

## BÖLÜM 23

# ENDOTEL DİSFONKSİYONUNDA GÖRÜNTÜLEME

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### GİRİŞ

Vasküler endotel, sıvıların, besinlerin ve metabolitlerin değişimini düzenlemek için yarı geçirgen bir bariyer görevi görür. Ayrıca hemostaz ve vasküler sağlık için kritik öneme sahiptir. (1,2) Sağlıklı arterlerde, endotel hücreleri laminer kan akımı, ve dolaşımdaki yüksek yoğunluklu lipoprotein gibi sitoprotektif faktörler tarafından sürdürülen hareketsiz bir durumda bulunur. (3) Bununla birlikte, kronik hastalık durumları, metabolik koşullar dahil olmak üzere çeşitli uyaranlar da (Örneğin tip 2 diabetes mellitus, obezite, dislipidemi, sigara, ve bozulmuş kan akışı), hareketsiz fenotipi kesintiye uğratar ve endotel işlev bozukluğunu tetikler. (4,5,6,7,8,9) 1998'de Hunt ve Jurd, işlevsiz vasküler endoteli beş temel karakteristik mekanizma ile tanımladı: ( i ) vasküler bütünlük kaybı, (ii) yapışma moleküllerinin ekspresyonunda artış, (iii) protrombotik fenotip, (iv) sitokin üretimi ve (v) insan lökosit antijen moleküllerinin yukarı regülasyonu. (10) Artık vasküler endotel disfonksiyonu tek patolojik bir durum olmayıp, bunun yerine vasküler tonusta, geçirgenlikte, inflamasyonda ve farklılaşmada patofizyolojik olarak heterojen değişikliklerle ilişkili bir fenotip spektrumunun temsilidir ve endotelin homeostatik fonksiyonlarının kaybına yol açtığı bi-

linmektedir (Şekil 1). Gerçekten de, son zamanlardaki tek hücreli RNA dizileme çalışmaları, örneğin anevrizmalar ve ateroskleroz gibi hastalıklar da çok sayıda farklı endotel hücre alt tipini ortaya çıkarmış, böylece hastalıklı dokularda endotel hücrelerin heterojenliğini vurgulamıştır. (11-14) Dokuda yerleşik endotelin yanı sıra, endotel hücre disfonksiyonu ayrıca dolaşımdaki endotel hücre değişiklikleri de içerir. Kardiyovasküler sağlık ve hastalıkta önemli rollere koloni oluşturan endotel hücreler ve endotel kaynaklı mikro veziküller sahiptir.

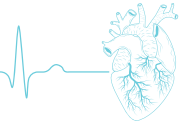
AA, amino asitler; EndMT, endotel hücre - mezenkimal geçiş; eNOS, endotel nitrik oksit sentaz (15)

### VASKÜLER DİSFONKSİYON

Fizyolojik koşullarda, uygun endotel fonksiyonunun sürdürülmesi, nitrik oksit (NO), prostasiklin (PGI<sub>2</sub>) ve/veya endotel kaynaklı hiperpolarize edici faktör gibi vazoaaktif maddelerin salınımı yoluyla vazorelaksan ve koruyucu özelliklere bağlıdır. (4,9,10)

Esas olarak vazorelaksasyon ve vasküler tonus regülasyonu yaptığı bilinen nitrik oksit (NO), oksidatif strese karşı koruma, trombosit aktivasyonu ve agregasyonu, inflamasyon ve düz kas hücresi (SMC)

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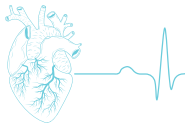


len kişinin bazal durumunun teste uygunluğunun kontrol edilmesi gereklidir.

Endotel disfonksiyonu aterosklerozun ilk basamağıdır. Kardiyovaküler hastalıkların yanında, diyabet, hiperlipidemi, hipertansiyon, sigara içimi, obezite ve inflamatuvar hastalıklarda endotel disfonksiyonu ve bozulmuş FMD değerleri izlenebilir. Bozulmuş FMD değerlerini saptamak, endotel disfonksiyonunu gösterme açısından oldukça önemli olup, hastalığın ilerlemesini değiştirme açısından önemli fırsat tanır

## KAYNAKLAR

1. Kalucka J, Bierhansl L, Conchinha NV, Missiaen R, Elia I, Bruning U, Scheinok S, Treps L, Cantelmo AR, Dubois C, de Zeeuw P, Goveia J, Zecchin A, Taverna F, Morales-Rodriguez F, Brajic A, Conradi LC, Schoors S, Harjesu, Vriens K, Pilz GA, Chen R, Cubbon R, Thienpont B, Cruys B, Wong BW, Ghesquiere B, Dewerchin M, De Bock K, Sagaert X, Jessberger S, Jones EAV, Gallez B, Lambrechts D, Mazzone M, Eelen G, Li X, Fendt SM, Carmeliet P. Quiescent endothelial cells upregulate fatty acid beta-oxidation for vasculoprotection via redox homeostasis. *Cell Metab* 2018;28:881–894.e13
2. Shah AV, Birdsey GM, Peghaire C, Pitulescu ME, Dufton NP, Yang Y, Weinberg I, Osuna Almagro L, Payne L, Mason JC, Gerhardt H, Adams RH, Randi AM. The endothelial transcription factor ERG mediates angiotensin-1-dependent control of Notch signalling and vascular stability. *Nat Commun*; 2017;8:16002
3. Cardner M, Yalcinkaya M, Goetze S, Luca E, Balaz M, Hunjadi M, Hartung J, Shemet A, Kränkel N, Radosavljevic S, Keel M, Othman A, Karsai G, Hornemann T, Claassen M, Liebisch G, Carreira E, Ritsch A, Landmesser U, Krützfeldt BJ, Wolfrum C, Wollscheid B, Beerenwinkel N, Rohrer L, von Eckardstein A. Structure–function relationships of HDL in diabetes and coronary heart disease. *JCI Insight* 2020;5:e131491.
4. Li X, Sun X, Carmeliet P. Hallmarks of endothelial cell metabolism in health and disease. *Cell Metab* 2019;30:414–433
5. Dikalov S, Itani H, Richmond B, Arslanbaeva L, Vergeade A, Rahman SMJ, Boutaud O, Blackwell T, Massion PP, Harrison DG, Dikalova A. Tobacco smoking induces cardiovascular mitochondrial oxidative stress, promotes endothelial dysfunction, and enhances hypertension. *Am J Physiol Heart Circ Physiol* 2019;316:H639–H646.
6. Miao H, Hu YL, Shiu YT, Yuan S, Zhao Y, Kaunas R, Wang Y, Jin G, Usami S, Chien S. Effects of flow patterns on the localization and expression of VE-cadherin at vascular endothelial cell junctions: in vivo and in vitro investigations. *J Vasc Res* 2005;42:77–89
7. Souilhol C, Serbanovic-Canic J, Fragiadaki M, Chico TJ, Ridger V, Roddie H, Evans PC. Endothelial responses to shear stress in atherosclerosis: a novel role for developmental genes. *Nat Rev Cardiol* 2020;17:52–63
8. Thoumine O, Nerem RM, Girard PR. Oscillatory shear stress and hydrostatic pressure modulate cell-matrix attachment proteins in cultured endothelial cells. *In Vitro Cell Dev Biol Anim* 1995;31:45–54.
9. Cai H, Harrison DG. Endothelial dysfunction in cardiovascular diseases: the role of oxidant stress.
10. Hunt BJ, Jurd KM. Endothelial cell activation. A central pathophysiological process. *BMJ* 1998;316:1328–1329.
11. Chen P-Y, Qin L, Li G, Wang Z, Dahlman JE, Malagon-Lopez J, Gujja S, Cilfone NA, Kauffman KJ, Sun L, Sun H, Zhang X, Aryal B, Canfran-Duque A, Liu R, Kusters P, Sehgal A, Jiao Y, Anderson DG, Gulcher J, Fernandez-Hernando C, Lutgens E, Schwartz MA, Pober JS, Chittenden TW, Tellides G, Simons M. Endothelial TGF- $\beta$  signalling drives vascular inflammation and atherosclerosis. *Nat Metab* 2019;1:912–926.
12. Kalluri AS, Vellarikkal SK, Edelman ER, Nguyen L, Subramanian A, Ellinor PT, Regev A, Kathiresan S, Gupta RM. Single-cell analysis of the normal mouse aorta reveals functionally distinct endothelial cell populations. *Circulation* 2019;140:147–163
13. Li Z, Solomonidis EG, Meloni M, Taylor RS, Duffin R, Dobie R, Magalhaes MS, Henderson BEP, Louwe PA, D'Amico G, Hodivala-Dilke KM, Shah AM, Mills NL, Simons BD, Gray GA, Henderson NC, Baker AH, Brittan M. Single-cell transcriptome analyses reveal novel targets modulating cardiac neovascularization by resident endothelial cells following myocardial infarction. *Eur Heart J* 2019;40:2507–2520.
14. Lukowski SW, Patel J, Andersen SB, Sim SL, Wong HY, Tay J, Winkler I, Powell JE, Khosrotehrani K. Single-cell transcriptional profiling of aortic endothelium identifies a hierarchy from endovascular progenitors to differentiated cells. *Cell Rep* 2019;27:2748–2758.e3
15. Yvonne Alexander, Elena Osto, Arno Schmidt-Trucksäss, Michael Shechter, Danijela Trifunovic, Dirk J Dunccker, Victor Aboyans, Magnus Bäck, Lina Badimon, Francesco Cosentino, Marco De Carlo, Maria Dorobantu, David G Harrison, Tomasz J Guzik, Imo Hoefer, Paul D Morris, Giuseppe D Norata, Rosa Suades, Stefano Taddei, Gemma Vilahur, Johannes Waltenberger, Christian Weber, Fiona Wilkinson, Marie-Luce Bochaton-Piallat, Paul C Evans. Endothelial function in cardiovascular medicine: a consensus paper of the European Society of Cardiology Working Groups on Atherosclerosis and Vascular Biology, Aorta and Peripheral Vascular Diseases, Coronary Pathophysiology and Microcirculation, and Thrombosis. *Cardiovascular Research*, Volume 117, Issue 1, 1 January 2021, Pages 29–42
16. Kojda G, Cheng YC, Burchfield J, Harrison DG. Dysfunctional regulation of endothelial nitric oxide synthase (eNOS) expression in response to exercise in mice lacking one eNOS gene. *Circulation* 2001;103:2839–2844
17. Deanfield JE, Halcox JP, Rabelink TJ. Endothelial function and dysfunction: testing and clinical relevance. *Circulation* 2007;115:1285–1295
18. Guzik TJ, West NEJ, Black E, McDonald D, Ratnatunga C, Pillai R, Channon KM. Vascular superoxide production by NAD(P)H oxidase – association with endothelial dysfunction and clinical risk factors. *Circ Res* 2000;86:E85–E90.



19. Guzik TJ, Chen W, Gongora MC, Guzik B, Lob HE, Mangal D, Hoch N, Dikalov S, Rudzinski P, Kapelak B, Sadowski J, Harrison DG. Calcium-dependent NOX5 nicotinamide adenine dinucleotide phosphate oxidase contributes to vascular oxidative stress in human coronary artery disease. *J Am Coll Cardiol* 2008;52:1803–1809
  20. Guzik TJ, Mussa S, Gastaldi D, Sadowski J, Ratnatunga C, Pillai R, Channon KM. Mechanisms of increased vascular superoxide production in human diabetes mellitus role of NAD(P)H oxidase and endothelial nitric oxide synthase. *Circulation* 2002;105:1656–1662.
  21. Guzik TJ, Sadowski J, Guzik B, Jopek A, Kapelak B, Przybyłowski P, Wierzbicki K, Korbut R, Harrison DG, Channon KM. Coronary artery superoxide production and NOX5 isoform expression in human coronary artery disease. *Arterioscler Thromb Vasc Biol* 2006;26:333–339
  22. Landmesser U, Dikalov S, Price SR, McCann L, Fukui T, Holland SM, Mitch WE, Harrison DG. Oxidation of tetrahydrobiopterin leads to uncoupling of endothelial cell nitric oxide synthase in hypertension. *J Clin Invest* 2003;111:1201–1209
  23. Mundi S, Massaro M, Scoditti E, Carluccio MA, van Hinsbergh VWM, Iruela-Arispe ML, De Caterina R. Endothelial permeability, LDL deposition, and cardiovascular risk factors—a review. *Cardiovasc Res* 2018;114:35–52.
  24. Caplan BA, Gerrity RG, Schwartz CJ. Endothelial cell morphology in focal areas of in vivo Evans blue uptake in the young pig aorta. I. Quantitative light microscopic findings. *Exp Mol Pathol* 1974;21:102–117
  25. de Jager SCA, Meeuwswen JAL, van Pijpen FM, Zoet GA, Barendrecht AD, Franx A, Pasterkamp G, van Rijn BB, Goumans MJ, den Ruijter HM. Preeclampsia and coronary plaque erosion: manifestations of endothelial dysfunction resulting in cardiovascular events in women. *Eur J Pharmacol* 2017;816:129–137.
  26. Dewey CF Jr, Bussolari SR, Gimbrone MA Jr, Davies PF. The dynamic response of vascular endothelial cells to fluid shear stress. *J Biomech Eng* 1981;103:177–185
  27. Gerrity RG, Richardson M, Caplan BA, Cade JE, Hirsch J, Schwartz CJ. Endotoxin-induced vascular endothelial injury and repair. II. Focal injury, en face morphology, (3H)thymidine uptake and circulating endothelial cells in the dog. *Exp Mol Pathol* 1976;24:59–69
  28. Premer C, Kanelidis AJ, Hare JM, Schulman IH. Rethinking endothelial dysfunction as a crucial target in fighting heart failure. *Mayo Clin Proc Innov Qual Outcomes* 2019;3:1–13.
  29. SchäChinger BV, Britten MB, Zeiher AM. Prognostic impact of coronary vasodilator dysfunction on adverse long-term outcome of coronary heart disease. *Circulation* 2000;101:1899–1906.
  30. Laurent S, Lacolley P, Brunel P, Laloux B, Pannier B, Safar M. Flow-dependent vasodilation of brachial artery in essential hypertension. *Am J Physiol* 1990;258:H1004–11.
  31. Anderson EA, Mark AL. Flow-mediated and reflex changes in large peripheral artery tone in humans. *Circulation* 1989;79:93–100.
  32. Celermajer DS, Sorensen KE, Gooch VM, et al. Non-invasive detection of endothelial dysfunction in children and adults at risk of atherosclerosis. *Lancet* 1992;340:1111–5.
  33. Sorensen KE, Celermajer DS, Spiegelhalter DJ, et al. Non-invasive measurement of human endothelium dependent arterial responses: accuracy and reproducibility. *Br Heart J* 1995;74:247–53
  34. Dick H. J. Thijssen, 1, 2 Mark A. Black, 1, 3 Kyra E. Pyke, 4 Jaume Padilla, 5 Greg Atkinson, 1 Ryan A. Harris, 6 Beth Parker, 7 Michael E. Widlansky, 8 Michael E. Tschakovsky, 9 and Daniel J. Green, 1, 10. Assessment of flow-mediated dilation in humans: a methodological and physiological guideline. *Am J Physiol Heart Circ Physiol* 300: H2–H12, 2011.
  35. Şekil 7: FMD testi sırasında gözlemlenen tipik bir hız ve çap yanıtının bireysel temsili
- Rodriguez-Miguel, P., Seigler, N., Harris, R.A. Ultrasound Assessment of Endothelial Function: A Technical Guideline of the Flow-mediated Dilation Test. *J. Vis. Exp.* (110), e54011, doi:10.3791/54011 (2016).