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Commentary

Prognosis of Heart Failure and Sympathetic Nerve Activity

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ABSTRACT

The prognosis of heart failure is poor and plasma noradrenaline level is a good predictor of the survival rate of heart failure patients. Sympathetic nerve activity is augmented in patients with heart failure as evidenced by a higher noradrenaline release rate from the sympathetic nerve endings. Drugs for heart failure such as β-blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, mineralocorticoid antagonists, ivabradine, Angiotensin Receptor-Neprilysin Inhibitor (ARNI), and Sodium-Glucose Transport Protein 2 (SGLT2) inhibitors have clinical evidences for improving prognosis of heart failure in large randomized-controlled clinical trials. Interestingly, the same characteristics in common of these drugs is to reduce sympathetic nerve activity. In addition, cardiac rehabilitation which causes a better prognosis of heart failure reduces the sympathetic nerve activity. In conclusion, to optimize excessively augmented sympathetic nerve activity may be related to an improvement of prognosis of heart failure.

Keywords: Heart failure; Sympathetic nerve activity; Prognosis; Anti-heart failure drugs; Cardiac rehabilitation

ABOUT THE STUDY

Heart failure is the end-stage phenotype of all kinds of cardiac diseases. The 5-year death rate of heart failure with a New York Heart Association functional classification (NYHA) IV (SCONSENSUS placebo) is comparable to lung cancer (Stage IIIA), and heart failure with NYHA II-III (Studies of Left Ventricular Dysfunction (SOLVD)-T placebo) or NYHA I-II (SOLVD-P placebo) to cancers such as stomach (Stage III), breast (Stage IIIA), and colorectal cancer (Dukes C) [1-3]. Since the prognosis of heart failure is very poor, to know what is the main factor that deteriorates prognosis of heart failure is important.

Plasma noradrenaline level is a prognostic factor of heart failure patients

Plasma noradrenaline levels are inversely correlated with cardiac index or Left Ventricular Ejection Fraction (LVEF) [4]. Plasma noradrenaline levels increase according to the severity of heart failure based on the NYHA classification [5]. These suggest that deterioration of LV function causes higher plasma noradrenaline levels in patients with heart failure. Plasma noradrenaline level has been reported to be a powerful predictor of the survival rate of heart failure patients [6,7]. Higher plasma noradrenaline level is a predictor of poor prognosis even in HFpEF patients [8]. Plasma noradrenaline level is determined by the balance between noradrenaline release rate from the sympathetic nerve endings and noradrenaline clearance rate from the blood [9]. Thus, to assess real sympathetic nerve activity, noradrenaline release rate (spillover rate) from the sympathetic nerve endings should be measured. In the rabbit model of heart failure, noradrenaline release rate was significantly greater than the control rabbits [9]. Furthermore, noradrenaline release rate was significantly higher in patients with heart failure than in the control, and the increase in noradrenaline release was mainly due to the heart and kidney [10].

Pharmacological therapies for heart failure patients

There are clinical evidences that anti-heart failure drugs show a better prognosis;

Beta blockers (CIBS-II, MERIT-HF, COPERNICUS) [11-13], ACE inhibitors (CONSENSUS, SOLVED) [14,15], ARBs (Val-HeFT) [16], MRAs (RALES, EMPHASIS-HF) [17,18], Ivabradine

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(SHIFT) [19], ARNI (PARADIGM-HF) [20], SGLT2 inhibitors (DAPA-HF, EMPEROR-Reduced, EMPEROR-Preserved) [21-23].

Effects of anti-heart failure drugs on sympathetic nerve activity

Beta-blockers block the sympathetic nerve activity at the postsynaptic beta-receptors. Captopril, an ACE inhibitor, and saralasin, an ARB decrease the noradrenaline release rate [24]. In an animal study of rabbits with heart failure, captopril decreased the noradrenaline release rate from the sympathetic nerve endings when corrected by hypotensive reflex [9]. In rats with heart failure induced by angiotensin II-infusion and salt-loading, chronic treatment with telmisartan, an ARB, significantly decreased the urinary noradrenaline level compared with the control [25]. In an animal study with rats, eplerenone, an MRA, decreased renal sympathetic nerve activity, which was recorded by stainless steel bipolar electrodes placed beneath the renal nerve [26]. In heart failure rats induced by coronary artery ligation, administration of ivabradine significantly decreased the plasma noradrenaline levels than in an untreated group [27]. ARNI produces BNP by blocking the enzyme neprilysin by sacubitril and blocks Ang II-receptors by valsartan. ARB decreases noradrenaline release rate [24]. It was reported that BNP decreased noradrenaline release in response to sympathetic nerve stimulation in an isolated atria preparation [28], and that infusion of BNP decreased noradrenaline release rate in patients with heart failure [29], suggesting that ARNI decreases sympathetic nerve activity. In Schlager mice (BPH/2J strain), oral administration of dapagliflozin reduced the sympathetic innervation in the kidney assessed by tyrosine hydroxylase staining, and reduced the noradrenaline content in the kidney as comparted with the control [30]. In HFpEF pigs induced by infusion of a combination of deoxycorticosterone and Ang II, dapagliflozin treatment decreased the expression of tyrosine hydroxylase and tissue content of noradrenaline in the aorta [31]. In ApoE-/-mice fed a western diet for 12 weeks, treatment with 10 mg/kg/day of oral empagliflozin for 12 weeks reduced the plasma noradrenaline levels significantly as compared with mice without treatment with empagliflozin [32].

All these reports mentioned above suggest that beta-blockers, ACE inhibitors, ARBs, MRAs, Ivabradine, ARNI and SGLT2 inhibitors have ability to reduce excessively augmented sympathetic nerve activity.

Cardiac rehabilitation

It has been reported that cardiac rehabilitation improves prognosis of heart failure patients [33]. It has been reported that bicycle exercise training for one month reduces plasma noradrenaline levels and total spillover rate of noradrenaline in healthy subjects [34] and that exercise training reduces the muscle sympathetic nerve activity in patients with heart failure [35]. The reduction of sympathetic nerve activity may be related to an improvement of prognosis of patients with heart failure.

Clinical perspective

Heart failure patients with a higher plasma noradrenaline level show a poor survival rate [6,7], suggesting that excessively augmented sympathetic nerve activity is involved in the poor survival rate of heart failure patients. Treatment to optimize excessively augmented sympathetic nerve activity may be an essential treatment for heart failure to improve the poor survival rate.

CONFLICT OF INTEREST

There is no conflict of interest to be declared.

REFERENCES

1. The Consensus Trial Study Group. Effect of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). N Engl J Med.1987; 316: 1429-35.
2. Yusuf S, Pitt B, Davis CE, Hood Jr WB, Cohn JN. Effect of enalapril on survival in patients with reduced left ventricular ejection fraction and congestive heart failure. N Engl J Med. 1991;325:293-302.
3. Yusuf S, Pitt B, Davis CE, Hood Jr WB, Cohn JN. Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fraction. N Engl J Med. 1992;372:685-91.
4. Delius W, Gerlach E, Grobecker H, Kubler W. Catecholamines and the heart. Recent advances in experimental and clinical research. Berlin, Heidelberg, New York: Springer-Verlag. 1981;236-46.
5. Minatoguchi S, Ito H, Ishimura K, Watanabe H, Imai Y, Koshiji M, et al. Modulation of noradrenaline release through presynaptic alpha 2-adrenoceptors in congestive heart failure. Am Heart J. 1995;130: 516-21.
6. Cohn JN, Levine TB, Olivari MT, Garberg V, Lura D, Francis GS, et al. Plasma norepinephrine as a guide to prognosis in patients with chronic congestive heart failure. N Engl J Med. 1984;311: 819-23.
7. Benedict CR, Shelton B, David E. Johnstone DE, Francis G, Greenberg B, et al. Prognostic significance of plasma norepinephrine in patients with asymptomatic left ventricular dysfunction. Circulation. 1996; 94: 690-7.
8. Vergaro G, Aimo A, Prontera C, Ghionzoli N, Arzilli C, Zyw L, et al. Sympathetic and renin-angiotensin-aldosterone system activation in heart failure with preserved, mid-range and reduced ejection fraction. Int J Cardiol. 2019; 296: 91-7.
9. Minatoguchi S, Majewski H. Modulation of norepinephrine release in Adriamycin-induced heart failure in rabbits: role of presynaptic a2-adrenoceptors and presynaptic angiotensin II receptors. J Cardiovasc Pharmacol. 1994; 23: 438-45.
10. Hasking GJ, Esler MD, Jennings GL, Burton D, Johns JA, Korner PI. Norepinephrine spillover in patients with congestive heart failure: evidence of increased overall and cardiorenal sympathetic nervous activity. Circulation. 1986; 73: 615-21.
11. CIBIS-II Investigators and Committees. The cardiac insufficiency bisoprolol study II (CIBIS-II): A randomized trial. Lancet. 1999;353:9-13.
12. MERIT-HF Study Group. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF). Lancet 1999;353: 2001-7.
13. Packer M, Coats AJ, Fowler MB, Katus HA, Krum H, Mohascsi P, et al. Effect of carvedilol on survival in survival in severe chronic heart failure. N Engl J Med 2001;344:1651-8.

14. The Consensus trial Study group. Effects of enalapril on mortality in severe congestive heart failure. N Engl J Med. 1987; 316:1429–35.
15. The Solvd investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. N Engl J Med. 1991; 325:293-302.
16. Cohn JN, Tognoni G, Valsartan Heart Failure Trial Investigators. A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. 2001; 345: 1667-75.
17. Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. N Engl J Med. 1999; 341:709-17.
18. Zannad F, McMurray JJV, Krum H, van Veldhuisen DJ, Swedberg K, et al. Eplerenone in patients with systolic heart failure and mild symptoms. N Eng J Med 2011; 364:11-21.
19. Swedberg K, Komajda M, Böhm M, Borer JB, Ford I, Dubost-Brama A, et al. Ivabradine and outcomes in chronic heart failure (SHIFT): A randomised placebo-controlled study. Lancet 2010; 376: 875-85.
20. McMurray JJV, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, et al. Angiotensin–neprilysin inhibition versus enalapril in heart failure. N Engl J Med. 2014; 371: 993-1004.
21. McMurray JJV, Solomon SD, Inzucchi SE, Køber L, Kosiborod MN, Martinez FA, et al. dapagliflozin in patients with heart failure and reduced ejection fraction. N Engl J Med. 2019; 381:1995-2008.
22. Packer M, Anker SD, Butler J, Filippatos G, Pocock SJ, Carson P, et al. Cardiovascular and renal outcomes with empagliflozin in heart failure. N Eng J Med. 2020;383:1413-23.
23. Anker SD, Butler J, Filippatos G, Ferreira JP, Bocchi E, Bohm M, et al. Empagliflozin in heart failure with a preserved ejection fraction. N Eng J Med. 2021.
24. Majewski H. Angiotensin II and noradrenergic transmission nin the pithed rat. J Cardiovasc Pharmacol. 1989; 14: 622-30.
25. Kishi T, Hirooka Y, Sunagawa K. Telmisartan reduces mortality and left ventricular hypertrophy with sympathoinhibition in rats with hypertensuin and heart failure. Am J Hypertens. 2014; 27: 260-7.
26. Nakagaki T, Hirooka Y, Matsukawa R, Nishihara M, Nakano M, Ito K, et al. Activation of mineralocorticoid receptors in the rostral ventrolateral medulla is involved in hypertensive mechanisms in stroke-prone spontaneously hypertensive rats. Hypertens Res. 2012; 35: 470-6.
27. Muller P, Barbier S, Chagraoui A, Richard V, Henry JP, Lallemand F, et al. Long-term heart rate reduction induced by the selective If current inhibitor ivabradine improves left ventricular function and intrinsic myocardial structure in congestive heart failure. Circulation. 2004; 109:1674-9.
28. Li D, Lu CJ, Hao G, Wright H, Woodward L, Liu K, et al. Efficacy of B-type natriuretic peptide is coupled to phosphodiesterase 2A in cardiac sympathetic neurons. Hypertension 2015; 66: 190-8.
29. Brunner-La Rocca HP, Kaye DM, Woods RI, Hastings J, Esler MD. Effects of intravenous brain natriuretic peptide on regional sympathetic activity in patients with chronic heart failure as compared with healthy control subjects. J Am Coll Cardiol. 2001; 37: 1221-7.
30. Herat LY, Magno AL, Rudnicka C, Hricova J, Carnagarin R, Ward NC, et al. SGLT2 inhibitor-induced sympathoinhibition: a novel mechanism for cardiorenal protection. JACC Basic Transl Sci. 29;5(2):169-79.
31. Zhang N, Feng B, Ma X, Sun K, Xu G, Zhou Y. Dapagliflozin improves left ventricular remodeling and aorta sympathetic tone in a pig model of heart failure with preserved ejection fraction. Cardiovasc Diabetol. 2019; 18:107.
32. Liu Y, Wu M, Xu B, Kang L. Empagliflozin alleviates atherosclerosis progression by inhibiting inflammation and sympathetic activity in a normoglycemic mouse model. J Inflamm Res. 2021; 14: 2277-87.
33. O'Connor CM, Whellan DJ, Lee KL, Keteyian SJ, Cooper LS, Ellis SJ, et al. Efficacy and safety of exercise training in patients with chronic heart failure: HF-ACTION randomized controlled trial. JAMA. 2009; 301: 1439-1450.
34. Meredith IT, Friberg P, Jennings GL, Dewar EM, Fazio VA, Lambert GW, et al. Exercise training lowers resting renal but not cardiac sympathetic activity in humans. Hypertension. 1991; 18: 575-582.
35. Besnier F, Labrunee M, Pathak A, Traon APL, Gales C, Senard JM, et al. Exercise training-induced modification in autonomic nervous system: An update for cariac patients. Ann Phys Rehabil Med. 2017; 60: 27-35.