

EVALUATION OF AUTONOMIC NERVOUS SYSTEM THROUGH SPECTRAL ANALYSIS IN PATIENTS WITH ISCHEMIC HEART FAILURE: A SYSTEMATIC REVIEW

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Abstract

Heart failure is one of the most complex pathologies and most prevalent diseases, with around 64 million people affected globally (2% of the total adult population). In the initial phase of heart failure, studies have shown that the autonomic nervous system is in a state of imbalance, with an increase in the influence of the sympathetic nervous system on the heart. Persistence of long-term activation of the autonomic nervous system produces a decrease in the levels of myocardial catecholamines and also promotes down-regulation of beta-1 receptors.

This article is a systematic review of papers from four well-known and important scientific databases on the subject of power spectral analysis of ECG Holter monitoring in patients with heart failure. The PRISMA technique was used to identify the most relevant articles on this subject, and their results were presented based on importance of their use for the diagnosis of heart failure, for risk stratification of sudden death or arrhythmias, for the evaluation of certain treatments used, or for other possible pathophysiological mechanisms involved in the evolution of the disease.

Keywords: heart failure, heart rate variability, spectral analysis, ECG Holter, autonomic nervous system



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Abstract

Insuficiența cardiacă reprezintă una dintre cele mai complexe patologii și una dintre cele mai prevalente boli, afectând aproximativ 64 de milioane de oameni la nivel global (2% din totalul adulților). În faza inițială a insuficienței cardiace, studiile au evidențiat că sistemul nervos autonom se află într-o stare de dezechilibru, cu un impact crescut al influenței sistemului nervos simpatic asupra inimii. Persistența unei activări pe termen lung a sistemului nervos autonom conduce la scăderea nivelurilor de catecolamine miocardice și favorizează, de asemenea, reducerea numărului receptorilor beta-1 disponibili.

Acest articol reprezintă un review sistematic al lucrărilor provenite din patru baze de date științifice bine cunoscute și importante, având ca temă analiza spectrală prin monitorizare Holter ECG la pacienții cu insuficiență cardiacă. Tehnica PRISMA a fost utilizată pentru identificarea celor mai relevante articole pe această temă, iar rezultatele lor au fost prezentate în funcție de importanța utilizării pentru diagnosticul insuficienței cardiace, pentru stratificarea riscului de dezvoltare a morții subite sau aritmii, pentru evaluarea anumitor tratamente utilizate sau pentru analiza altor posibile mecanisme fiziopatologice implicate în evoluția bolii.

Cuvinte cheie: *insuficiență cardiacă, variabilitatea ritmului cardiac, analiză spectrală, holter ECG, sistem nervos autonom*

Introduction

The autonomic nervous system predominantly controls heart rate, with the parasympathetic influence exhibiting a quicker response⁽¹⁾. Heart rate variability (HRV) is a method widely used either in short electrocardiogram (ECG) recordings or in Holter ECG monitoring to assess the autonomic nervous system influence on the heart, higher HRV being associated with a better cardiovascular system⁽²⁾. Heart rate variability (HRV) is

computed through the utilisation of both time-domain and frequency-domain parameters. Analysing the spectrum of 24-hour ECG Holter recordings provides a straightforward and non-intrusive means of evaluating the impact of the autonomic nervous system on the heart. High frequency (HF) power is a representation of the parasympathetic vagal function and low frequency (LF) power is influenced by the entire autonomic nervous system but appears to reflect more of the sympathetic activity, especially from its increase in heart failure in

initial stages⁽³⁾. Physical activity and renin-angiotensin-aldosterone system influence very low frequency (VLF) power and LF/HF ratio assesses the overall sympatho-vagal tone, having normal values at rest between 1 and 2.

Low reactivity to stimuli of the sinus node produced by sympathetic hyperactivation in advanced stages of heart failure leads to a decrease in LF power value⁽⁴⁾.

Objectives

The aim of this paper is to present a systematic review of the existing research on the spectral analysis in patients with ischemic heart failure. PRISMA technique was used to extract relevant papers based on various search and screening criteria. The selected 36 papers and their results were then discussed based on various criteria (e.g. medical procedures used, drugs prescribed, type of the study) and their conclusions were presented in a clear manner.

Materials and methods

In order to evaluate the current stage of the research on this matter, we conducted a thorough methodology based on the PRISMA technique (the Preferred Reporting Items for Systematic Reviews and Meta-Analyses)⁽⁵⁾. We have thus extracted scientific papers from four important databases: ScienceDirect, SpringerLink, PubMed and Nature; we performed several screening steps based on custom criteria, selected a number of possibly eligible papers and included a final number with the most relevant ones to be analysed in our review.

Our PRISMA analysis (Figure 1) included three major steps: identification, screening, and inclusion, with the screening process being

the most detailed one and including various sub-steps that will be further detailed.

In the identification step, we established a relevant formula that would return the corresponding papers to our research goal. The key terms were automatically searched in titles, abstracts, or keywords. Testing the proposed formulas in the ScienceDirect database, we observed that formula (1) returned few results (10 results), as the ECG abbreviation is not often used in titles, abstracts, or keywords; formula (2) was, on the contrary, too broad and returned many papers that were outside our specific topic (2843 results); and finally, formula (3) was the preferred one, focusing on mostly relevant papers for our review (1008). Table 1 shows the number of identified papers from each one of the four databases, using the previously chosen formula.

"Heart failure" AND "Autonomic Nervous System" AND "Heart rate Variability" (1)

"Heart failure" AND "Autonomic Nervous System" AND "Heart rate Variability" AND "Power spectral analysis" (2)

"Heart failure" AND "Autonomic Nervous System" AND "Heart rate Variability" AND "Power spectral analysis" AND "ECG Holter" (3)

In the screening step, we eliminated a major part of the scientific papers that were not the basis of our review. For the first sub-steps, we preferred to use the filtering and exclusion criteria available on their platforms in order to automate the process. The number of records excluded is thus available for each particular database. We will further detail each sub-step of the screening process, including the justification for the exclusion of those specific papers.

- **Screening A:** excluding books, chapters, abstracts, conference proceedings, posters, or encyclopedias. - as the focus is on studying individual, innovative, and



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original research papers, we decided to exclude records that were either too broad (e.g. books) or had insufficient content (e.g. posters). We have thus eliminated 2200 records from SpringerLink (693 books, 775 book chapters, 291 full conference proceedings, 441 abstracts, and posters), 203 from ScienceDirect (13 encyclopaedias, 80 book chapters, and 110 abstracts), and 71 books from Nature.

- **Screening B:** excluding papers that focus on a different field, not the medical one - our research topic has great potential in a lot of additional domains, including computer science (e.g. machine learning algorithms to improve prediction of various disorders), engineering (e.g. innovative wearable devices in the field), physics, astronomy, mathematics, or psychology (e.g. associate neurological disorders, including anxiety or depression). In this substep, we managed to exclude 341 records from SpringerLink, 122 papers from ScienceDirect, and 3 from Nature.
- **Screening C:** excluding papers before 1990 - the topic of spectral analysis in patients with ischemic heart failure has been studied for decades, yet useful information can still be extracted from papers written in the 1990s. We decided to eliminate only the papers published prior to 1990, excluding 25 records from SpringerLink, 2 from ScienceDirect, and 8 from Nature.
- **Screening D:** excluding papers written in a language that is not spoken by the authors of the current paper (e.g. German, Italian) - 87 papers excluded from SpringerLink.
- **Screening E:** excluding papers that are studying HRV on animals, fetuses, or children - since our goal is to make an analysis only on human adults, we excluded 32 papers from SpringerLink, 59 from ScienceDirect, 15 from PubMed, and 51 from Nature.
- After these initial screening operations, performed individually on each one of the databases, we decided to merge the remaining scientific articles, obtaining a total of 1578 records (SpringerLink - 639; ScienceDirect - 622; PubMed - 179; Nature - 138). The following screening sub-steps have been applied to the merged dataset in order to assess the remaining papers for eligibility and involve manual analysis of the papers.
- **Screening F:** After reading the titles, we excluded an additional 1238 articles. We have thus managed to manually exclude papers based on the same criteria from the Screening B - Screening E steps that were missed by the automatic filtering process. In addition, we eliminated papers whose content was focused on the

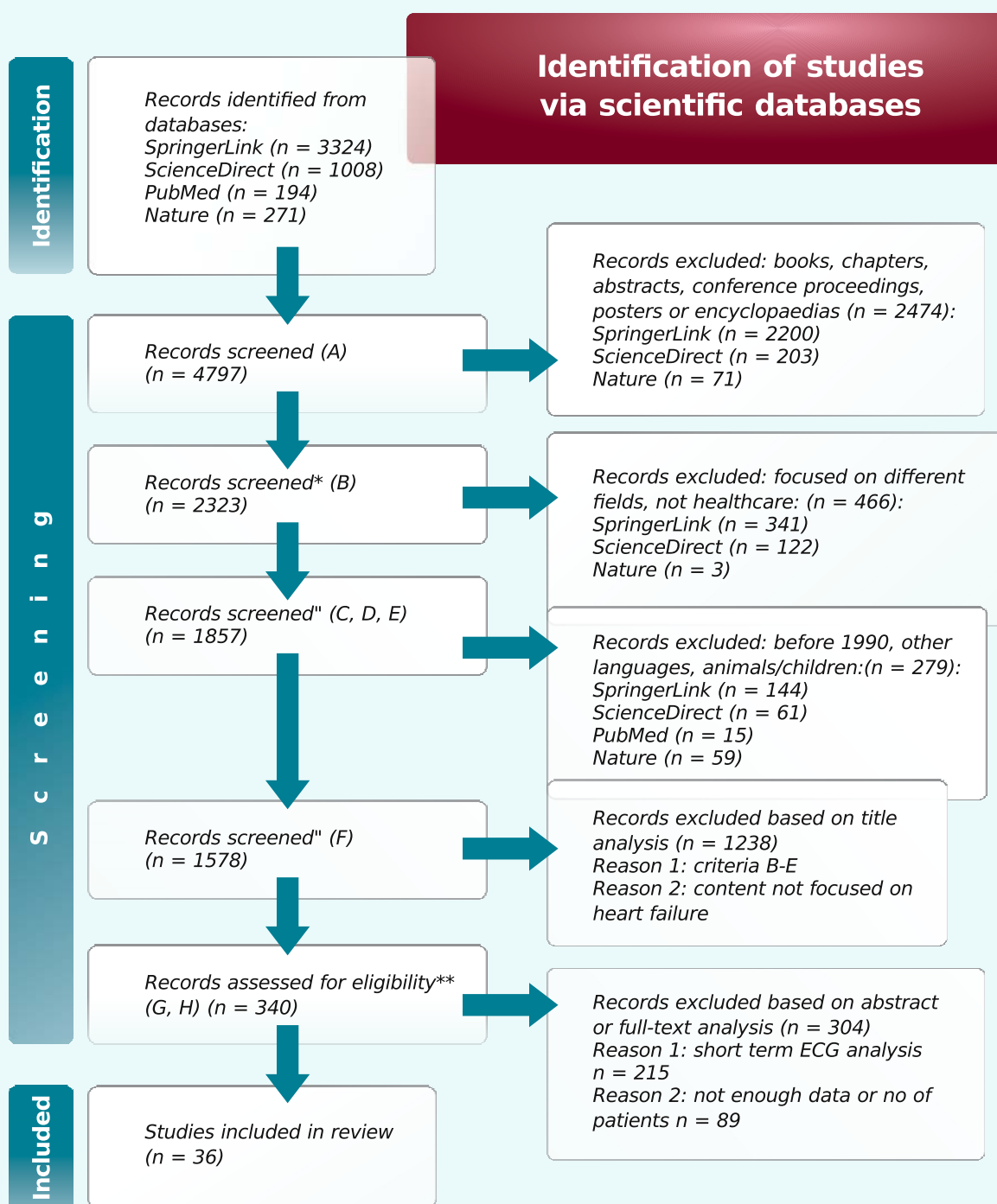


Figure 1. PRISMA methodology for selecting relevant studies for the systematic review

*using automation tools **human / manual screening

SpringerLink	ScienceDirect	PubMed	Nature		Total
3324	1008	194	271		4797

Table 1. Number of scientific papers identified in the four databases



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parasympathetic system and/or HRV in other conditions without including heart failure. There are a total of 340 possibly eligible papers remaining.

- **Screening G:** We examined the abstracts of the remaining papers and excluded 215 of them, in which spectral analysis was performed just by short term ECG recordings. There are 125 papers remaining.
- **Screening H:** We performed a full text analysis and excluded other papers that had inconclusive data or very specific groups of patients included (e.g. only intensive care unit - ICU - patients with major trauma).

Results and discussions

The remaining 36 papers were classified based on the type of the study (Figure 2) and we assessed their relevance by the number of patients included (Figure 3).

Early studies demonstrated the usefulness of HRV parameters in assessing progression of chronic heart failure (CHF) even in patients who did not receive Angiotensin-converting-enzyme inhibitor (ACE-inhibitor) treatment. LF and TP (total power) components were significantly lower in patients with a higher NYHA (New York Heart Association) class, but only LF was close to reaching significance in correlation with left ventricular ejection

fraction (LVEF). (49) LVEF and risk of arrhythmia are the major variables that generate a prognosis for CHF patients and by assessing autonomic dysfunction through HRV analysis, we can have a tool for classification for these patients⁽⁶⁾.

Guzzetti et al. performed a pioneer prospective study on 50 patients (30 with stable CHF and 20 control) followed for 2 years with multiple ECG Holter recordings to assess non-linear and spectral analysis as independent prognostic factors for CHF. Results showed that both methods have prognostic value independent of time-domain parameters with LF power being the best indicator of all those studied⁽⁷⁾. More recently, the idea of evaluating the association between HRV holter-derived indices and the development of CHF was used by Patel et al. who performed a large study on 1401 patients (260 of them with CHF) and the results showed that an increase in very low frequency (VLF) power is strongly linked to CHF development and ventricular arrhythmias⁽⁸⁾.

Galinier et. al. used time and frequency domain measures of HRV as a prognostic tool for all-cause and sudden death in chronic heart failure patients, and their results showed that spectral analysis can identify individuals at risk of sudden death, especially by assessing the daytime LF power (if the value is $< 3.3 \ln(\text{ms}^2)$)⁽⁹⁾.

Guzzetti et al. continued their research on HRV usefulness in heart failure patients, with one of the most relevant early studies using ECG Holter recordings in 330 CHF patients to evaluate HRV as a predictor for the cause of death (pump failure vs. sudden death). The results showed that a decrease in nocturnal HRV and high values of VLF are predictors for pump failure, while LF nocturnal reduction suggested a higher risk for sudden death, all being independent risk factors⁽¹⁰⁾. These findings are complementary to even earlier ones such as the paper by Ponikowski et al. that showed in their study on 50 subjects with CHF that decreased HRV indices on 24-hour ambulatory ECG monitoring are associated with an increase in the risk of ventricular tachycardia and death, making it a useful tool for risk stratification in these patients. The difference from later studies was that for all HRV parameters, only HF power was an independent predictor of ventricular tachycardia, irrespective of LVEF and mean R-R interval duration⁽¹¹⁾.

Further studies and literature reviews evaluated the impact of using HRV analysis indices such as spectral power to evaluate specific etiologies of heart failure and compare patients with different causes of developing CHF. Such an example is the study by Notarius et al. that evaluated short-term recordings for HRV parameters showing a decrease in total spectral power and LF power with a decrease in effort tolerance and a sympathetic hyperactivation in patients with ischemic heart failure compared to dilated cardiomyopathy patients, which suggests an additional ischemic stimulus for hyperactivity of the sympathetic system in this group⁽¹²⁾.

Voss et al. compared linear and non-linear HRV analysis indices between short-term and 24-hour ECG recordings and demonstrated their usefulness in risk stratification of

patients with ischemic heart failure. LF/HF ratio which is a marker of sympathovagal balance decreased in high-risk patients compared to low-risk patients, irrespective of the type of recording. LF power was decreased significantly in high-risk patients and HF power was increased, further confirming the sympathetic-parasympathetic imbalance in subjects with a more severe prognosis⁽¹³⁾.

Considering ischemic aetiology as being more prevalent and representing a more important factor for autonomic imbalance in CHF patients, there were a significant number of studies that followed patients who developed this condition after a myocardial infarction. Sztajel et al. conducted an early systematic review on subjects who suffered a myocardial infarction and secondary heart failure and demonstrated an independent association between HRV parameters that represent a strong predictor of increased cardiac and/or arrhythmic mortality. Also, this review supported the idea that in the initial phase of heart failure, the vagal tone is decreased and there is sympathetic activation, while in the late stages, the LF power is very low, even undetectable, which demonstrates a central regulation anomaly and beta receptor failure⁽¹⁴⁾. Others, such as Chattipakorn et al. performed a systematic review on HRV parameters in CHF and myocardial infarction in order to discover the role of HRV as a cardiovascular mortality predictor and to outline patients in need of an implantable cardioverter defibrillator (ICD) to prevent sudden death. Results showed that a low SDNN (time-domain HRV index) is a predictor for mortality in CHF and decreased LF power is a predictor of sudden death in these patients⁽¹⁵⁾. More recent papers emphasised the need of additional studies in order to introduce HRV measurement as a



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tool for stratification of risk in acute myocardial infarction (AMI) patients with consequent heart failure⁽¹⁶⁾.

From a pathophysiological point of view, there was a study by Atherton et al. which demonstrated that in heart failure patients, a decrease in baroreflex control of vascular resistance produces a change in the interventricular interaction during diastole, which leads to a worse filling of the left ventricle (LV) and, subsequently, a worse outcome in the evolution of the disease. Their results showed that an intervention of acute volume unloading created a decrease in right ventricle (RV) volume and an increase in LV end-diastolic volume, which correlated negatively with SDNN, rMSSD, TP, LF power, and HF power, thus suggesting that this interventricular interaction in CHF patients is accompanied by an activation of the sympathetic nervous system, and by using a method of unloading, we can induce an improvement in the autonomic nervous system action on the heart as well⁽¹⁷⁾.

Other areas of interest represented the association between inflammation and activation of the autonomic nervous system in CHF patients. Malave et al. performed a study on 29 patients with chronic heart failure and 10 control patients evaluating the link between HRV parameters and tumoral necrosis factor (TNF) plasma levels, showing significant reverse correlation and

concluding that TNF levels represent an independent predictor of HRV parameters decrease in CHF patients⁽¹⁸⁾.

Use of HRV indices and spectral power analysis was not limited to diagnosis or risk factors and was used in a systematic review and meta-analysis to assess the response of autonomic nervous system to exercise training in patients with heart failure. The paper demonstrates increases in some parameters such as heart rate reserve (HRR), HRV and muscle sympathetic nerve activity (MSNA) after exercise training, which suggests a decrease in sympathetic activation and a better parasympathetic tone after exercise⁽¹⁹⁾.

With the purpose of finding which intensity level should be recommended, Besnier et al. conducted a study on 31 patients with heart failure with an ejection fraction (EF) < 45% and randomised them for medium intensity training or high intensity interval training and demonstrated the superiority of the latter in improving HRV parameters, increasing the parasympathetic tone, and improving peak oxygen uptake⁽²⁰⁾.

Different papers tried to use HRV parameters, including spectral power, to evaluate the effect of different medications used in the treatment of CHF. A very early study by Brouwer et al. assessed neurohormonal modulation by digoxin in mild to moderate CHF with reduced EF, and results showed that

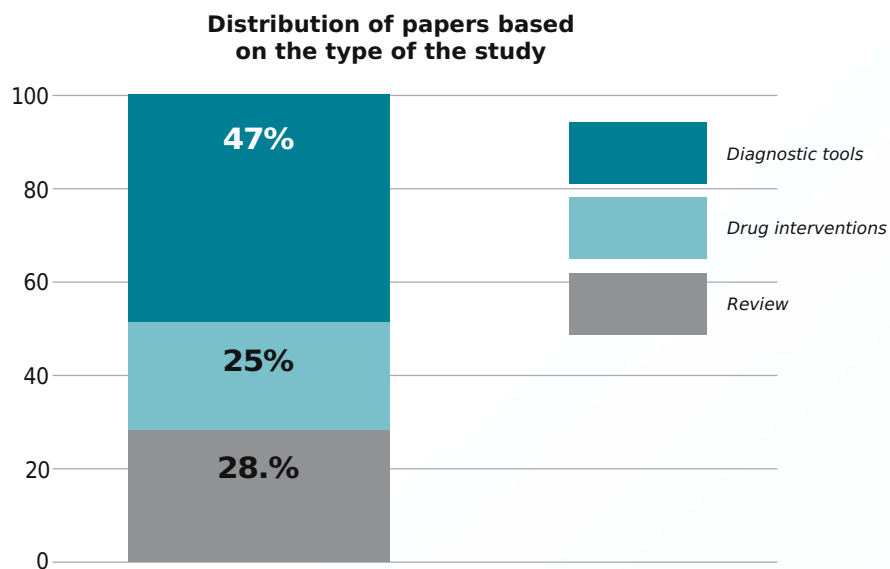


Figure 2. Chart representing the distribution of selected papers using the type of the study as a criterion

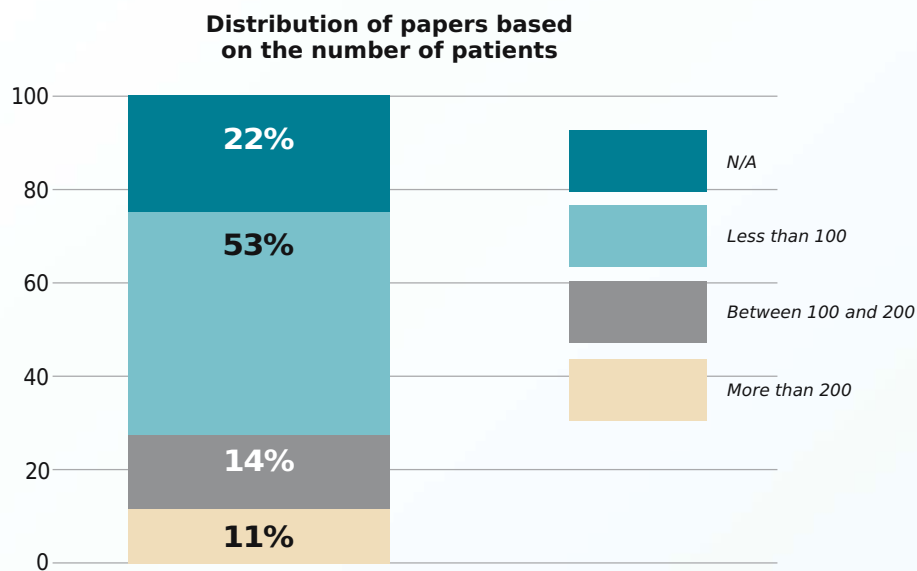


Figure 3. Chart representing the distribution of selected papers using the number of patients present in the study as a criterion



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digoxin prevented deterioration of HRV parameters in early stages of CHF, with an improvement in vagal tone in the context of neuroendocrine activation⁽²¹⁾. Guedon-Moreau et al.⁽²²⁾, Pousset et al.⁽²³⁾, Bozkut et al.⁽²⁴⁾ and Tomiyama et al.⁽²⁵⁾ performed other early studies on different medications in CHF like Ramipril⁽²²⁾, Bisoprolol⁽²³⁾, Perindopril⁽²⁴⁾ and Furosemide⁽²⁵⁾ and their effect on HRV in patients with CHF.

Ramipril showed a decrease in ventricular tachycardia (VT) episodes without altering HRV⁽²²⁾. Bisoprolol increased time-domain HRV parameters (rMSSD, pNN50, daytime SDNN) and daytime HF power, demonstrating an improvement in vagal tone (protective effect)⁽²³⁾. Perindopril increased parasympathetic modulation and decreased the sympathetic tone, also improving LV function in CHF patients post-MI⁽²⁴⁾. Furosemide had a slight improvement in HRV parameters compared to Azosemide in CHF patients⁽²⁵⁾. Aronson et al. studied the effect of beta-blockers on autonomic modulation in decompensated heart failure and demonstrated the improvement of sympathetic nervous system regulation by decreasing sympathetic hyperactivation in this patient cohort. Also, the use of beta-blockers showed an improvement in arrhythmia prevention⁽²⁶⁾.

Kokmaz et al. conducted a study on 126 patients with congestive heart failure and

coronary artery disease to evaluate the effects of spironolactone on HRV in this group. Results demonstrated a partially significant correlation between LF power and EF ($p < 0.07$) and showed a marked decrease in LF power and total power in higher NYHA class patients⁽²⁷⁾. Similarly, Yee et al.⁽²⁸⁾ and Davies et al.⁽²⁹⁾ also evaluated aldosterone blockers and spironolactone in particular in patients with CHF to assess the effects on HRV. Both studies (the first a review and the other a randomised control trial) showed that spironolactone had favourable effects on the autonomic nervous system, improving HRV parameters and even partially reversing autonomic disturbances in CHF, with a decrease in cardiac sudden death as observed in the RALES and EPHESUS trials. The review of Yee et al. also discovered an interesting precaution, as the HRV parameters were worse in diabetic patients without CHF⁽²⁸⁾.

More recent papers, such as Hamaad et al., used short-term ECG recordings to demonstrate an improvement in spectral power parameters and sympathetic tone in systolic CHF patients (EF < 45%) who were randomised for 12 weeks to receive 40 mg of Atorvastatin compared to the ones who received placebo⁽³⁰⁾.

The latest studies expanded the use of HRV parameters in patients with coronary artery disease (CAD), but without CHF. Spallone et

al. performed a review on diabetic patients with coronary artery disease following the effects of SGLT2 inhibitor empagliflozin on the autonomic nervous system with 66 patients undergoing ECG Holter monitoring for measuring HRV parameters, but the results did not reach statistical significance⁽³¹⁾.

Other studies, however, understate the importance of HRV measurement in assessing arrhythmic death risk. Burger et al. showed that HRV parameters known to suggest a possible adverse outcome in heart failure did not differ significantly between diabetic and non-diabetic patients and demonstrated a decrease in activation of the sympathetic nervous system in diabetic patients by showing an important reduction in LF and LF:HF ratio, which does not produce an increase in the arrhythmic risk⁽³²⁾. Mortara et al. performed a study of baroreflex sensitivity (BRS) and HRV in CHF patients, both parameters known to be reduced in this illness and associated with its progression. Time and frequency parameters were not significantly different in surviving patients compared to those who were deceased, showing just a frail link between these indices and survival⁽³³⁾. Myers et al. concluded in their study of 34 CHF patients that HRV study and analysis of the power spectrum are unreliable in the presence of frequent ectopic beats, and including them in the analysis will apparently increase LF power⁽³⁴⁾.

Regarding the ECG Holter recording potential errors, Wu et al. studied 3 groups of patients (young, elderly, and heart failure patients) with the intention of discriminating random noise from autonomic spectral pictures related to heart failure. By performing a noise-titration on the ECG Holter tachographs, the results showed age-related decreases in LF and HF power, but with similar HF chaos levels in healthy patients

(young and old), while in the heart failure group, heartbeats were non-chaotic with the exception of some undetected ectopic beats⁽³⁵⁾.

Conclusions

The results of this literature review demonstrate the usefulness of HRV power spectral indices as an assessment tool for diagnosing heart failure and stratifying the risk of developing arrhythmic events or sudden death in these patients. The use of HRV indices and spectral power analysis extends beyond the diagnosis of CHF, with exercise training showing positive effects on increased heart rate reserve, HRV, and parasympathetic tone. Additionally, high-intensity interval training enhanced HRV parameters and peak oxygen uptake for heart failure patients with low ejection fraction.

There are earlier studies that demonstrate the effect of well-established medications in CHF with reduced EF such as beta-blockers, ACE inhibitors, diuretics and aldosterone blockers on the autonomic nervous system changes induced by heart failure, showing improved values of power spectral indices after treatment initiation. There are also more recent studies that evaluate the impact of atorvastatin or empagliflozin on power spectral indices and consequently on the autonomic nervous system influence on a failing heart with results that show only partial significance.

These pathophysiological mechanisms linked to the autonomic nervous system that are involved in the development of heart failure and progression of this illness have been studied intensely but focusing mainly on heart failure with reduced ejection fraction. Further studies can improve knowledge



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regarding patients with heart failure with preserved ejection fraction or patients with heart failure with mid-range ejection fraction.

References

1. S. Guzzetti et al., "Symbolic dynamics of heart rate variability: a probe to investigate cardiac autonomic modulation," *Circulation*, vol. 112, no. 4, pp. 465–470, Jul. 2005, doi: 10.1161/CIRCULATIONAHA.104.518449.
2. H. V. Huikuri, T. Mäkitallio, K. E. Juhani Airaksinen, R. Mitrani, A. Castellanos, and R. J. Myerburg, "Measurement of Heart Rate Variability: A Clinical Tool or a Research Toy?," *J. Am. Coll. Cardiol.*, vol. 34, pp. 1878–1883, 1999, doi: 10.1016/S0735-1097(99)00468-4.
3. J. Achten and A. E. Jeukendrup, "Heart rate monitoring: applications and limitations," *Sports Med.*, vol. 33, no. 7, pp. 517–538, 2003, doi: 10.2165/00007256-200333070-00004.
4. M. Sadaka, A. Aboelela, S. Arab, and M. Nawar, "Electrocardiogram as prognostic and diagnostic parameter in follow up of patients with heart failure," *Alexandria J. Med.*, vol. 49, no. 2, pp. 145–152, Jun. 2013, doi: 10.1016/J.AJME.2012.09.002.
5. D. Moher et al., "Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement," *PLoS Medicine*, vol. 6, no. 7, Jul. 2009, doi: 10.1371/journal.pmed.1000097.
6. B. M. Szabó, D. J. van Veldhuisen, J. Brouwer, J. Haaksma, and K. I. Lie, "Relation between severity of disease and impairment of heart rate variability parameters in patients with chronic congestive heart failure secondary to coronary artery disease," *Am. J. Cardiol.*, vol. 76, no. 10, pp. 713–716, Oct. 1995, doi: 10.1016/S0002-9149(99)80204-5.
7. S. Guzzetti et al., "Linear and nonlinear 24 h heart rate variability in chronic heart failure," *Auton. Neurosci.*, vol. 86, no. 1–2, pp. 114–119, Dec. 2000, doi: 10.1016/S1566-0702(00)00239-3.
8. V. N. Patel, B. R. Pierce, R. K. Bodapati, D. L. Brown, D. G. Ives, and P. K. Stein, "Association of Holter-Derived Heart Rate Variability Parameters With the Development of Congestive Heart Failure in the Cardiovascular Health Study," *JACC. Heart Fail.*, vol. 5, no. 6, pp. 423–431, Jun. 2017, doi: 10.1016/J.JCHF.2016.12.015.
9. M. Galinier et al., "Depressed low frequency power of heart rate variability as an independent predictor of sudden death in chronic heart failure," *Eur. Heart J.*, vol. 21, no. 6, pp. 475–482, Mar. 2000, doi: 10.1053/EUHFJ.1999.1875.
10. S. Guzzetti et al., "Different spectral components of 24 h heart rate variability are related to different modes of death in chronic heart failure," *Eur. Heart J.*, vol. 26, no. 4, pp. 357–362, Feb. 2005, doi: 10.1093/EURHEARTJ/EHI067.
11. P. Ponikowski et al., "Heart rhythms, ventricular arrhythmias, and death in chronic heart failure," *J. Card. Fail.*, vol. 2, no. 3, pp. 177–183, 1996, doi: 10.1016/S1071-9164(96)80039-X.
12. C. F. Notarius, J. Spaak, B. L. Morris, and J. S. Floras, "Comparison of muscle sympathetic activity in ischemic and nonischemic heart failure," *J. Card. Fail.*, vol. 13, no. 6, pp. 470–475, Aug. 2007, doi: 10.1016/J.CARDFAIL.2007.03.014.
13. A. Voss et al., "Short-term vs. long-term heart rate variability in ischemic cardiomyopathy risk stratification," *Front. Physiol.*, vol. 4, 2013, doi: 10.3389/FPHYS.2013.00364.
14. J. Sztajzel, "Heart rate variability: a noninvasive electrocardiographic method to measure the autonomic nervous system," *Swiss Med. Wkly.*, vol. 134, no. 35–36, pp. 514–522, Sep. 2004, doi: 10.4414/SMW.2004.10321.
15. N. Chattipakorn, T. Incharoen, N. Kanlop, and S. Chattipakorn, "Heart rate variability in myocardial infarction and heart failure," *Int. J. Cardiol.*, vol. 120, no. 3, pp. 289–296, Sep. 2007, doi: 10.1016/J.IJCARD.2006.11.221.
16. H. V. Huikuri and P. K. Stein, "Heart rate variability in risk stratification of cardiac patients," *Prog. Cardiovasc. Dis.*, vol. 56, no. 2, pp. 153–159, Sep. 2013, doi: 10.1016/J.PCAD.2013.07.003.
17. J. J. Atherton et al., "Diastolic ventricular interaction in chronic heart failure: relation to heart rate variability and neurohumoral status," *Heart Vessels*, vol. 13, no. 6, pp.

269-277, 1998, doi: 10.1007/BF03257231.

18. H. A. Malave, A. A. Taylor, J. Nattama, A. Deswal, and D. L. Mann, "Circulating levels of tumor necrosis factor correlate with indexes of depressed heart rate variability: a study in patients with mild-to-moderate heart failure," *Chest*, vol. 123, no. 3, pp. 716-724, Mar. 2003, doi: 10.1378/CHEST.123.3.716.

19. M. J. Pearson and N. A. Smart, "Exercise therapy and autonomic function in heart failure patients: a systematic review and meta-analysis," *Heart Fail. Rev.*, vol. 23, no. 1, pp. 91-108, Jan. 2018, doi: 10.1007/S10741-017-9662-Z.

20. F. Besnier et al., "Short-term effects of a 3-week interval training program on heart rate variability in chronic heart failure. A randomised controlled trial," *Ann. Phys. Rehabil. Med.*, vol. 62, no. 5, pp. 321-328, Sep. 2019, doi: 10.1016/J.REHAB.2019.06.013.

21. J. Brouwer et al., "Heart rate variability in patients with mild to moderate heart failure: Effects of neurohormonal modulation by digoxin and ibopamine," *J. Am. Coll. Cardiol.*, vol. 26, no. 4, pp. 983-990, 1995, doi: 10.1016/0735-1097(95)00285-3.

22. L. Guedon-Moreau et al., "Effect of ramipril on heart rate variability in digitalis-treated patients with chronic heart failure," *Cardiovasc. Drugs Ther.*, vol. 11, no. 4, pp. 531-536, 1997, doi: 10.1023/A:1007763131888/METRICS.

23. F. Pousset et al., "Effects of Bisoprolol on heart rate variability in heart failure," *Am. J. Cardiol.*, vol. 77, no. 8, pp. 612-617, Mar. 1996, doi: 10.1016/S0002-9149(97)89316-2.

24. A. Bozkurt, A. Birand, and G. Z. Kudaiberdieva, "Effects of perindopril on autonomic modulation of the heart and left ventricular function: An open-label study," *Curr. Ther. Res.*, vol. 63, no. 1, pp. 43-51, Jan. 2002, doi: 10.1016/S0011-393X(02)80006-6.

25. H. Tomiyama et al., "Effects of short-acting and long-acting loop diuretics on heart rate variability in patients with chronic compensated congestive heart failure," *Am. Heart J.*, vol. 137, no. 3, pp. 543-548, Mar. 1999, doi: 10.1016/S0002-8703(99)70504-1.

26. D. Aronson and A. J. Burger, "Effect of beta-blockade on autonomic modulation of heart rate and neurohormonal profile in decompensated heart failure," *Ann. Noninvasive Electrocardiol.*, vol. 6, no. 2, pp. 98-106, 2001, doi: 10.1111/J.1542-474X.2001.TB00093.X.

27. M. E. Korkmaz, H. Müderrisoglu, M. Uluçam, and B. Özin, "Effects of spironolactone on heart rate variability and left ventricular systolic function in severe ischemic heart failure," *Am. J. Cardiol.*, vol. 86, no. 6, pp. 649-653, Sep. 2000, doi: 10.1016/S0002-9149(00)01046-8.

28. K. M. Yee, S. D. Pringle, and A. D. Struthers, "Circadian variation in the effects of aldosterone blockade on heart rate variability and QT dispersion in congestive heart failure," *J. Am. Coll. Cardiol.*, vol. 37, no. 7, pp. 1800-1807, Jun. 2001, doi: 10.1016/S0735-1097(01)01243-8.

29. J. I. Davies, M. D. Witham, and A. D. Struthers, "Autonomic effects of spironolactone and MR blockers in heart failure," *Heart Fail. Rev.*, vol. 10, no. 1, pp. 63-69, Jan. 2005, doi: 10.1007/S10741-005-2350-4.

30. A. Hamaad, M. Sosin, G. Y. H. Lip, and R. J. MacFadyen, "Short-term adjuvant atorvastatin improves frequency domain indices of heart rate variability in stable systolic heart failure," *Cardiovasc. drugs Ther.*, vol. 19, no. 3, pp. 183-187, May 2005, doi: 10.1007/S10557-005-2219-8.

31. V. Spallone and P. Valensi, "SGLT2 inhibitors and the autonomic nervous system in diabetes: A promising challenge to better understand multiple target improvement," *Diabetes Metab.*, vol. 47, no. 4, p. 101224, Jul. 2021, doi: 10.1016/J.DIABET.2021.101224.

32. A. J. Burger and D. Aronson, "Effect of Diabetes Mellitus on Heart Rate Variability in Patients with Congestive Heart Failure," *Pacing Clin. Electrophysiol.*, vol. 24, no. 1, pp. 53-59, Jan. 2001, doi: 10.1046/J.1460-9592.2001.00053.X.

33. A. Mortara and L. Tavazzi, "Prognostic implications of autonomic nervous system analysis in chronic heart failure: Role of heart rate variability and baroreflex sensitivity," *Arch. Gerontol. Geriatr.*, vol. 23, no. 3, pp. 265-275, Nov. 1996, doi: 10.1016/S0167-4943(96)00727-3.

34. G. Myers, M. Workman, C. Birkett, D. Ferguson, and M. Kienzie, "Problems in measuring heart rate variability of patients with congestive heart failure," *J. Electrocardiol.*, vol. 25 Suppl, no. SUPPL., pp. 214-219, 1992, doi: 10.1016/0022-0736(92)90105-9.

35. G. Q. Wu et al., "Chaotic signatures of heart rate variability and its power spectrum in health, aging and heart failure," *PLoS One*, vol. 4, no. 2, Feb. 2009, doi: 10.1371/JOURNAL.PONE.0004323.