmann ED, Watts GF, Fatemi-Langroudi B, Gosling R. Aortic compliance in young patients with heterozygous familial hypercholesterolemia. *Clin Sci* 1992;83:717-721.
42. Lehmann E, Watts GF, Gosling R. Aortic distensibility and hypercholesterolemia. Lancet 1992;340:1171–1172.
43. Lehmann ED, Hopkins KD, Parker JR, Gosling RS. Hyperlipidaemia, hypertension and coronary heart disease. Lancet 1995;345:862-863.
44. Avolio AP, Deng FQ, Li WQ, Luo YF, Huang ZD, Xing LF, O'Rourke MF. Effects of aging on arterial distensibility in populations with high and low prevalence of hypertension: comparison between urban and rural communities in China. Circulation. 1985;71:202-10.
45. Dart AM, Lacombe F, Yeoh JK, Cameron JD, Jennings GL, Laufer E, Esmore DS. Aortic distensibility in patients with isolated hypercholesterolemia, coronary disease or cardiac transplant. Lancet 1991;338:270–273.