

24. BÖLÜM

KARDİYAK TRANSPLANTLI HASTALARDA HİPERTANSİYON TEDAVİSİ

İsmail TATLI¹
Muhammed SÜLEYMANOĞLU²

GİRİŞ

Kardiyak transplantasyon, son dönem kalp yetmezliği olan hastalarda altın standart tedavi olmaya devam etmektedir. Cerrahi tekniklerde ve immünsüpresif rejimlerde kaydedilen büyük ilerleme sayesinde kardiyak transplantasyon sonrası sağ kalım ortalamaları 1 yılda %90, 5 yılda %72.5'e ulaşmıştır. Sağ kalımdaki iyileşmeye rağmen kardiyak allogreftin yol açtığı benzersiz fizyoloji, immünsüpresif tedaviler (kortikosteroid, kalsinörin inhibitörleri vb.) cerrahi denervasyon, kısıtlayıcı fizyolojiye bağlı gelişen sıvı hassasiyeti ve ventriküler hipertrofiye bağlı olarak bir dizi komplikasyon ortaya çıkmaktadır (1,2).

Hipertansiyon kalp yetmezliği için en güçlü risk faktörlerinden biridir ve kalp yetmezliği hastalarının %91'inde görülmektedir (3). Son dönem kalp yetmezliği hastalarının birçoğunda, düşük kardiyak output nedeniyle kan basıncı düşük olmasına rağmen, kardiyak transplantasyon sonrası fizyolojik değişikliklere bağlı olarak kan basıncında yükseliğe neden olur. Uluslararası Kalp ve Akciğer Transplantasyon derneğinin en son raporuna göre; kardiyak transplantlı hastalarda hipertansiyon tahmini prevalansı 1 yılda %72, 5 yılda %92'dir (4).

HİPERTANSİYON GELİŞİM MEKANİZMALARI

Hormonal Eetki

Su ve sodyum tutulumu sonucu Renin Angiotensin ve Aldosteron Sistemi aktifleşir (5). Sodyum ve su homeostazında ortaya çıkan bu bozulma, erken kardiyak transplantasyon aşamasında hipertansiyona katkıda bulunan güçlü bir faktör olarak tanımlanmıştır (6,7). Kardiyak transplantasyonu takiben kan basıncında gece düşüşün olmaması da hipertansiyonun bir nedeni olarak gösterilmiştir. Kalp nakli yapılmış 34 hastadan oluşan bir çalışmada, hastaların %50'sinde kan basıncında

¹ Arş. Gör. Dr., Gazi Yaşargil Eğitim ve Araştırma Hastanesi Kardiyoloji Kliniği.
drismailtatli@gmail.com

² Dr. Öğr. Üyesi, Kafkas Üniversitesi Tıp Fakültesi, Kardiyoloji AD, msagarti@hotmail.com

lardan nebivolol, endojen nitrik oksit uyarımı yoluyla vazodilatatör etkinlik sunar. Beta blokerler, olumsuz kronotropik etkileri ve sağ ventrikül üzerindeki olası olumsuz etkileri nedeniyle genellikle nakil sonrası erken dönemde önerilmez (60,63). Doksazosin gibi alfa blokerlerin güvenli ve etkili olduğu gösterilmiştir. Merkezi etkili alfa blokerler kullanılabilir, ancak yan etki profilinden dolayı daha az tercih edilir. Hidralazin renal disfonksiyonda güvenlidir ve çok az ilaç etkileşimi vardır. Bununla beraber, gerekli doz sıklığı ve öngörülemez doz-yanıt eğrisi uzun vadeli kullanımını sınırlandırmaktadır (68).

SONUÇ

Hipertansiyon kalp nakli sonrası yaygın bir sorun olmaya devam etmektedir. Tedavi özellikle erken dönemde zor olsa da farklı patofizyolojik mekanizmaların anlaşılmasıyla tedavi seçenekleri artmakta ve kan basıncı kontrolü daha hızlı sağlanmaktadır. Su ve tuz kısıtlaması, immünsüpresif ajan seçimi, kombinasyon tedavileri genellikle kan basıncı kontrolünü sağlamada yeterlidir. Son olarak antihipertansif ajanın seçimi zamanlama (erken veya geç transplant dönemi) böbrek fonksiyonları, komorbiditeler ve potansiyel ilaç etkileşimi düşünülerek yapılmalıdır.

KAYNAKLAR

1. Costanzo MR, Dipchand A, Starling R, et al. The International Society of Heart and Lung Transplantation Guidelines for the care of heart transplant recipients. *J Heart Lung Transplant* 2010; 29:914–956.
2. Lund LH, Edwards LB, Dipchand AI, et al. The registry of the International Society for Heart and Lung Transplantation: thirty-third adult heart transplantation report-2016; focus theme: primary diagnostic indications for transplant. *J Heart Lung Transplant* 2016; 35:1158–1169.
3. Heidenreich PA, Albert NM, Allen LA, et al. Forecasting the impact of heart failure in the united states a policy statement from the american heart association. *Circ Hear Fail* 2013; 6:606–619.
4. Lund LH, Edwards LB, Kucheryavaya AY, et al. The registry of the International Society for Heart and Lung Transplantation: thirty-first official adult heart transplant report – focus theme: retransplantation. *J Heart Lung Transplant* 2014; 33:996–1008.
5. Singer DRJ, Banner NR, Cox A, et al. Response to dynamic exercise in cardiac transplant recipients: implications for control of the sodium regulatory hormone atrial natriuretic peptide. *Clin Sci* 1990; 78:159–163.
6. Braith RW, Mills RM Jr, Wilcox CS, et al. Fluid homeostasis after heart transplantation: the role of cardiac denervation. *J Heart Lung Transplant* 1996; 15:872–880.
7. Braith RW, Plunkett MB, Mills RM. Cardiac output responses during exercise in volume-expanded heart transplant recipients. *Am J Cardiol* 1998;81:1152–1156.
8. Cugini P, Chiera A, Petrangeli CM, et al. Describing and interpreting systemic hypertension in heart transplantation with noninvasive arterial pressure monitoring. *Cardiologia* 1996; 41:653–659.

9. Cugini P, Chiera A, Scibilia G, et al. Who are the 'nondippers': an insight from the ambulatory monitoring of arterial pressure in heart transplant patients. *Recenti Prog Med* 1997; 88:212–216
10. Jenkins GH, Singer DR. Hypertension in thoracic transplant recipients. *J Hum Hypertens* 1998; 12:813–823
11. Olivari MT, Antolick A, Ring S. Arterial hypertension in heart transplant recipients treated with triple drug immunosuppressive therapy. *J Heart Transplant* 1989;8:34–9.
12. Martí 'nez-Dolz L, Sa 'nchez-La 'zaro IJ, Almenar-Bonet L, et al. Metabolic syndrome in heart transplantation: impact on survival and renal function. *Transpl Int* 2013;26(9):910–8.
13. Reichart B. Size matching in heart transplantation. *J Heart Lung Transplant* 1992; 11(4 Pt 2):S199–S202
14. Ozdogan E, Banner N, Fitzgerald M, et al. Factors influencing the development of hypertension following cardiac transplantation. *J Heart Transplant* 1990; 5:548–553.
15. Veenstra DL, Best JH, Hornberger J, et al. Incidence and long-term cost of steroid-related side effects after renal transplantation. *Am J Kidney Dis* 1999; 33(5):829–39
16. Langford HG, Snively JR. Effect of DCA on development of renoprival hypertension. *Am J Physiol* 1959;196:449–50.
17. Ciresi DL, Lloyd MA, Sandberg SM, et al. The sodium retaining effects of cyclosporine. *Kidney Int* 1992; 41:1599–1605.
18. Gaston RS. Chronic calcineurin inhibitor nephrotoxicity: reflections on an evolving paradigm. *Clin J Am Soc Nephrol* 2009; 4:2029–2034.
19. Wallerath T, Witte K, Schafer SC, et al. Down-regulation of the expression of endothelial NO synthase is likely to contribute to glucocorticoid-mediated hypertension. *Proc Natl Acad Sci U S A* 1999;96:13357–62.
20. Baum M, Quigley R. Glucocorticoids stimulate rabbit proximal convoluted tubule acidification. *J Clin Invest* 1993; 91:110–114.
21. DiBardino DJ. The history and development of cardiac transplantation. *Texas Hear Inst J* 1999; 26:198–205
22. Denton MD, Magee CC, Sayegh MH. Immunosuppressive strategies in transplantation. *Lancet* 1999; 353:1083–1091.
23. Ventura HO, Mehra MR, Stapleton DD, Smart FW. Cyclosporine-induced hypertension in cardiac transplantation. *Med Clin North Am* 1997; 81:1347–1357.
24. Ventura HO, Malik FS, Mehra MR, et al. Mechanisms of hypertension in cardiac transplantation and the role of cyclosporine. *Curr Opin Cardiol* 1997; 12:375–381.
25. Luke RG, Curtis JJ. Biology and treatment of transplant hypertension. In: Laragh JH, Brenner BM, editors. *Hypertension: pathophysiology, diagnosis and management*. 2nd edition. New York: Raven Press; 1995. p. 2471–81.
26. Sanders M, Victor RG. Hypertension after cardiac transplantation: pathophysiology and management. *Curr Opin Nephrol Hypertens* 1995;4:443–51.
27. Ventura HO, Lavie CJ, Messerli FH, et al. Cardiovascular adaptation to cyclosporine-induced hypertension. *J Hum Hypertens* 1994;8:233–7.
28. Kahan BD. Cyclosporine nephrotoxicity: pathogenesis, prophylaxis, therapy, and prognosis. *Am J Kidney Dis* 1986;8:323–31.
29. Murray BM, Paller MS, Ferris TF. Effect of cyclosporine administration on renal hemodynamics in conscious rats. *Kidney Int* 1985;28:767–74.
30. Karabesheh S, Verma DR, Jain M, et al. Clinical and hemodynamic effects of renin-angiotensin system blockade in cardiac transplant recipients. *Am J Cardiol* 2011;108(12):1836–9.

31. Bantle JP, Nath KA, Sutherland DE, et al. Effects of cyclosporine on the reninangiotensin-aldosterone system and potassium excretion in renal transplant recipients. *Arch Intern Med* 1985;145(3):505–8.
32. Melnikov S, Mayan H, Uchida S, et al. Cyclosporine metabolic side effects: association with the WNK4 system. *Eur J Clin Invest* 2011;41(10):1113–20.
33. Hoorn EJ, Walsh SB, McCormick JA, et al. The calcineurin inhibitor tacrolimus activates the renal sodium chloride cotransporter to cause hypertension. *Nat Med* 2011;17(10):1304–9.
34. Stogsdill G, Gonzales D, Hays N, et al. Post-liver transplant weight gain and its effect on cardiovascular disease risk factors. *FASEB J* 2011;25:971.39.
35. Canzanello VJ, Schwartz L, Taler SJ, et al. Evolution of cardiovascular risk after liver transplantation: a comparison of cyclosporine A and tacrolimus (FK506). *Liver Transpl Surg* 1997;3(1):1–9.
36. Victor RG, Thomas GD, Marban E, et al. Presynaptic modulation of cortical synaptic activity by calcineurin. *Proc Natl Acad Sci U S A* 1995;92(14):6269–73.
37. Humen DP, McKenzie FN, Kostuk WJ. Restricted myocardial compliance one year following cardiac transplantation. *J Heart Transplant* 1984;3:341–5.
38. Cotts WG, Oren RM. Function of the transplanted heart: unique physiology and therapeutic implications. *Am J Med Sci* 1997;314(3):164–72.
39. Murali S, Uretsky BF, Reddy S, et al. Hemodynamic abnormalities following cardiac transplantation: relationship to hypertension and survival. *Am Heart J* 1989;118:334–41.
40. Patel ND, Weiss ES, Nwakanma LU, et al. Cardiac transplantation and surgery for heart failure impact of donor-to-recipient weight ratio on survival after heart transplantation: analysis of the United Network for organ sharing database. *Circulation* 2008;118:S83–8.
41. Ambrosi P, Kreitmann B, Habib G. Does heart rate predict allograft vasculopathy in heart transplant recipients? *Int J Cardiol* 2010;145:256–7.
42. Murphy DA, Thompson GW, Ardell JL, et al. The heart reinnervates after transplantation. *Ann Thorac Surg* 2000;69(6):1769–81.
43. Palatini P, Casiglia E, Pauletto P, et al. Relationship of tachycardia with high blood pressure and metabolic abnormalities: a study with mixture analysis in three populations. *Hypertension* 1997;30:1267–73.
44. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: executive summary: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines. *J Am Coll Cardiol* 2018; 71:2199–2269.
45. Costanzo MR, Dipchand A, Starling R, et al. The International Society of Heart and Lung Transplantation Guidelines for the care of heart transplant recipients. *J Heart Lung Transplant* 2010; 29:914–956.
46. Singer DR, Markandu ND, Buckley MG, et al. Blood pressure and endocrine responses to changes in dietary sodium intake in cardiac transplant recipients: implications for the control of sodium balance. *Circulation* 1994; 89:1153–1159.
47. Rosenbaum DH, Adams BC, Mitchell JD, et al. Effects of early steroid withdrawal after heart transplantation. *Ann Thorac Surg* 2006; 82:637–644.
48. Baraldo M, Gregoraci G, Livi U. Steroid-free and steroid withdrawal protocols in heart transplantation: the review of literature. *Transpl Int* 2014;27:515–529.
49. Baran DA, Rosenfeld C, Zucker MJ. Corticosteroid weaning in stable heart transplant patients: guidance by serum cortisol level. *J Transplant* 2018.

50. Pelletier RP, Akin B, Ferugson RM. Prospective, randomized trial of steroid withdrawal in kidney recipients treated with mycophenolate mofetil and cyclosporine. *Clin Transpl* 2006; 20:10–18
51. Veenstra DL, Best JH, Hornsberger J, et al. Incidence and long-term cost of steroid related side effects after renal transplantation. *Am J Kidney Dis* 1999;5:829–839
52. Helal I, Chan L. Steroid and calcineurin inhibitor sparing protocols in kidney transplantation. *Transpl Proc* 2011; 43:472–477.
53. Sivaraman P, Nussbaumer G, Landsberg D. Lack of long-term benefits of steroid withdrawal in renal transplant recipients. *Am J Kidney Dis* 2001;37:1162–1169
54. Groetzner J, Meiser B, Landwehr P, et al. Mycophenolate mofetil and sirolimus as calcineurin inhibitor-free immunosuppression for cardiac transplant recipients with chronic renal failure. *Transplantation* 2004; 77:568.
55. Groetzner J, Kaczmarek I, Schulz U, et al. Mycophenolate and sirolimus as calcineurin inhibitor-free immunosuppression improves renal function better than calcineurin inhibitor-reduction in late cardiac transplant recipients with chronic renal failure. *Transplantation* 2009; 87:726–733.
56. Przybylowski P, Malyszko J, Malyszko JS, et al. Blood pressure control in orthotopic heart transplant and kidney allograft recipients is far from satisfactory. *Transpl Proc* 2010; 42:4263–4266.
57. Keogh A, Richardson M, Ruygrok P, et al. Sirolimus in de novo heart transplant recipients reduces acute rejection and prevents coronary artery disease at 2 years: a randomized clinical trial. *Circulation* 2004; 110:2694–2700
58. Eisen H, Tuzcu EM, Dorent R, et al. Everolimus for the prevention of allograft rejection and vasculopathy in cardiac-transplant recipients. *N Engl J Med* 2003; 349:847.
59. Qi H, Liu Z, Cao H, et al. Comparative efficacy of antihypertensive agents in salt-sensitive hypertensive patients: a network meta-analysis. *Am J Hypertens* 2018; 7:835–846
60. Starling RC, Cody RJ. Cardiac transplant hypertension. *Am J Cardiol* 1990; 65:106–111.
61. Braith RW, Mills RM, Wilcox CS, et al. Breakdown of blood pressure and body fluid homeostasis in heart transplant recipients. *J Am Coll Cardiol* 1996; 27:375–383
62. Weir MR, Salzberg DJ. Management of hypertension in the transplant patient. *J Am Soc Hypertens* 2011; 5:425–432.
63. Sennesael JJ, Lamote JG, Violet I, et al. Divergent effects of calcium channel and angiotensin converting enzyme blockade on glomerulotubular function in cyclosporine-treated renal allograft recipients. *Am J Kidney Dis* 1996;27:701–708.
64. van der Schaaf MR, Hene RJ, Floor M, et al. Hypertension after renal transplantation. Calcium channel or converting enzyme blockade? *Hypertension* 1995; 25:77–81
65. Schroder JS, Gao SZ, Alderman EC, et al. A preliminary study of diltiazem in prevention of coronary artery disease in the heart transplant recipients. *N Engl J Med* 1993; 328:164–170
66. Braith RW, Mills RM, Wilcox CS, et al. High-dose angiotensin-converting enzyme inhibition restores body fluid homeostasis in heart-transplant recipients. *J Am Coll Cardiol* 2003; 41:426–432.
67. Hausberg M, Barenbrock M, Hohage H, et al. ACE inhibitor versus B-blocker for the treatment of hypertension in renal allograft recipients. *Hypertension* 1999; 33:862–868.
68. Marti'nez Castela'o A, Ibero'n M, Sarrias X, et al. Doxazosin GITS trough to peak ratio and 24-h blood pressure monitoring in the management of hypertension in renal transplant patients. *Transplant Proc* 2003; 35:1736–1738.