16.
BÖLÜM

ATEROSKLEROZ VE ATEROSKLEROTİK KALP HASTALIĞI HAYVAN MODELLERİ

Sadık Volkan EMREN [1]
Zeynep EMREN [2]

Aterosklerotik kardiyovasküler hastalıklar tüm dünyada ölüm nedenleri arasında ilk sırada yer almaktadır. Ateroskleroz patofizyolojisinde halen belirsizlikler olmakla birlikte altta yatan temel patolojik sürecin ortaya konmasında hayvan deneylerinin çok büyük etkisi olmuştur. Bu bölümde ateroskleroz oluşturmada çalışılan hayvan modelleri ve bunun yönteminden bahsedilecektir. Ateroskleroz, klinik spektrumu çok geniş bir hastalıktır. Aort, koroner arter, karotis arter ve periferik arter aterosklerozun meydana geldiği başlıca vasküler yapılardır. Bilindiği üzere ateroskleroz çok erken yaşlarda başlayan ilerleyici kronik inflamatuvar bir hastalıktır. Aterokslerozun temel özelliği arter duvarında plak oluşumudur. Oluşan plak büyüyerek uzun dönemde damar lümeninde daralmaya neden olabilmektedir. Bazen de plak yüzeyinde ani çatlak veya yırtılma gelişmesine bağlı koagulasyon mekanizması tetiklenmektedir. Bunun sonunda oluşan trombotik süreç damar lümenini kısmen veya tamamen tıkayabilmektedir. Bu durumda ateroseklerotik plak stabil olmaktan çıkıp unstabil hale gelmektedir. Bu süreç klinik olarak akut kardiyovasküler olay olarak yansımaktadır. Ateroskleroz modellemesine geçmeden önce plak patofizyolojinden bahsetmekte fayda vardır. Aterosklerotik plak oluşumunun temelinde apolipoprotein B içeren lipoproteinlerin özellikle LDL kolesterolünün başat rol oynadığı düşünülmektedir (1). LDL kolesterol damarın subintimal bölgesinde birikip oksidasyona uğramaktadır. Okside olmuş LDL (oxLDL) inflamatuvar yanıtı başlatmaktadır. Bazı kemotaktik faktörler bunlar monosit kemoatraktan protein-1 (MCP-1), endotelden salınan adezyon molekülleri (vasküler adezyon molekülü-1 (VCAM-1), E- selektin ve P-selektin) etkisiyle monositler damar intimasından geçmektedirler

[1] Doç.Dr. Kâtip Çelebi Üniversitesi Tıp Fakültesi Kardiyoloji Ana Bilim Dalı
[2] Uzm. Dr. Çiğli Bölge Eğitim ve Araştırma Hastanesi Kardiyoloji Kliniği

larda olduğu gibi erkekler ateroskleroza daha duyarlıdır (4). Ateroskleroz çalışmalarında daha çok eski dünya maymunları tercih edilmiştir. Bunlar stumptail, rhesus, cynomolgous ve pigtail türleridir. Rhesus maymunlarında yüksek yağlı, yüksek kolesterollü diyetle intimal kalınlaşma ve kompleks koroner lezyon hatta akut miyokard infarktüsü geliştirebilmektedir (72, 73). Cynomolgus maymunlarında yüksek kolesterollü diyete bağlı ateroskleroz gelişimi, köpük hücre oluşumu Rhesus tip maymunlara göre daha yüksektir (74). Yine yeni dünya primatlarından Suqirrel, Afrika yeşil maymunu ve baboonlarda yüksek kolesterollü beslenme ile yağlı çizgilenme gözlenmiştir (75).

Maymunlarda ateroskleroz çalışmaları pahalı, kanunlarla sınırlandırılmış olması, kapsamlı laboratuvar olanağı gerektirmesi ve bazı türlerin koruma altında olması ateroskleroz çalışmalarını sınırlandırmaktadır.

Sonuç itibarıyla hayvan modelleri ateroskleroz patofizyolojisinin anlaşılmasında önemli ışık tutmuştur. Özellikle hayvan çalışmalarında aterosklerotik plak oluşumu başarıyla gerçekleştirilebilmiştir. Fakat hayvan modellerinde insanlarda gerçekleştiği şekilde aynı planda hassas plak oluşumu, plak rüptürü ve plak trombozu gerçekleştirilememiştir. Bunun yansıra ateroskleroza yönelik elde ettiğimiz bilgilerin önemli bir kısmı farelerden elde edilmiştir. Fareler her ne kadar ateroskleroz modellemesi açısından elverişli olsa da fizyolojik yapısının insanlara uzak olması önemli dezavantaj oluşturmuştur. Buna rağmen genetik ve diyet modifikasyonlarının hala geliştirilebilir olması ateroskleroz açısından hayvan modellerini vazgeçilmez kılmaktadır

KAYNAKLAR

1. Veseli BE, Perrotta P, De Meyer GR, Roth L, Van der Donckt C, Martinet W, et al. Animal models of atherosclerosis. European journal of pharmacology. 2017;816:3-13.
2. Tabas I, García-Cardeña G, Owens GK. Recent insights into the cellular biology of atherosclerosis. Journal of Cell Biology. 2015;209(1):13-22.
3. Sakakura K, Nakano M, Otsuka F, Ladich E, Kolodgie FD, Virmani R. Pathophysiology of atherosclerosis plaque progression. Heart, Lung and Circulation. 2013;22(6):399-411.
4. Getz GS, Reardon CA. Animal models of atherosclerosis. Arteriosclerosis, thrombosis, and vascular biology. 2012;32(5):1104-15.
5. Ignatowski A. Influence of animal food on the organsim of rabbits. Izvest Imper Voennomed Akad St Petersburg. 1908;16:154-73.
6. Zhang Y, Ramos BF, Jakschik BA. Neutrophil recruitment by tumor necrosis factor from mast cells in immune complex peritonitis. Science. 1992;258(5090):1957-9.
7. Shim J, Al-Mashhadi RH, Sørensen CB, Bentzon JF. Large animal models of atherosclerosis–new tools for persistent problems in cardiovascular medicine. The Journal of pathology. 2016;238(2):257-66.
8. Fernandez ML, Wilson TA, Conde K, Vergara-Jimenez M, Nicolosi RJ. Hamsters and guinea pigs differ in their plasma lipoprotein cholesterol distribution when fed diets varying in animal protein, soluble fiber, or cholesterol content. The Journal of nutrition. 1999;129(7):1323-32.

9. Carter CP, Howles PN, Hui DY. Genetic variation in cholesterol absorption efficiency among inbred strains of mice. The Journal of nutrition. 1997;127(7):1344-8.
10. Hobbs HH, Russell DW, Brown MS, Goldstein JL. The LDL receptor locus in familial hypercholesterolemia: mutational analysis of a membrane protein. Annual review of genetics. 1990;24(1):133-70.
11. Smith JD, James D, Dansky HM, Wittkowski KM, Moore KJ, Breslow JL. In Silico Quantitative Trait Locus Map for Atherosclerosis Susceptibility in Apolipoprotein E–Deficient Mice. Arteriosclerosis, thrombosis, and vascular biology. 2003;23(1):117-22.
12. Homanics GE, de Silva HV, Osada J, Zhang SH, Wong H, Borensztajn J, et al. Mild dyslipidemia in mice following targeted inactivation of the hepatic lipase gene. Journal of Biological Chemistry. 1995;270(7):2974-80.
13. Greeve J, Altkemper I, Dieterich J-H, Greten H, Windler E. Apolipoprotein B mRNA editing in 12 different mammalian species: hepatic expression is reflected in low concentrations of apoB-containing plasma lipoproteins. Journal of lipid research. 1993;34(8):1367-83.
14. Föger B, Chase M, Amar MJ, Vaisman BL, Shamburek RD, Paigen B, et al. Cholesteryl ester transfer protein corrects dysfunctional high density lipoproteins and reduces aortic atherosclerosis in lecithin cholesterol acyltransferase transgenic mice. Journal of Biological Chemistry. 1999;274(52):36912-20.
15. Kapourchali FR, Surendiran G, Chen L, Uitz E, Bahadori B, Moghadasian MH. Animal models of atherosclerosis. World Journal of Clinical Cases: WJCC. 2014;2(5):126.
16. Okamoto K, Aoki K, Nosaka S, Fukushima M. Cardiovascular diseases in the spontaneously hypertensive rat. Japanese circulation journal. 1964;28(12):943-52.
17. Joris I, Zand T, Nunnari J, Krolikowski F, Majno G. Studies on the pathogenesis of atherosclerosis. I. Adhesion and emigration of mononuclear cells in the aorta of hypercholesterolemic rats. The American journal of pathology. 1983;113(3):341.
18. Zhang SH, Reddick RL, Piedrahita JA, Maeda N. Spontaneous hypercholesterolemia and arterial lesions in mice lacking apolipoprotein E. Science. 1992;258(5081):468-71.
19. Ishibashi S, Brown MS, Goldstein JL, Gerard RD, Hammer RE, Herz J. Hypercholesterolemia in low density lipoprotein receptor knockout mice and its reversal by adenovirus-mediated gene delivery. The Journal of clinical investigation. 1993;92(2):883-93.
20. Witting PK, Pettersson K, Östlund-Lindqvist AM, Westerlund C, Eriksson AW, Stocker R. Inhibition by a coantioxidant of aortic lipoprotein lipid peroxidation and atherosclerosis in apolipoprotein E and low density lipoprotein receptor gene double knockout mice. The Faseb journal. 1999;13(6):667-75.
21. Lutgens E, Daemen M, Kockx M, Doevendans P, Hofker M, Havekes L, et al. Atherosclerosis in APOE* 3-Leiden transgenic mice: from proliferative to atheromatous stage. Circulation. 1999;99(2):276-83.
22. Roche-Molina M, Sanz-Rosa D, Cruz FM, García-Prieto J, López S, Abia R, et al. Induction of sustained hypercholesterolemia by single adeno-associated virus–mediated gene transfer of mutant hPCSK9. Arteriosclerosis, thrombosis, and vascular biology. 2015;35(1):50-9.
23. Rigotti A, Trigatti BL, Penman M, Rayburn H, Herz J, Krieger M. A targeted mutation in the murine gene encoding the high density lipoprotein (HDL) receptor scavenger receptor class B type I reveals its key role in HDL metabolism. Proceedings of the National Academy of Sciences. 1997;94(23):12610-5.
24. Buchanan J, Mazumder PK, Hu P, Chakrabarti G, Roberts MW, Yun UJ, et al. Reduced cardiac efficiency and altered substrate metabolism precedes the onset of hyperglycemia and contractile dysfunction in two mouse models of insulin resistance and obesity. Endocrinology. 2005;146(12):5341-9.
25. Winters B, Mo Z, Brooks-Asplund E, Kim S, Shoukas A, Li D, et al. Reduction of obesity, as induced by leptin, reverses endothelial dysfunction in obese (Lepob) mice. Journal of Applied Physiology. 2000;89(6):2382-90.
26. Zucker LM, Antoniades HN. Insulin and obesity in the Zucker genetically obese rat "fatty". Endocrinology. 1972;90(5):1320-30.

27. Zak Z, Gautier T, Dumont L, Masson D, Deckert V, Duverneuil L, et al. Effect of cholesteryl ester transfer protein (CETP) expression on diet-induced hyperlipidemias in transgenic rats. Atherosclerosis. 2005;178(2):279-86.
28. Santamarina-Fojo S, González-Navarro H, Freeman L, Wagner E, Nong Z. Hepatic lipase, lipoprotein metabolism, and atherogenesis. Arteriosclerosis, thrombosis, and vascular biology. 2004;24(10):1750-4.
29. Mezdour H, Jones R, Dengremont C, Castro G, Maeda N. Hepatic lipase deficiency increases plasma cholesterol but reduces susceptibility to atherosclerosis in apolipoprotein E-deficient mice. Journal of Biological Chemistry. 1997;272(21):13570-5.
30. Freeman L, Amar MJ, Shamburek R, Paigen B, Brewer HB, Santamarina-Fojo S, et al. Lipolytic and ligand-binding functions of hepatic lipase protect against atherosclerosis in LDL receptor-deficient mice. Journal of lipid research. 2007;48(1):104-13.
31. Hanniman EA, Lambert G, McCarthy TC, Sinal CJ. Loss of functional farnesoid X receptor increases atherosclerotic lesions in apolipoprotein E-deficient mice. Journal of lipid research. 2005;46(12):2595-604.
32. Zhang Y, Wang X, Vales C, Lee FY, Lee H, Lusis AJ, et al. FXR deficiency causes reduced atherosclerosis in Ldlr−/− mice. Arteriosclerosis, thrombosis, and vascular biology. 2006;26(10):2316-21.
33. Leong X-F, Ng C-Y, Jaarin K. Animal models in cardiovascular research: hypertension and atherosclerosis. BioMed research international. 2015;2015.
34. Nistor A, Bulla A, Filip DA, Radu A. The hyperlipidemic hamster as a model of experimental atherosclerosis. Atherosclerosis. 1987;68(1-2):159-73.
35. Dillard A, Matthan NR, Lichtenstein AH. Use of hamster as a model to study diet-induced atherosclerosis. Nutrition & metabolism. 2010;7(1):89.
36. Bentzon JF, Falk E. Atherosclerotic lesions in mouse and man: is it the same disease? Current opinion in lipidology. 2010;21(5):434-40.
37. Reddick RL, Zhang SH, Maeda N. Aortic atherosclerotic plaque injury in apolipoprotein E deficient mice. Atherosclerosis. 1998;140(2):297-305.
38. Chen Y-C, Bui AV, Diesch J, Manasseh R, Hausding C, Rivera J, et al. A novel mouse model of atherosclerotic plaque instability for drug testing and mechanistic/therapeutic discoveries using gene and microRNA expression profiling. Circulation research. 2013;113(3):252-65.
39. Eitzman DT, Westrick RJ, Xu Z, Tyson J, Ginsburg D. Hyperlipidemia promotes thrombosis after injury to atherosclerotic vessels in apolipoprotein E–deficient mice. Arteriosclerosis, thrombosis, and vascular biology. 2000;20(7):1831-4.
40. Herck JL, De Meyer GR, Martinet W, Van Hove CE, Foubert K, Theunis MH, et al. Clinical Perspective. Circulation. 2009;120(24):2478-87.
41. Mariko B, Pezet M, Escoubet B, Bouillot S, Andrieu JP, Starcher B, et al. Fibrillin-1 genetic deficiency leads to pathological ageing of arteries in mice. The Journal of pathology. 2011;224(1):33-44.
42. Van der Donckt C, Van Herck JL, Schrijvers DM, Vanhoutte G, Verhoye M, Blockx I, et al. Elastin fragmentation in atherosclerotic mice leads to intraplaque neovascularization, plaque rupture, myocardial infarction, stroke, and sudden death. European heart journal. 2015;36(17):1049-58.
43. Fan J, McCormick SP, Krauss RM, Taylor S, Quan R, Taylor JM, et al. Overexpression of human apolipoprotein B-100 in transgenic rabbits results in increased levels of LDL and decreased levels of HDL. Arteriosclerosis, thrombosis, and vascular biology. 1995;15(11):1889-99.
44. Duverger N, Kruth H, Emmanuel F, Caillaud J-M, Viglietta Cl, Castro G, et al. Inhibition of atherosclerosis development in cholesterol-fed human apolipoprotein AI–transgenic rabbits. Circulation. 1996;94(4):713-7.
45. Hoeg JM, Santamarina-Fojo S, Bérard AM, Cornhill JF, Herderick EE, Feldman SH, et al. Overexpression of lecithin: cholesterol acyltransferase in transgenic rabbits prevents diet-in-

duced atherosclerosis. Proceedings of the National Academy of Sciences. 1996;93(21):11448-53.
46. Warren RJ, Ebert DL, Mitchell A, Barter PJ. Rabbit hepatic lipase cDNA sequence: low activity is associated with low messenger RNA levels. Journal of lipid research. 1991;32(8):1333-9.
47. Bocan TM, Mueller SB, Mazur MJ, Uhlendorf PD, Brown EQ, Kieft KA. The relationship between the degree of dietary-induced hypercholesterolemia in the rabbit and atherosclerotic lesion formation. Atherosclerosis. 1993;102(1):9-22.
48. Burnstock G, Aliev G. Watanabe rabbits with heritable hypercholesterolaemia: a model of atherosclerosis. Histology and histopathology. 1998;13(3):797-817.
49. Beaty T, Prenger V, Virgil D, Lewis B, Kwiterovich P, Bachorik P. A genetic model for control of hypertriglyceridemia and apolipoprotein B levels in the Johns Hopkins colony of St. Thomas Hospital rabbits. Genetics. 1992;132(4):1095-104.
50. Fan J, Shimoyamada H, Sun H, Marcovina S, Honda K, Watanabe T. Transgenic rabbits expressing human apolipoprotein (a) develop more extensive atherosclerotic lesions in response to a cholesterol-rich diet. Arteriosclerosis, thrombosis, and vascular biology. 2001;21(1):88-94.
51. Taylor JM, Fan J. Transgenic rabbit models for the study of atherosclerosis. vascular. 1997;1:10.
52. Hoeg J. Development of transgenic Watanabe heritable hyperlipidemic rabbits expressing human apolipoprotein AI. Circulation. 1993;88:I-2 (Abstract).
53. Niimi M, Yang D, Kitajima S, Ning B, Wang C, Li S, et al. ApoE knockout rabbits: a novel model for the study of human hyperlipidemia. Atherosclerosis. 2016;245:187-93.
54. Spagnoli LG, Orlandi A, Mauriello A, Santeusanio G, de Angelis C, Lucreziotti R, et al. Aging and atherosclerosis in the rabbit: 1. Distribution, prevalence and morphology of atherosclerotic lesions. Atherosclerosis. 1991;89(1):11-24.
55. Johnstone MT, Botnar RM, Perez AS, Stewart R, Quist WC, Hamilton JA, et al. In vivo magnetic resonance imaging of experimental thrombosis in a rabbit model. Arteriosclerosis, thrombosis, and vascular biology. 2001;21(9):1556-60.
56. Kolodgie FD, Katocs Jr AS, Largis EE, Wrenn SM, Cornhill JF, Herderick EE, et al. Hypercholesterolemia in the rabbit induced by feeding graded amounts of low-level cholesterol: methodological considerations regarding individual variability in response to dietary cholesterol and development of lesion type. Arteriosclerosis, thrombosis, and vascular biology. 1996;16(12):1454-64.
57. Gertz SD, Fallon JT, Gallo R, Taubman MB, Banai S, Barry WL, et al. Hirudin reduces tissue factor expression in neointima after balloon injury in rabbit femoral and porcine coronary arteries. Circulation. 1998;98(6):580-7.
58. Abela GS, Picon PD, Friedl SE, Gebara OC, Miyamoto A, Federman M, et al. Triggering of plaque disruption and arterial thrombosis in an atherosclerotic rabbit model. Circulation. 1995;91(3):776-84.
59. Al-Mashhadi RH, Sørensen CB, Kragh PM, Christoffersen C, Mortensen MB, Tolbod LP, et al. Familial hypercholesterolemia and atherosclerosis in cloned minipigs created by DNA transposition of a human PCSK9 gain-of-function mutant. Science translational medicine. 2013;5(166):166ra1-ra1.
60. Hamamdzic D, Wilensky RL. Porcine models of accelerated coronary atherosclerosis: role of diabetes mellitus and hypercholesterolemia. Journal of diabetes research. 2013;2013.
61. Gerrity RG, Natarajan R, Nadler JL, Kimsey T. Diabetes-induced accelerated atherosclerosis in swine. Diabetes. 2001;50(7):1654-65.
62. Soutar AK. Unexpected roles for PCSK9 in lipid metabolism. Current opinion in lipidology. 2011;22(3):192-6.
63. Davis BT, Wang X-J, Rohret JA, Struzynski JT, Merricks EP, Bellinger DA, et al. Targeted disruption of LDLR causes hypercholesterolemia and atherosclerosis in Yucatan miniature pigs. PloS one. 2014;9(4).

64. Prescott MF, McBride C, Hasler-Rapacz J, Von Linden J, Rapacz J. Development of complex atherosclerotic lesions in pigs with inherited hyper-LDL cholesterolemia bearing mutant alleles for apolipoprotein B. The American journal of pathology. 1991;139(1):139.
65. Poledne R, Jurcikova-Novotna L. Experimental models of hyperlipoproteinemia and atherosclerosis. Physiological research. 2017;66:S69.
66. St C, Richard W. The contribution of avian models to our understanding of atherosclerosis and their promise for the future. Comparative Medicine. 1998;48(6):565-8.
67. Taylor RG, Lewis J. Endothelial cell proliferation and monocyte adhesion to atherosclerotic lesions of white carneau pigeons. The American journal of pathology. 1986;125(1):152.
68. Shih JC, Pullman E, Kao K. Genetic selection, general characterization, and histology of atherosclerosis-susceptible and-resistant Japanese quail. Atherosclerosis. 1983;49(1):41-53.
69. Fabricant C, Fabricant J, Minick C, Litrenta M, editors. Herpesvirus-induced atherosclerosis in chickens. Fed Proc; 1983.
70. Wasan KM, Ramaswamy M, Ng SP, Wong W, Parrott SC, Ojwang JO, et al. Differences in the lipoprotein distribution of free and liposome-associated all-trans-retinoic acid in human, dog, and rat plasma are due to variations in lipoprotein lipid and protein content. Antimicrob Agents Chemother. 1998;42(7):1646-53.
71. Mahley RW, Weisgraber KH, Innerarity T. Canine lipoproteins and atherosclerosis: II. Characterization of the plasma lipoproteins associated with atherogenic and nonatherogenic hyperlipidemia. Circulation Research. 1974;35(5):722-33.
72. Heistad D, Armstrong M. Blood flow through vasa vasorum of coronary arteries in atherosclerotic monkeys. Arteriosclerosis: An Official Journal of the American Heart Association, Inc. 1986;6(3):326-31.
73. Taylor C, Cox G, Counts M, Yogi N, editors. Fatal myocardial infarction in the rhesus monkey with diet-induced hypercholesterolemia. American Journal of Pathology; 1959: Amer Soc Investigative Pathology, Inc 428 East Preston St, Baltimore.
74. Davis HR, Vesselinovitch D, Wissler RW. Reticuloendothelial system response to hyperlipidemia in rhesus and cynomolgus monkeys. Journal of leukocyte biology. 1984;36(1):63-80.
75. Strong JP, MCGill Jr H. Diet and experimental atherosclerosis in baboons. The American journal of pathology. 1967;50(4):669.