β-Blockers in Heart Failure

Subjects: Cardiac & Cardiovascular Systems

Contributor: Daniele Masarone

Cardiac β-receptor dysfunction in HFrEF is characterized by a reduced β1-receptor density and by the uncoupling of β1- and β2-receptors from the membrane G proteins, resulting in their functional desensitization. This mechanism is mediated by increased G protein-coupled receptor kinase 2 activity, resulting in reduced cardiac β-receptor density and reactivity, with consequent reduced cardiac inotropic reserve. In addition, catecholamines themselves are cardiotoxic, contributing to myocardial damage.

Keywords: β-blockers ; heart failure with reduced ejection fraction ; pharmacologic therapy

1. Introduction

Heart failure (HF) is the leading cardiovascular disease, affecting approximately 26 million people worldwide [1][2]. Fortunately, in the last 30 years, the knowledge of the pathophysiology of this clinical syndrome has developed considerably, leading to the identification of drugs which can significantly improve the prognosis of these patients, called disease-modifying drugs [3][4][5].

Among them, β-blockers are indicated by international guidelines as the cornerstone of therapy for patients with HF with reduced ejection fraction (HFrEF) [6][7][8]. The optimal use of β-blockers has been shown to improve symptoms, reduce hospitalizations, induce left ventricular reverse remodelling, and increase survival in HFrEF patients [9][10]. Despite the proven benefit of β-blockers in chronic HF, they are often underutilized in current clinical practice [11][12]. There are a lot of well written reviews on the use of β-blockers in HFrEF; however, they only partially analyze the clinical aspects regarding this matter.

2. Use of β-Blockers in HFrEF: Pathophysiology and Clinical Pharmacology

After a myocardial insult—whether acute (e.g., myocardial infarction or myocarditis) or chronic (e.g., hypertension or mitral valve insufficiency), which results in left ventricular dysfunction—the renin–angiotensin–aldosterone system and the sympathetic nervous system (SNS) are hyperactivated [13][14]. Persistent activation of the SNS in patients with HFrEF is evidenced by increased plasma levels of epinephrine and norepinephrine [15] and an increased spillover of the latter from sympathetic nerve endings into the bloodstream [16]. This increase in the catecholamines release leads to chronic and persistent stimulation of myocardial β-receptors, with consequent dysfunction and harmful repercussions for the failing heart [17][18].

Clinical consequences of these processes consist of reduced systolic function and left ventricular ejection fraction, acceleration of the left ventricular remodelling process, and the appearance of life-threatening ventricular arrhythmias [19].

All this action leads to improvements in the structure and function of the left ventricle (reverse remodelling). Other beneficial activities in patients with HFrEF include reducing heart rate [20] and blood pressure, reducing the burden of atrial and ventricular arrhythmias [21], and anti-ischaemic effects [22]. Moreover, β-blockers improve the contractility of viable but noncontractile myocardium in patients with ischaemic (hibernating myocardium) [23] and non-ischaemic (stunning myocardium) HFrEF [24].

β-blockers can be broadly classified [25] into: (1) Nonselective β-blockers with similar β1 and β2 activity (none of the β-blockers belonging to this class is indicated for HFrEF); (2) β1-selective with a higher affinity for β1-adrenoreceptors (metoprolol, bisoprolol, and nebivolol), preferred in patients with chronic obstructive pulmonary disease or mild asthma (nebivolol also facilitates nitric oxide release and is preferred in patients with arterial hypertension); (3) β-blockers with additional α-1-adrenoreceptor antagonism and consequent peripheral vasodilation (carvedilol), preferred in patients with hypertension or documented higher peripheral vascular resistance.

3. Evidence Supporting the Use of β-Blockers in HFrEF

The activation of the SNS is one of the significant pathophysiological abnormalities in HFrEF patients. Since the 1970s, it has been known that patients with HFrEF have higher plasmatic norepinephrine levels and that prognosis is directly related to catecholamine plasma levels. However, the first multicenter randomized trial was not conducted until the early 1990s, and carvedilol was approved for the treatment of HFrEF only in 1997. The reason for such a slow acceptance of the use of β-blocker therapy for HFrEF was the transient negative inotropic effect of the β-blockade and the subsequent risk of decompensation in patients with HFrEF.

Carvedilol: The 1996 U.S. Carvedilol Heart Failure Study enrolled 1094 HF patients with FE < 35%; 696 patients were treated with carvedilol (target dose: 25–50 mg twice daily), 398 with placebo [26]. The study was stopped early because carvedilol therapy was accompanied by a 27% reduction in the risk of hospitalization for cardiovascular causes (19.6% vs. 14.1%, p = 0.036), as well as a 38% reduction in the combined risk of hospitalization or death (24.6% vs. 15.8%, p < 0.001). In the randomized multicenter trial Carvedilol Post-Infarct Survival Control in Left Ventricular Dysfunction (CAPRICORN), the effects of carvedilol on morbidity and mortality in patients with prior myocardial infarction and EF < 40% were evaluated. The trial enrolled 1959 patients, randomly assigned to receive carvedilol (n = 975) or placebo (n = 984). The study demonstrated reduced cardiovascular and non-cardiovascular mortality in patients in the carvedilol group (12% vs. 15%, hazard ratio 0.77 (95% CI 0.60–098), p = 0.03) [27].

In the Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) study, 2289 patients with advanced HF and EF < 25% were randomized to receive carvedilol or placebo. After an average follow-up period of 10.4 months, mortality was reduced by 34% in the carvedilol group [28]. Carvedilol also reduced the number of days spent in hospital by 27% for any cause and by 40% for heart failure. Patients in the carvedilol group felt better and were less likely to have a severe adverse event related to HF.

Bisoprolol: In the trial Cardiac Insufficiency Bisoprolol Study I (CIBIS-I), 641 patients with HF and EF < 40% were randomly assigned to bisoprolol or placebo groups [29]. The observed difference in mortality between groups did not reach statistical significance (relative risk, 0.80; (95% CI 0.56–1.15), p = 0.22); however, bisoprolol significantly improved the New York Heart Association (NYHA) class (p = 0.04). In the Cardiac Insufficiency Bisoprolol Study II (CIBIS-II), 2647 patients with symptomatic HF (NYHA class III–IV) and EF < 35% were randomly assigned to receive bisoprolol or placebo [30]. The trial was stopped after the second interim analysis because bisoprolol showed a significant mortality benefit. All-cause mortality was significantly lower with bisoprolol than placebo (11.8% vs. 17.3%, hazard ratio of 0.66 (95% CI 0.54–0.81) p < 0.0001); there were also significantly fewer sudden deaths among patients on bisoprolol than in those on placebo (3.6% vs. 83 6.3%, hazard ratio of 0.56 (95% CI 0.39–0.80), p = 0.0011).

4. Use of β-Blockers in Patients with Heart Failure and Comorbidities: A Practical Approach

Comorbidities are highly prevalent in patients with HFrEF with a significant impact on disease progression and long-term prognosis [31]. Recent evidence shows that, in patients with HFrEF and multiple comorbidities, β-blockers are still able to achieve favorable prognostic effects [32]. Therefore, the optimization of β-blockers therapy and the appropriate selection of the best suited β-blocker (**Table 1**) is of paramount importance in this specific subgroup of patients.

Table 1. Choice of β-blockers according to clinical scenario.

Clinical Scenario	β-Blockers
Hypertension	**Carvedilol, nebivolol**
Asthma and Chronic Obstructive Pulmonary Disease	**Bisoprolol, nebivolol**
Diabetes mellitus	**Carvedilol, bisoprolol**
Atrial fibrillation	**Metoprolol, bisoprolol**
Peripheral Artery Disease	**Carvedilol, nebivolol**
Hypercholesterolemia	**Carvedilol**
Hyperthyroidism	**Metoprolol**

The use of β-blockers in patients with HFrEF and diabetes has historically been controversial [33]. The main reason for concern is the negative effect of β-blockers on glucose metabolism. Indeed, β-blockers might contribute to the development of hyperglycaemia by impairing the release of insulin from pancreatic β-cells [34]. In addition, β-blockers may mask the catecholamine-mediated symptoms of hypoglycaemia [35]. An analysis of six pivotal β-blocker trials, including 3230 patients with diabetes, showed that β-blockers significantly reduced mortality in individuals with (relative risk: 0.84 (95% CI 0.73–0.91)) and without (relative risk: 0.72 (95% CI 0.65–0.79)) diabetes [36]. Furthermore, concerns about worsening glycaemic control in patients with type 2 DM treated with β-blockers seem unfounded; in a recent study, in which 125 diabetic patients were enrolled, the use of carvedilol or bisoprolol did not worsen glycaemic control [37]. Therefore, the use of β-blockers should not be avoided in patients with HFrEF and diabetes. Carvedilol and bisoprolol should be used preferentially because they do not adversely affect the patients' glycaemic profile.

These data, like real-world data, document a prognostic advantage of β-blockers in all patients with HFrEF regardless of the presence of atrial fibrillation. Another important question is to what level of mean ventricular rate the patient with HFrEF and atrial fibrillation should be taken. The European Society of Cardiology guidelines state that the optimal resting heart rate in patients with AF and HF is unknown but may be between 60 and 100 beats per minute [38]. Randomized clinical trials that may clarify the optimal resting ventricular rate in patients with HFrEF and atrial fibrillation are pending, but it is the authors' opinion that excessive rate control, associated with increased pauses, poses a risk in such patients. The use of β-blockers in these patients should therefore not be aimed at reaching target doses but at achieving a mean ventricular frequency of 70–80 beats/min to avoid prognostically unfavorable effects.

In conclusion, therapy with β-blockers can be safely conducted in patients with peripheral artery disease, in cases of severe intermittent claudication preferring those with vasodilation activity, such as carvedilol and nebivolol.

References

1. Savarese, G.; Lund, L.H. Global public health burden of heart failure. Card. Fail. Rev. 2017, 3, 7–11.
2. Benjamin, E.J.; Virani, S.S.; Callaway, C.W.; Chamberlain, A.M.; Chang, A.R.; Cheng, S.; Chiuve, S.E.; Cushman, M.; Delling, F.N.; Deo, R.; et al. Heart disease and stroke statistics-2018 update: A report from the American Heart Association. Circulation 2018, 137, e67.
3. Komajda, M.; Böhm, M.; Borer, J.S.; Ford, I.; Tavazzi, L.; Pannaux, M.; Swedberg, K. Incremental benefit of drug therapies for chronic heart failure with reduced ejection fraction: A network meta-analysis. Eur. J. Heart Fail. 2018, 20, 1315–1322.
4. McMurray, J.J. Systolic heart failure. N. Engl. J. Med. 2010, 362, 228–238.
5. Metra, M.; Teerlink, J.R. Heart failure. Lancet 2017, 390, 1981–1995.
6. Ponikowski, P.; Voors, A.A.; Anker, S.D.; Bueno, H.; Cleland, J.G.; Coats, A.J.; Falk, V.; Gonzalez-Juanatey, J.R.; Harjola, V.P.; Jankowska, E.A.; et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur. J. Heart Fail. 2016, 18, 891–975.
7. Maddox, T.M.; Januzzi, J.L., Jr.; Allen, L.A.; Breathett, K.; Butler, J.; Davis, L.L.; Fonarow, G.C.; Ibrahim, N.E.; Lindenfeld, J.; Masoudi, F.A.; et al. 2021 Update to the 2017 ACC Expert Consensus Decision Pathway for Optimization of Heart Failure Treatment: Answers to 10 Pivotal Issues About Heart Failure with Reduced Ejection Fraction: A Report of the American College of Cardiology Solution Set Oversight Committee. J. Am. Coll. Cardiol. 2021, 77, 772–810.
8. McDonald, M.; Virani, S.; Chan, M.; Ducharme, A.; Ezekowitz, J.A.; Giannetti, N.; Heckman, G.A.; Howlett, J.G.; Koshman, S.L.; Lepage, S.; et al. CCS/CHFS Heart Failure Guidelines Update: Defining a New Pharmacologic Standard of Care for Heart Failure With Reduced Ejection Fraction. Can. J. Cardiol. 2021, 37, 531–546.
9. Barrese, V.; Taglialatela, M. New advances in beta-blocker therapy in heart failure. Front. Physiol. 2013, 4, 323.
10. Lymperopoulos, A.; Rengo, G.; Koch, W.J. Adrenergic nervous system in heart failure: Pathophysiology and therapy. Circ. Res. 2013, 113, 739–753.
11. Berthelot, E.; Eicher, J.; Salvat, M.; Seronde, M.; de Groote, P. Medical inertia in the optimization of heart failure treatment after discharge and its relationship to outcome. Health Care Curr. Rev. 2018, 6, 2.
12. Loop, M.S.; Van Dyke, M.K.; Chen, L.; Safford, M.M.; Kilgore, M.L.; Brown, T.M.; Durant, R.W.; Levitan, E.B. Low Utilization of Beta-Blockers Among Medicare Beneficiaries Hospitalized for Heart Failure with Reduced Ejection

Fraction. J. Card. Fail. 2018, 16, 31102–31107.

13. Mann, D.L.; Bristow, M.R. Mechanisms and models in heart failure: The biomechanical model and beyond. Circulation 2005, 111, 2837–2849.
14. Mudd, J.O.; Kass, D.A. Tackling heart failure in the twenty-first century. Nature 2008, 451, 919–928.
15. Triposkiadis, F.; Karayannis, G.; Giamouzis, G.; Skoularigis, J.; Louridas, G.; Butler, J. The sympathetic nervous system in heart failure physiology, pathophysiology, and clinical implications. J. Am. Coll. Cardiol. 2009, 54, 1747–1762.
16. Armour, J.A. Cardiac neuronal hierarchy in health and disease. Am. J. Physiol. Regul. Integr. Comp. Physiol. 2004, 287, R262–R271.
17. Brodde, O.E. Beta-adrenoceptors in cardiac disease. Pharmacol. Ther. 1993, 60, 405–430.
18. Lohse, M.J.; Engelhardt, S.; Eschenhagen, T. What is the role of beta-adrenergic signaling in heart failure? Circ. Res. 2003, 93, 896–906.
19. Lefkowitz, R.J.; Rockman, H.A.; Koch, W.J. Catecholamines, cardiac beta-adrenergic receptors, and heart failure. Circulation 2000, 101, 1634–1637.
20. Kitai, T.; Tang, W.H. Pathophysiologic insights into heart rate reduction in heart failure: Implications in the use of beta-blockers and ivabradine. Curr. Treat. Options Cardiovasc. Med. 2016, 18, 13.
21. Grandi, E.; Ripplinger, C.M. Antiarrhythmic mechanisms of beta blocker therapy. Pharmacol. Res. 2019, 146, 104274.
22. Martínez-Milla, J.; Raposeiras-Roubín, S.; Pascual-Figal, D.A.; Ibáñez, B. Role of Beta-blockers in Cardiovascular Disease in 2019. Rev. Esp. Cardiol. (Engl. Ed.) 2019, 72, 844–852.
23. Doughty, R.N.; White, H.D. Carvedilol: Use in chronic heart failure. Expert Rev. Cardiovasc. Ther. 2007, 5, 21–31.
24. Kloner, R.A. Stunned and Hibernating Myocardium: Where Are We Nearly 4 Decades Later? J. Am. Heart Assoc. 2020, 9, e015502.
25. Bristow, M. Antiadrenergic therapy of chronic heart failure: Surprises and new opportunities. Circulation 2003, 107, 1100–1102.
26. Packer, M.; Bristow, M.R.; Cohn, J.N.; Colucci, W.S.; Fowler, M.B.; Gilbert, E.M.; Shusterman, N.H. The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. U.S. Carvedilol Heart Failure Study Group. N. Engl. J. Med. 1996, 334, 1349–1355.
27. Dargie, H.J. Effect of carvedilol on outcome after myocardial infarction in patients with left-ventricular dysfunction: The CAPRICORN randomized trial. Lancet 2001, 357, 1385–1390.
28. Fowler, M.B. Carvedilol prospective randomized cumulative survival (COPERNICUS) trial: Carvedilol in severe heart failure. Am. J. Cardiol. 2004, 93, 35–39.
29. The Cardiac Insufficiency Bisoprolol Study (CIBIS). CIBIS Investigators and Committees. A randomized trial of beta-blockade in heart failure. Circulation 1994, 90, 1765–1773.
30. CIBIS-II Investigators. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): A randomized trial. Lancet 1999, 353, 9–13.
31. Correale, M.; Paolillo, S.; Mercurio, V.; Limongelli, G.; Barillà, F.; Ruocco, G.; Palazzuoli, A.; Scrutinio, D.; Lagioia, R.; Lombardi, C.; et al. Comorbidities in chronic heart failure: An update from Italian Society of Cardiology (SIC) Working Group on Heart Failure. Eur. J. Intern. Med. 2020, 71, 23–31.
32. Straw, S.; McGinlay, M.; Relton, S.D.; Koshy, A.O.; Gierula, J.; Paton, M.F.; Drozd, M.; Lowry, J.E.; Cole, C.; Cubbon, R.M.; et al. Effect of disease-modifying agents and their association with mortality in multi-morbid patients with heart failure with reduced ejection fraction. ESC. Heart Fail. 2020, 7, 3859–3870.
33. Cruickshank, J.M. Beta-blockers and diabetes: The bad guys come good. Cardiovasc. Drugs Ther. 2002, 16, 457–470.
34. Mills, G.A.; Horn, J.R. Beta-blockers and glucose control. Drug Intell. Clin. Pharm. 1985, 19, 246–251.
35. Sanon, V.P.; Sanon, S.; Kanakia, R.; Yu, H.; Araj, F.; Oliveros, R.; Chilton, R. Hypoglycemia from a cardiologist's perspective. Clin. Cardiol. 2014, 37, 499–504.
36. Haas, S.J.; Vos, T.; Gilbert, R.E.; Krum, H. Are beta-blockers as efficacious in patients with diabetes mellitus as in patients without diabetes mellitus who have chronic heart failure? A meta-analysis of large-scale clinical trials. Am. Heart J. 2003, 146, 848–853.
37. Wai, B.; Kearney, L.G.; Hare, D.L.; Ord, M.; Burrell, L.M.; Srivastava, P.M. Beta blocker use in subjects with type 2 diabetes mellitus and systolic heart failure does not worsen glycaemic control. Cardiovasc. Diabetol. 2012, 11, 14.

38. Baher, A.; Marrouche, N.F. Treatment of Atrial Fibrillation in Patients with Co-existing Heart Failure and Reduced Ejection Fraction: Time to Revisit the Management Guidelines? Arrhythm. Electrophysiol. Rev. 2018, 7, 91–94.