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The efficacy of baroreflex activation therapy for heart failure

A meta-analysis of randomized controlled trials

Guoqiang Cai, MD[a], Kai Guo, MD[a], Dongyin Zhang, MD[b,*], Shu Qin, MD[b]

Abstract

Introduction: The efficacy of baroreflex activation therapy for heart failure is elusive. This meta-analysis aims to evaluate the impact of baroreflex activation therapy on treatment efficacy of heart failure.

Methods: Several databases including PubMed, EMbase, Web of science, EBSCO, and Cochrane library databases have been searched, and we include randomized controlled trials (RCTs) regarding the efficacy of baroreflex activation therapy for patients with heart failure.

Results: This meta-analysis includes 4 RCTs. Baroreflex activation therapy shows significantly positive impact on the quality of life score (standard mean difference SMD = −4.61; 95% confidence interval CI = −6.24 to −2.98; $P < .00001$), 6-minute hall walk (6MHW) distance (SMD = 2.83; 95% CI = 1.44– 4.22; $P < .0001$), New York Heart Association (NYHA) Class (SMD = −3.23; 95% CI = −4.76 to −1.69; $P < .0001$), N-terminal pro-brain natriuretic peptide (NT-proBNP) (SMD = −1.24; 95% CI = −1.58 to −0.89; $P < .00001$) and the duration of hospitalization (SMD = −1.65; 95% CI = −2.90 to −0.39; $P = .01$) compared with control group for heart failure, but has no obvious effect on left ventricular ejection fraction (LVEF) (SMD = 1.43; 95% CI = −0.15–3.01; $P = .08$), or the number of hospitalization per year (SMD = −1.17; 95% CI = −2.56–0.22; $P = .10$).

Conclusions: Baroreflex activation therapy can improve the treatment efficacy for heart failure.

Abbreviations: CI = confidence interval, PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses, RCTs = randomized controlled trials, SMD = standard mean difference.

Keywords: baroreflex activation therapy, heart failure, meta-analysis, randomized controlled trials

1. Introduction

Patients with heart failure have increased sympathetic tone, decreased parasympathetic tone and relatively low sensitivity to inhibitory baroreflex.[1–3] These imbalances result in vasoconstriction, activation of renin-angiotensin-aldosterone system and cardiac remodeling.[1,4] Many ischemic and non-ischemic factors can lead to heart failure with reduced ejection fraction. The classifications of ischemic or non-ischemic cardiomyopathy are associated with prognostic implications, the selection of device-based therapies and therapeutic response.[5–8]

Baroreflex activation therapy is defined as an electrical stimulation technology delivered by an implanted device, and results in centrally mediated reduction of sympathetic outflow and increased parasympathetic activity via stimulating the carotid baroreceptor. Subsequently, arterial and venous compliance is increased and peripheral resistance is reduced.[9–11] Baroreflex activation therapy can lead to the reduction of −30% in sympathetic nerve activity.[9,12] In 1 RCT involving heart failure, the results revealed that the rate of neurological and cardiovascular event-free rate was up to 97.2% after baroreflex activation therapy.[13]

In addition, baroreflex activation therapy was reported to result in the decrease in New York Heart Association (NYHA) Class ranking and N-terminal pro-brain natriuretic peptide (NT-proBNP), the increase in 6-minute hall walk (6MHW) distance for heart failure patients.[11] However, the efficacy of baroreflex activation therapy for heart failure is not clear, and the results of several studies are conflicting.[11,13–15] This meta-analysis is performed to evaluate the efficacy of baroreflex activation therapy for heart failure.

2. Materials and methods

This meta-analysis did not require ethical approval and patient consent, because it was the secondary analysis of previously published studies based on the guidance of PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses).[16]

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Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

[a] Department of Cardiology, Dianjiang Traditional Chinese Medicine Hospital, Dianjiang, [b] Department of Cardiology, The First Affiliated Hospital of Chongqing Medical University, Chongqing, PR China.

[*] Correspondence: Dongyin Zhang, Department of Cardiology, The First Affiliated Hospital of Chongqing Medical University, No. 1 Youyi Road, Yuzhong District, Chongqing 400016, P R China (e-mail: zdycy123456789@sina.com).

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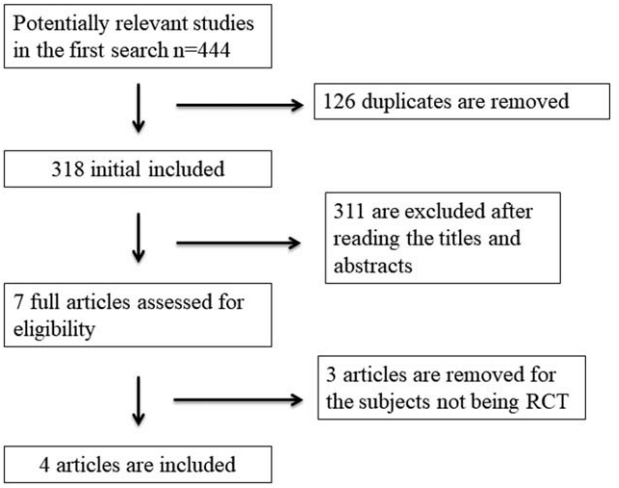

Figure 1. Flow diagram of study searching and selection process.

2.1. Search strategy and study selection

Several databases including PubMed, EMbase, Web of science, EBSCO, and Cochrane library databases were searched from inception to September 2018. The electronic search strategy was conducted using the following keywords: "baroreflex activation" and "heart failure". The inclusive selection criteria included:

1. patients were diagnosed with heart failure;
2. intervention treatments were medical and device therapy plus baroreflex activation therapy versus medical and device therapy;
3. study design was RCT.

2.2. Data extraction and outcome measures

Some information (e.g., the number of patients, age, female, body mass index and detail methods) was extracted. Two investigators independently extracted these data, and discrepancies were resolved by consensus. The primary outcome was the quality of life score. Secondary outcomes included 6MHW distance, NYHA Class, NT-proBNP, left ventricular ejection fraction (LVEF), the number of hospitalization per year and the duration of hospitalization.

2.3. Quality assessment in individual studies

We assessed the methodological quality of each study by the modified Jadad scale, which consisted of 3 items: randomization (0–2 points), blinding (0–2 points), dropouts and withdrawals (0–1 points).[17] The total score of Jadad Scale ranged from 0 to 5 points. The study had high quality if the Jadad score≥3, while the study with Jadad score <2 was thought to have low quality.[18]

2.4. Statistical analysis

The standard mean difference (SMD) with 95% confidence interval (CI) was calculated for all continuous outcomes. We used the random-effects model regardless of heterogeneity. I^2 value more than 50% indicated significant heterogeneity.[19] The heterogeneity was detected through omitting 1 study in turn or performing subgroup analysis. All statistical analyses were conducted by Review Manager Version 5.3 (The Cochrane Collaboration, Software Update, Oxford, UK).

3. Results

3.1. Literature search, study characteristics and quality assessment

Figure 1 demonstrated the search and selection results. We initially searched for 444 potentially articles and 4 RCTs were finally included in this meta-analysis.[11,13–15]

Table 1 showed the baseline characteristics of 4 eligible RCTs. The 4 studies were published between 2015 and 2018, and total 566 patients were involved. These studies included heart failure patients with coronary artery disease[14] or cardiac resynchronization therapy (CRT).[11] When performing the meta-analysis, Halfbach 2018

1. represented patients with coronary artery disease, while Halfbach 2018
2. represented patients without coronary artery disease.

Zile 2015

1. represented patients with CRT, while Zile 2015
2. represented patients without CRT.

These may result in some heterogeneity.

Among the 4 studies included here, 4 studies reported the quality of life score and 6MHW distance,[11,13–15] 2 studies reported NYHA Class,[11,14] 3 studies reported NT-proBNP,[11,14,15] and 2 studies reported LVEF, the number of hospitalization per year and the duration of hospitalization.[11,14] Jadad scores of the included RCTs ranged from 3 to 5, and thus they were all considered to have high-quality.

3.2. Primary outcome: the quality of life score

Compared to control group for heart failure, baroreflex activation therapy resulted in significantly reduced quality of

Table 1

Characteristics of included studies.

No.	Author	Group	Number	Age (years)	Female (n)	Body mass index (kg/m2)	NYHA: class III	Group	Number	Age (years)	Female (n)	Body mass index (kg/m2)	NYHA: class III	Jada scores
1	Halbach 2018	CAD	101	67±10	11	29±5	101	No-CAD	39	60±13	9	28±6	38	5
2	Weaver 2016	baroreflex activation	76	–	–	–	–	control	70	–	–	–	–	4
3	Zile 2015	CRT	45	68±9	4	29±4	45	No-CRT	95	63±12	16	29±5	94	5
4	Abraham 2015	baroreflex activation	71	64±11	9	–	–	control	69	66±12	11	–	–	4

BMI = body mass index, CAD = coronary artery disease, CRT = cardiac resynchronization therapy, NYHA = New York Heart Association.

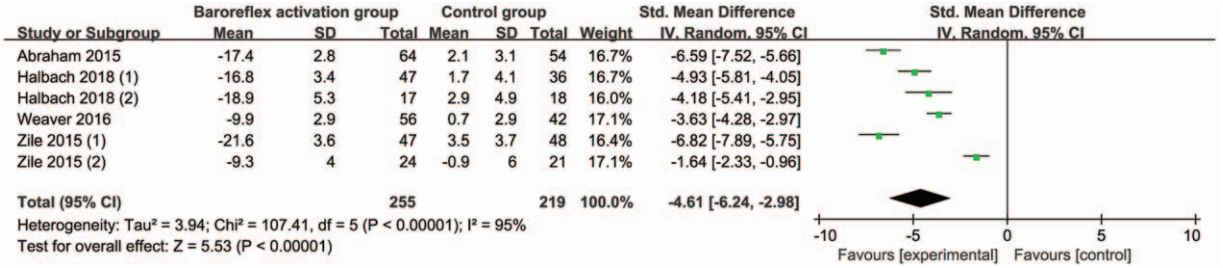

Figure 2. Forest plot for the meta-analysis of the quality of life score.

life score (SMD = −4.61; 95% CI = −6.24 to −2.98; $P < .00001$) with significant heterogeneity among the studies ($I^2 = 95\%$, heterogeneity $P < .00001$) (Fig. 2).

3.3. Sensitivity analysis

Significant heterogeneity was observed for the quality of life score. However, significant heterogeneity still remained when conducting sensitivity analysis via omitting 1 study in turn.

3.4. Secondary outcomes

In comparison with control group for heart failure, baroreflex activation therapy was associated with remarkably improved 6MHW distance (SMD = 2.83; 95% CI = 1.44–4.22; $P < .0001$; Fig. 3), decreased NYHA Class (SMD = −3.23; 95% CI = −4.76 to −1.69; $P < .0001$; Fig. 4) and NT-proBNP (SMD = −1.24; 95% CI = −1.58 to −0.89; **P** < .00001; Fig. 5), but showed no obvious impact on LVEF (SMD = 1.43; 95% CI = −0.15–3.01; $P = .08$; Fig. 6) or the number of hospitalization per year (SMD = −1.17; 95% CI = −2.56–0.22; $P = .10$; Fig. 7). In addition, the duration of hospitalization in baroreflex activation therapy was obviously shorter than that in control intervention (SMD = −1.65; 95% CI = −2.90 to −0.39; $P = .01$; Fig. 8).

4. Discussion

Patients with cardiovascular diseases commonly suffer from the dysregulation of autonomic function.[20,21] Pharmacologic therapies have been described to improve the outcomes and quality of life in patients with cardiovascular disease via addressing autonomic dysfunction. Furthermore, implantable defibrillators and resynchronization devices have been developed to treat heart failure patients with reduced ejection fraction. Several implantable devices such as baroreflex activation therapy were documented to significantly improve ejection fraction, functional capacity and quality of life for heart failure patients.[15]

Our meta-analysis suggests that compared to control intervention for heart failure, baroreflex activation therapy has a significantly favorable influence on the quality of life score, 6MHW distance, NYHA Class, NT-proBNP and the duration of hospitalization, but shows no obvious influence on LVEF or the

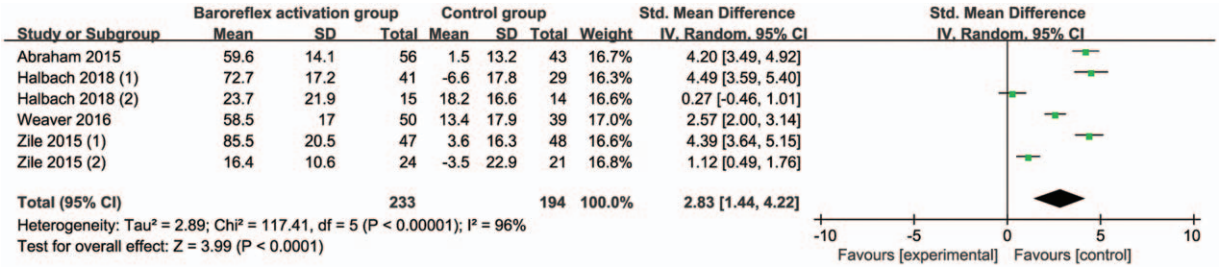

Figure 3. Forest plot for the meta-analysis of 6MHW distance.

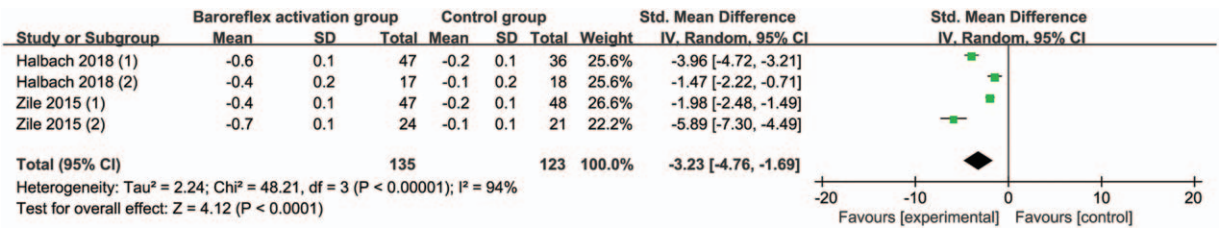

Figure 4. Forest plot for the meta-analysis of NYHA Class.

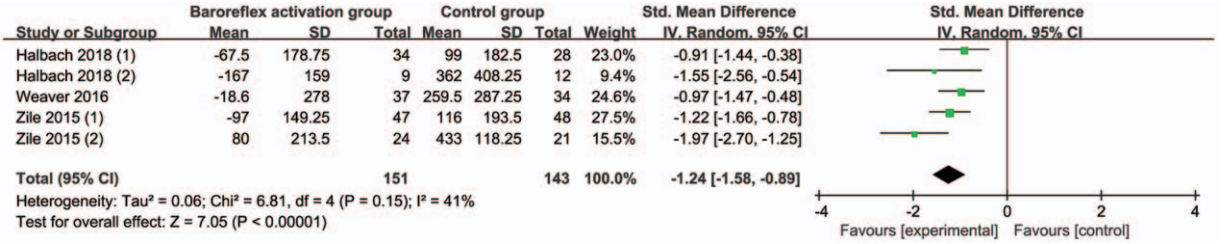

Figure 5. Forest plot for the meta-analysis of NT-proBNP.

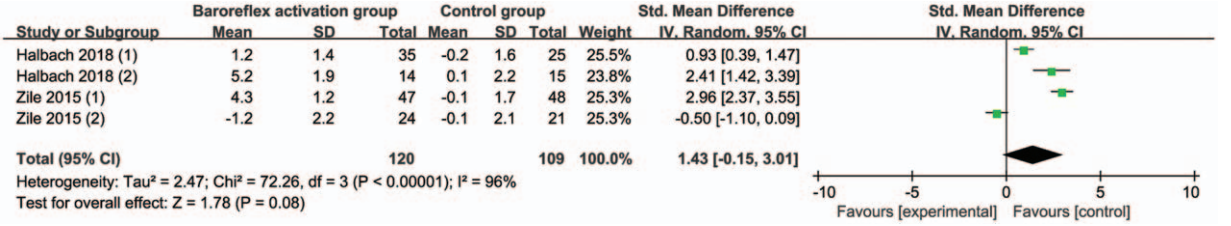

Figure 6. Forest plot for the meta-analysis of LVEF.

number of hospitalization per year. These indicate that baroreflex activation therapy substantially benefits to improve exercise capacity and the quality of life for these patients, and should be recommended in clinical work. Patients with heart failure symptoms and disease progression have increased sympathetic and decreased parasympathetic activity. Baroreflex activation therapy is capable to induce centrally mediated reduction of sympathetic outflow and increase parasympathetic activity. The baroreflex pathway has been used for various medical and device therapies.[22,23]

Patients with ischemic cardiomyopathy are characterized by reduced contractility because of the scar formation and hibernation of myocardium.[24] Furthermore, the impairment of reperfused myocardium may result in adverse remodeling and the reduction in global systolic function.[24] Non-ischemic dilated cardiomyopathy can be caused by many factors.[25] Different responses to treatments are observed between ischemic cardiomyopathy and non-ischemic cardiomyopathy.[26] For instance, device-based therapies such as CRT have better ability to reverse left ventricular remodeling in non-ischemic patients than that in ischemic patients.[7]

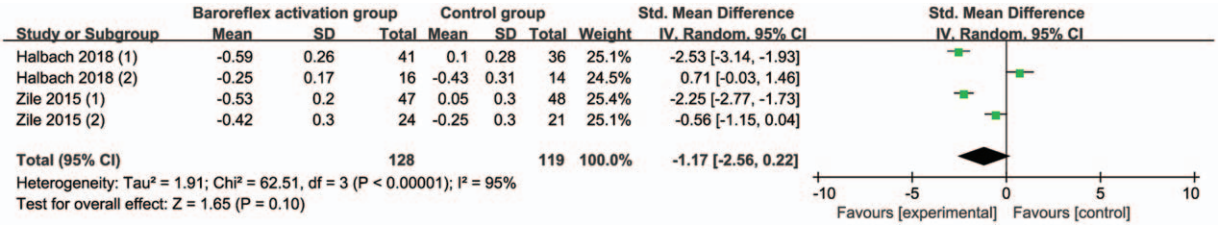

Figure 7. Forest plot for the meta-analysis of the number of hospitalization per year.

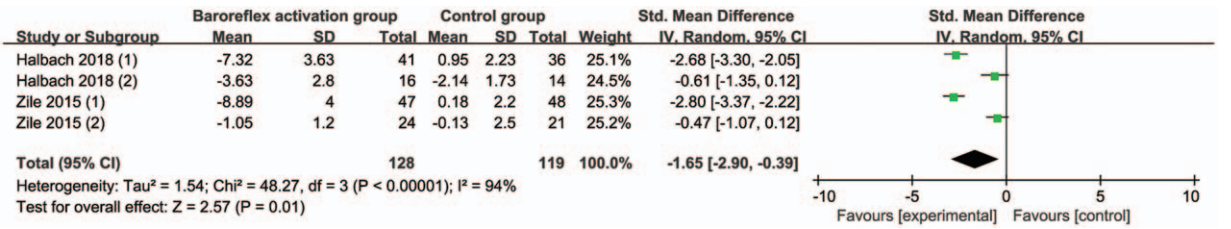

Figure 8. Forest plot for the meta-analysis of the duration of hospitalization.

Regarding the sensitivity analysis, there is significant heterogeneity. Different patient populations may account for this significant heterogeneity. Firstly, 1 included RCT revealed that the improved outcomes were more pronounced in patients without CRT than those patients with CRT.[11] Secondly, etiology-dependent responses to therapies was crucial for the outcomes, and baroreflex sensitivity was reported to be lower in patients with coronary artery diseases than those patients without coronary lesions.[27] In addition, baroreflex activation therapy showed similar efficacy in heart failure patients with and without coronary artery disease.[14]

The overall rate of major adverse neurological and cardiovascular events is 2.8% after baroreflex activation therapy.[28] The complication rate of baroreflex activation therapy is 10% in hypertensive patients.[10] In non-CRT patients, baroreflex activation therapy results in significant increase in pulse pressure possibly due to reduced vascular resistance and improved stroke volume. In contrast, this baroreflex activation therapy-induced effect on pulse pressure and systolic pressure is not observed in CRT patients.[29] Interaction testing has found that baroreflex activation therapy is compatible with pacemakers and implantable cardioverter defibrillator.[30,31] There is no statistical difference of safety profile between the CRT and no-CRT patients.[11] This meta-analysis has several limitations. Firstly, only 4 RCTs are included in this meta-analysis, and more RCTs with large sample size should be conducted to explore this issue. Next, there is significant heterogeneity, which may be caused by different causes and severity of heart function. Finally, some unpublished data may lead to some bias for the pooled results.

5. Conclusions

Baroreflex activation therapy is effective to alleviate heart failure.

Author contributions

Conceptualization: Guoqiang Cai, Dongyin Zhang.
Formal analysis: Guoqiang Cai, Dongyin Zhang.
Investigation: Kai Guo.
Methodology: Kai Guo.
Supervision: Kai Guo, Shu Qin.
Writing – original draft: Shu Qin.
Writing – review & editing: Shu Qin.

References

[1] Sabbah HN, Gupta RC, Imai M, et al. Chronic electrical stimulation of the carotid sinus baroreflex improves left ventricular function and promotes reversal of ventricular remodeling in dogs with advanced heart failure. Circ Heart Fail 2011;4:65–70.

[2] Felker GM, Anstrom KJ, Adams KF, et al. Effect of natriuretic peptide-guided therapy on hospitalization or cardiovascular mortality in high-risk patients with heart failure and reduced ejection fraction: a randomized clinical trial. JAMA 2017;318: 713–20.

[3] Yancy CW, Jessup M, Bozkurt B, et al. 2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the American college of cardiology/American Heart Association task force on clinical practice guidelines and the heart failure society of America. Circulation 2017;136:e137–61.

[4] Brunner-La Rocca HP, Esler MD, Jennings GL, et al. Effect of cardiac sympathetic nervous activity on mode of death in congestive heart failure. Eur Heart J 2001;22:1136–43.

[5] Felker GM, Shaw LK, O'Connor CM. A standardized definition of ischemic cardiomyopathy for use in clinical research. J Am Coll Cardiol 2002;39:210–8.

[6] Lipinski MJ, Luger D, Epstein SE. Mesenchymal stem cell therapy for the treatment of heart failure caused by ischemic or non-ischemic cardiomyopathy: immunosuppression and its implications. Handb Exp Pharmacol 2017;243:329–53.

[7] Sutton MG, Plappert T, Hilpisch KE, et al. Sustained reverse left ventricular structural remodeling with cardiac resynchronization at one year is a function of etiology: quantitative Doppler echocardiographic evidence from the Multicenter InSync Randomized Clinical Evaluation (MIRACLE). Circulation 2006;113:266–72.

[8] Godino C, Scotti A, Taramasso M, et al. Two-year cardiac mortality after MitraClip treatment of functional mitral regurgitation in ischemic and non-ischemic dilated cardiomyopathy. Int J Cardiol 2018;269:33–9.

[9] Gronda E, Seravalle G, Brambilla G, et al. Chronic baroreflex activation effects on sympathetic nerve traffic, baroreflex function, and cardiac haemodynamics in heart failure: a proof-of-concept study. Eur J Heart Fail 2014;16:977–83.

[10] Hoppe UC, Brandt MC, Wachter R, et al. Minimally invasive system for baroreflex activation therapy chronically lowers blood pressure with pacemaker-like safety profile: results from the Barostim neo trial. J Am Soc Hypertens 2012;6:270–6.

[11] Zile MR, Abraham WT, Weaver FA, et al. Baroreflex activation therapy for the treatment of heart failure with a reduced ejection fraction: safety and efficacy in patients with and without cardiac resynchronization therapy. Eur J Heart Fail 2015;17:1066–74.

[12] Gronda E, Seravalle G, Trevano FQ, et al. Long-term chronic baroreflex activation: persistent efficacy in patients with heart failure and reduced ejection fraction. Journal of hypertension 2015;33:1704–8.

[13] Abraham WT, Zile MR, Weaver FA, et al. Baroreflex activation therapy for the treatment of heart failure with a reduced ejection fraction. JACC Heart Fail 2015;3:487–96.

[14] Halbach M, Abraham WT, Butter C, et al. Baroreflex activation therapy for the treatment of heart failure with reduced ejection fraction in patients with and without coronary artery disease. Int J Cardiol 2018;266:187–92.

[15] Weaver FA, Abraham WT, Little WC, et al. Surgical experience and long-term results of baroreflex activation therapy for heart failure with reduced ejection fraction. Semin Thorac Cardiovasc Surg 2016;28: 320–8.

[16] Moher D, Liberati A, Tetzlaff J, et al. Group P.Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. J Clin Epidemiol 2009;62:1006–12.

[17] Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: Is blinding necessary? Control Clin Trials 1996;17:1–2.

[18] Kjaergard LL, Villumsen J, Gluud C. Reported methodologic quality and discrepancies between large and small randomized trials in meta-analyses. Ann Intern Med 2001;135:982–9.

[19] Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med 2002;21:1539–58.

[20] Wulsin L, Herman J, Thayer JF. Stress, autonomic imbalance, and the prediction of metabolic risk: a model and a proposal for research. Neurosci Biobehav Rev 2018;86:12–20.

[21] Jarrin DC, Ivers H, Lamy M, et al. Cardiovascular autonomic dysfunction in insomnia patients with objective short sleep duration. J Sleep Res 2018;27:e12663.

[22] Rathore SS, Curtis JP, Wang Y, et al. Association of serum digoxin concentration and outcomes in patients with heart failure. JAMA 2003;289:871–8.

[23] Ferguson DW, Berg WJ, Sanders JS, et al. Sympathoinhibitory responses to digitalis glycosides in heart failure patients. Direct evidence from sympathetic neural recordings. Circulation 1989;80:65–77.

[24] Briceno N, Schuster A, Lumley M, et al. Ischaemic cardiomyopathy: pathophysiology, assessment and the role of revascularisation. Heart 2016;102:397–406.

[25] Sisakian H. Cardiomyopathies: Evolution of pathogenesis concepts and potential for new therapies. World J Cardiol 2014;6:478–94.

[26] Follath F, Cleland JG, Klein W, et al. Etiology and response to drug treatment in heart failure. J Am Coll Cardiol 1998;32:1167–72.

[27] Katsube Y, Saro H, Naka M, et al. Decreased baroreflex sensitivity in patients with stable coronary artery disease is correlated with the severity of coronary narrowing. Am J Cardiol 1996;78:1007–10.

[28] Udo EO, Zuithoff NP, van Hemel NM, et al. Incidence and predictors of short- and long-term complications in pacemaker therapy: the follow pace study. Heart Rhythm 2012;9:728–35.
[29] O'Connor CM, Abraham WT, Albert NM, et al. Predictors of mortality after discharge in patients hospitalized with heart failure: an analysis from the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF). Am Heart J 2008;156:662–73.
[30] Madershahian N, Scherner M, Muller-Ehmsen J, et al. Baroreflex activation therapy in patients with pre-existing implantable cardioverter-defibrillator: compatible, complementary therapies. Europace 2014;16: 861–5.
[31] Kuffer L, Steven D, Halbach M, et al. Combination of a subcutaneous ICD in a patient with a baroreceptor activation device: Feasibility, safety, and precautions: a case report. Pacing Clin Electrophysiol V 40 2017; 1486–8.