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REVIEW / *DERLEME*

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Which Measures and Parameters of HRV Analysis May be Useful for Early Detection and Predicting Prognosis of Sepsis? A systematic review

Sepsis'in Erken Teşhisi ve Prognoz Tahmininde Hangi Kalp Atım Hızı Analiz Ölçümleri ve Parametreleri Kullanışlı Olabilir? Bir Sistemik İnceleme

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ABSTRACT Sepsis causes a series of pathological changes in the systems such as cardiovascular, respiratory, and thermoregulation. These changes cause alterations in heart rate variability (HRV). Even without any changes in the vital signs or clinical presentation of the disease, HRV may still be altered due to sympathetic nervous system activation caused by infection. Our aim in this review was to present the sepsis-related HRV measures and parameters by examining the literature and their possible role in the predicting severity and mortality of sepsis. Databases were searched for original research articles reporting human studies with HRV on sepsis, published in the English language between April 1996 – May 2023. After completion of the article search, a total of 79 articles were selected for further evaluation where the full text of the articles was reviewed and 13 of the articles meet the criteria for inclusion. Mean values of each HRV parameter were corrected to the sample size of each study and overall means were calculated accordingly. Statistical comparisons were performed after sample size correction by Willcoxon signed ranked test. Nine studies were included, with a total of 1453 patients, the weighted mean age was 64.24 years and 53.9% were male. Of the studies included, all performed frequency domain analysis, and four performed nonlinear analysis. Seven out of nine studies were conducted in emergency departments and two were in intensive care units of the hospitals. 6 studies compared parameters between survivors and non-survivors, and 3 studies compared between different severity levels of sepsis. SDNN, RMSSD, SDNN, HTI, LF (nu), HF (nu), LF/HF ratio, SD1, SD2, DFAα1, and DFAα2 appear to be related to mortality in patients with sepsis outcome. Therefore, it can be concluded that monitoring these parameters for the early detection of sepsis may be beneficial.
Keywords: Sepsis, heart rate variability, time domain parameters, frequency domain parameters, non-linear analysis

ÖZ Sepsis, kardiyovasküler, solunum ve termoregülasyon gibi sistemlerde patolojik değişikliklere neden olur. Bu değişiklikler de kalp hızı değişkenliğinde (HRV) alterasyonlara neden olur. Vital bulgularda veya hastalığın klinik sunumunda herhangi bir değişiklik olmasa bile, enfeksiyona bağlı olarak sempatik sinir sistemi aktivasyonu nedeniyle HRV parametreleri değişebilir. Bu sistematik derlemedeki amacımız, literatürü inceleyerek sepsise ilişkin HRV ölçümlerini ve parametrelerini sunmak ve bunların sepsisin şiddetini ve ölüm riskini tahmin etmedeki olası rolünü araştırmaktı. Veritabanları, Nisan 1996 - Mayıs 2023 tarihleri arasında İngilizce dilinde yayınlanmış sepsis üzerine HRV analizlerini insan çalışmalarını bildiren orijinal araştırma makaleleri için tarandı. Makale araması tamamlandıktan sonra, 79 makale daha ayrıntılı bir değerlendirmeye tabi tutulmak üzere seçildi ve bu makalelerin tam metinleri incelendikten sonra 13 makale kriterlere uygun olarak sınıflandırıldı. Her HRV parametrelerinin ortalama değerleri her çalışmanın örnek büyüklüğüne göre düzeltildi ve genel ortalamalar hesaplandı. İstatistiksel karşılaştırmalar wilcoxon eşleştirilmiş diziler testi ile yapıldı.
Toplam 1453 hastanın yer aldığı dokuz çalışma dahil edildi, ortalama yaş 64.24 yıl ve tüm katılımcıların %53.9'u erkekti. Dahil edilen çalışmaların hepsi zaman, frekans domain analizi gerçekleştirdi ve dört tanesi bu analizlere ek olarak doğrusal olmayan analizler gerçekleştirdi. Dokuz çalışmanın yedisini acil serviste ve ikisini hastanelerin yoğun bakım ünitelerinde gerçekleştirildi. Altı çalışma sağ kalanlar ile hayatını kaybedenler arasındaki parametreleri, üç çalışma ise sepsisin farklı şiddet seviyeleri arasındaki parametreleri karşılaştırdı.
SDNN, RMSSD, SDNN, HTI, LF (nu), HF (nu), LF/HF oranı, SD1, SD2, DFAα1 ve DFAα2, sepsis sonucuyla ilişkili gibi görünmektedir. Bu nedenle, sepsisin erken teşhisi için bu parametrelerin izlenmesinin faydalı olabilir.
Anahtar Kelimeler: Sepsis, Kalp atım hızı değişkenliği, zaman tabanlı parametreler, frekans tabanlı parametreler, doğrusal olmayan analizler

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Introduction

Sepsis is a disorder that refers to the presence of infectious organisms in regions of the body that should ordinarily be devoid of bacteria or viruses, such as blood or tissues, because of a bacterial or viral infection. Sepsis can cause a heightened inflammatory response throughout the body. And, as a result of the body's overreaction, some organs may receive less oxygen and/or blood perfusion, a condition known as septic shock [1]. The sympathetic nervous system (SNS) plays a crucial role in the pathophysiology of septic shock. Studies have highlighted the dysfunction of the sympathetic branch of the autonomic nervous system (ANS) in septic shock, leading to impaired autonomic control of the heart and vessels, contributing to circulatory failure [2]. During septic shock, there is a maladaptive response to hypotensive and inflammatory stress, resulting in impaired sympathetic modulation of the cardiovascular system [3]. The onset of septic shock is characterized by high concentrations of circulating catecholamines but impaired sympathetic modulation of the heart and vessels, indicating central autonomic regulatory impairment contributing to circulatory failure [4]. Therefore, monitoring activity of the autonomic nervous system in patients with sepsis or septicemia is important. There are various ways for assessing ANS function, but heart rate variability (HRV) analysis has gained popularity in recent years due to its ease of use, noninvasive nature, and low cost. Both electrocardiography (ECG) and photoplethysmography (PPG) can be used to assess HRV, namely autonomic nervous function. The RR interval time series, or the sequence of intervals between successive R waves of QRS complexes in ECG or PPG, is used to calculate HRV [5].

HRV analysis includes several methods, with the most commonly used method being time domain analysis. This method involves extracting numerical data through basic mathematical examination of the time intervals between successive heartbeats. These figures quantify the extent of HRV across different time scales, whether from extensive recordings spanning 24 hours or brief recordings lasting only a few minutes [5]. The most commonly examined parameters include the standard deviation of normal heartbeats (SDNN), the root mean square of successive heartbeat intervals (RMSSD), and the number of normal heartbeats occurring within intervals under 50 milliseconds (NN50) [6]. The second most common method is the frequency domain analysis. Frequency domain analysis is an intricate analytical method revealing the distribution of a signal across specific frequency bands. High-frequency power (HF) denotes activity within the 0.15 - 0.40 Hz range, while low-frequency power (LF) represents activity within the 0.04 - 0.15 Hz range [7]. The LF/HF ratio, a comparison of low frequency to high frequency, is sometimes interpreted as indicative of sympathovagal balance, although this interpretation is subject to controversy [8], [9]. On the other hand, nonlinear methods differ from the above mentioned "classical" HRV analysis methods because they do not assess the variability of the heart rate but rather the quality, scaling, and the correlation characteristics of the signal [10].

Patients with sepsis who need to be admitted to an intensive care unit are in the minority, but they can have a stormy course due to a pathological inflammatory response known as "Cytokine Storm." The onset of a cytokine storm is accompanied by an increase in inflammatory indicators such as C-reactive protein (CRP). Hence, these indicators helps clinicians decide when to institute pharmacological interventions since it is vastly important to initiate early pharmacological interventions for better outcomes [11]. However, one disadvantage of this laboratory tests is that it may not alert clinicians to start treatment promptly enough [12].

Sepsis causes a series of pathological changes of the systems such as cardiovascular, respiratory, thermoregulation. These changes cause alterations in the heart rate variability (HRV). Even without any changes in the vital signs or clinical presentation of the disease, HRV may still be altered due to sympathetic nervous system activation caused by infection [13]. This may enable us to begin pharmacological interventions at the very early phases even 12 to 24 hours prior to clinical changes (such as fever, tachycardia or positive culture results) [13]. As a new and promising tool, continuous monitoring of heart rate variability and even complexity in ICU settings may also provide useful information regarding overall health of the patients. When compared to existing risk stratification measures, a sepsis severity predictive model combining HRV and laboratory values outperformed individual models constructed from a single domain (clinical, laboratory, or HRV) and demonstrated comparable or superior discrimination with more balanced sensitivity and specificity [14].

To this date, apart from sepsis which is a pathological condition caused by a positive-feedback mechanism triggered by an infection, changes of HRV parameters have been associated with cardiomyopathies[15], arterial hypertension[16], myocardial infarction[17], kidney failure[18]. However, HRV analysis includes several components that represented different dynamics of autonomic nervous system. There are more than 25 different parameters of HRV analysis, and this variety of parameters belong to different HRV measures, such as time and frequency domain analysis and non-linear methods [6]. Related with the mechanism of the pathology, HRV parameters may be affected differently [5]. Thus, it is crucial to select the most sensitive HRV measures and parameters corresponding to the underlying pathology and physio-pathological mechanism, to interpret HRV analysis results as correctly as possible. So, our aim in this review is to present the sepsis related HRV measures and parameters by examining the literature and their possible role in the predicting severity and mortality of sepsis. Therefore, provide a hypothesis about which parameters maybe useful for potential use in detecting sepsis patients and predicting the prognosis of the disease.

Methods

PubMed, Web of Science and EBSCO electronic databases were searched for original research articles reporting human studies with sepsis on HRV, published in English language between April 1996 – May 2023. This timeframe was chosen because The Task Force of The European Society of Cardiology published "the guidelines for HRV measurement, interpretation and clinical "in 1996 [5].

Titles, abstracts, and methods of the articles were screened by both authors for relevance based on the inclusion criteria. The articles selected as relevant were examined for further consideration. Other types of articles such as reviews, meta-analyses and letters to editors, conference abstracts were excluded. The studies were included if both authors decided that abstracts of the articles are relevant, if consensus was not reached, full text of the article was reviewed. Disagreements on articles were discussed until consensus was reached in all cases.

Search Terminology

Search terms for this systematic literature review included: "autonomic nervous system" OR "ANS" OR "heart rate variability" OR "HRV" OR "heart rate dynamics" OR "heart rate characteristics" OR "heart rate complexity" OR "heart rate fluctuations" OR "spectral analysis", AND "sepsis" OR "septic shock" OR "septicemia" OR "infection" OR "endotoxemia" OR "inflammation", AND "human", AND "ICU" OR "intensive care" OR "emergency department" OR "ER" OR "hospital".

Selection Criteria and Data Extraction

Studies that possess the following criteria were selected after final review: (1) were published between April 1996 – May 2023; (2) examined ANS activity of human subjects in

hospital settings (3) analyzed ANS activity via time domain and/or frequency domain and/or non-linear analysis; (4) followed the guidelines for valid and reliable HRV measurement proposed by The Task Force of The European Society of Cardiology [5], (5) provide frequency domain analysis results in normalized units since interstudy comparison are not recommended with absolute powers [7].

All selected papers were imported into Mendeley (version 1.19.4, London, UK), where all duplicates were removed. After completion of the article search, a total of 79 articles were selected for further evaluation where full text of the articles was reviewed and 13 of the articles were classified as meeting the criteria for inclusion.

Risk of Bias Assessment

The risk of bias in the included studies was assessed using the Cochrane Collaboration's 'Risk of Bias' tool for randomized controlled trials (RCTs) and the Risk of Bias in Non-randomized Studies - of Interventions (ROBINS-I) tool for observational studies. Two independent reviewers evaluated each study, and any discrepancies were resolved through discussion and consensus.

Statistical Analysis

There was insufficient data included in the studies to perform a meta-analysis, so descriptive analysis was performed. The descriptive analysis was used if there was high clinical or statistical heterogeneity, and the subgroup analysis was used for high and low quality included studies or different interventions. Mean values of each HRV parameter LF (nu), HF (nu), LF/HF, RMSSD, SDNN, HTI, SD1, SD2, DFAα_1, and DFAα_2 was corrected to the sample size of each study and overall means were calculated accordingly. Combined results were presented as means and standard derivations (STDs). Statistical comparisons were performed after sample size correction by Willcoxon signed ranked test.

HRV Measures Used in Included Studies with Sepsis

HRV analysis can be performed using different measures, each of them reveals specific information. Most used HRV analysis measures are time-domain, frequency-domain, and non-linear. In this section, some basic information will be given about these measurements and followed by their possible role (advantages/disadvantages) in early detection, severity and prognosis of sepsis.

Time Domain Analysis

The quantity of HRV detected throughout monitoring durations ranging from 1 minute to >24 hours is quantified by heart rate variability time-domain indices[6]. SDNN, RMSSD, NN50, pNN50, HRV Triangular Index (HTI) and TINN, are some of these indices [5], [6].

SDNN (standard deviation of the time differences between normal sinus beats) is expressed in milliseconds. While the standard for short-term recording is 5 minutes, researchers have proposed ultra-short recording periods ranging from 1 to 4 minutes. The predominant source of variance in short-term resting recordings is parasympathetically-mediated RSA, especially with slow, timed breathing techniques. When recorded over a 24-hour period, the SDNN is the "gold standard" for medical categorization of cardiac risk. Both morbidity and death are predicted by SDNN levels [6].

The number of consecutive NN intervals that differ by more than 50 milliseconds is called NN50. The percentage of consecutive NN intervals that differ by more than 50 milliseconds is known as pNN50. The pNN50 has a strong relationship with PNS activity. However, most researchers prefer the RMSSD to the pNN50 because it often provides a better evaluation of RSA (particularly in older subjects). RMSSD is the root mean square of consecutive deviations between normal heartbeats calculated by first calculating each subsequent time difference between heartbeats in milliseconds. Before getting the square root of the total, each of the numbers is squared and the result is averaged. The RMSSD is the key time-domain metric used to assess the vagally mediated changes seen in HRV. It reflects the beat-to-beat variance in HR. The RMSSD and the non-linear metric SD1 correlates highly. RMSSD readings over a 24-hour period are highly associated with pNN50 and HF power. HTI is a geometric measure that estimates the integral of the density of the RR interval histogram divided by its height and TINN represents the baseline width of the NN interval histogram [6].

Frequency Domain Analysis

Frequency Domain Analysis of HRV is a complex analysis technique that shows how much of a signal lies within certain frequency bands. Researchers has identified certain frequency bands that correlate with certain physiological phenomenon. Most investigated bands in human HRV analysis are ultra-low frequency (ULF), very-low frequency (VLF), low frequency (LF) and high frequency (HF) bands, and LF/HF ratio. ULF band requires at least 24 hours of a recording period and which is not easy to obtain [19]. However there is not any agreement on the mechanism(s) that generate ULF power, experimental evidences suggest that very slow acting biological mechanisms such as circadian rhythms may be the primary driver of the ULF band [20]. VLF band is generated by the activation of afferent sensory neurons in the heart and may be modulated by stress responses [21], [22], [23]. This activation of afferent sensory neurons stimulates various levels of the feedback and feed-forward reflex mechanisms in the heart's intrinsic nervous system, also extrinsic cardiac ganglia in the thoracic cavity, and spinal cord [6]. Whereas LF, which is previously called the baroreceptor range since it mainly reflects baroreceptor activity [24], may be effected by both the PNS and SNS, and baroreceptors [5], [25], [26], [27]. HF band reflects parasympathetic or vagal activity, which is also called the respiratory band since it corresponds to the variations of HR related to the respiration [24]. LF/HF ratio is often proposed to reflect sympatho-vagal balance since the LF component is effected by modulation of the both the sympathetic and parasympathetic branches of ANS and the HF component reflects parasympathetic activity [5].

Normalized HRV parameters (LFnu, HFnu) can be computed from the raw values of LF or HF divided by the spectral total power (generally LF + HF). The obtained value of this expressed as a percentage [7]. These variables are of particular interest in comparing the articles since normalized values ensure interpretability between studies. Because the proportional changes of frequency bands can be showed as roughly equivalent regardless of the used spectral method [7]. On the other hand, the use of normalized units may cause a series of significant limitations. Most important one is normalized LF band (LFnu) and normalized HF band (HFnu) are equivalent, as LFnu = 1-HFnu. This means that calculations may not be duplicated, since LFnu calculations are linearly related (i.e., identically calculational) to HFnu [28]. Including both LFnu and HFnu values doesn't provide any additional significance rather than only one parameter (LFnu or HFnu), and change in one parameter is identical to change in the other parameter [7].

Non-linear Analysis Methods

The cardiovascular system has complex dynamics as with all other biological systems. Goldberger hypothesized that a decrease in variability and complexity may be a sign of existence of pathological conditions [29]. Heart rate is one of the most important dynamic parameters affected by neural, hormonal and hemodynamical alterations arising from other systems and organs.

The term of nonlinearity is used to describe where there is not a linear line or a direct relationship between variables. Namely, a relationship between variables cannot be plotted as a straight line. Non-linear measurements reveal the uncertainty of a time series, which results from the complexity of the mechanisms that regulate the heart rate.

Some pathologies like myocardial infarction (MI), diabetes and mood disorders may decrease complexity [17], [30]. In this section we reviewed the most investigated non-linear measurements; Poincaré Plot parameters SD1, SD2, SD2/SD1, Detrended Fluctuation Analysis (DFA) exponents DFAα_1 and DFAα_2.

Poincaré Plot

The analysis of the Poincaré plot can be performed by drawing an ellipse to the plotted points. The standard deviation (hence SD) of the distance of each point from the y = x axis (SD1), determines the width of ellipse and the standard deviation of each point from the y=x+ average R–R interval (SD2) determines the length of the ellipse [6]. SD1 considered correlating with blood pressure changes, and power in the LF and HF, and total power of short-term recordings of 5 minutes [31], [32]. SD2 thought to reflect LF band power and baroreflex sensitivity [33], [34], [35]. SD2/SD1 is the ratio of SD2 to SD1. SD2/SD1 considered being the analog of LF/HF ratio from frequency domain HRV analysis [36], [37].

Detrended Fluctuation Analysis

DFA extracts the self-similarity (correlations) between consecutive RR intervals. DFA calculates the scaling exponents (short-term, DFAα_1 and long-term, DFAα_2) from the time series and reflects fractal correlation characteristics of complex dynamic heart rate series [6]. While the DFAα_1 proposed to reflect the baroreceptor reflex, DFAα_2 thought to reflect the regulatory mechanisms that limit fluctuation of the beat cycle [38].

Results

Nine studies were included, with a total of 1453 patients, weighted mean age was 64.24 years and 53.9% were male [39], [40], [41], [42], [43], [44], [45], [46], [47]. Table 1 shows the main characteristics of all studies, such as sample size, mean age, study settings, and significant HRV findings ($p \le 0.05$).

The included studies evaluated the following HRV parameters in the time domain: RMSSD, SDNN, NN50, pNN50, TINN; frequency domain: Normalized Low Frequency Power (LFnu), Normalized High Frequency Power (HFnu), ratio of LFnu to HFnu (LFnu/HFnu), Total Power (TP); nonlinear methods: Poincare Plot standard deviation 1 (SD1), Poincare Plot standard deviation 2 (SD2), ratio of SD1 to SD2 (SD1/SD2), Short-term (α_1) and long-term (α_2) fractal scaling coefficients from Detrended Fluctuation Analysis (DFA). Significant HRV findings are given in Table 1.

Of the studies included all of them performed frequency domain analysis, four of them also performed nonlinear analysis (Table 1). Seven out of nine studies were performed at emergency departments and two were in intensive care units of the hospitals. 6 studies compared parameters between survivors and non-survivors [40], [41], [42], [43], [44], [45], 3 studies compared between different severity levels of sepsis [45], [46], [47].

Table 2 shows combined results of LF (nu), HF (nu), LF/HF, RMSSD, SDNN, HTI, SD1, SD2, DFAα_1, and DFAα_2 parameters of the selected studies comparing the parameters between survivors and non-survivors of the sepsis [41], [43], [44], [45]. LF (nu), LF/HF, SD2, DFAα_1, and DFAα_2 were lower in the non-survivor whereas HF (nu), RMSSD, SDNN, HTI, and SD1 were higher in non-survivor group.

Discussion

In this review we found that LF (nu), LF/HF ratio, SD2, DFAα_1, and DFAα_2 were decreased and HF (nu), RMSSD, SDNN, HTI and SD1 were increased in non-survivors of the sepsis patients compared to those who survived. This finding suggests that monitoring these parameters HRV could be a valuable technique for predicting the probability of death in sepsis. However, there was no convincing indication of a link between HRV parameters and sepsis severity in the literature which may be attributed to few numbers of studies comparing the HRV parameters according to the sepsis severity.

Table 1.						
First Author (Year)	**Sample Size (n)**	**Sex (% of male)**	**Mean Age (overall)**	**Study Setting**	**Study Groups**	**Significant HRV findings**
Arbo et al. (2020) [34]	72	61.1	60.4 ± 20.3	Emergency Department	1. Sepsis 2. Severe Sepsis 3. Septic Shock	Decreased LF (nu), Increased HF (nu), Decreased LF/HF ratio correlate with the severity of the sepsis.
Bonjorno et al. (2019) [35]	60	58.3	50.3 ± 13.0	Intensive care unit	1. Survivor 2. Non-survivor	Higher HTI and SD1 in surviving group.
Chen et al. (2008) [36]	132	47.0	66.7 ± 10.2	Emergency Department	1. Survivor 2. Non-survivor	Lower SDNN, Total Power (nu), LF (nu)/HF (nu) in non-survivors and higher HF (nu) in survivors.
Kim et al. (2014) [42]	189	56.1	57,5 ± 17,6	Emergency Department	1. Severe sepsis patients admitted to ICU 2. Sepsis patients admitted to general ward, 3. Sepsis patients discharged within 24 hours 4. Healthy volunteers.	Total Power and LF (nu) were decreased in all groups compared to healthy individuals. HF (nu) was decreased in severe sepsis and sepsis patients admitted to general ward groups compared to healthy individuals.
Papaioannou et al. (2009) [37]	45	57.8	57.8	Intensive care unit	1. Survivor 2. Non-survivor	CRP negatively correlates with SDNN, LF nu, LF/HF and positively with HF (nu) and SD1/SD2 ratio. SDNN and HF are independent predictors of severity of sepsis.
Pong et al. (2019) [38]	364	49.2	67.1 ± 16.1	Emergency Department	1. No 30 day in-hospital mortality 2. 30 day in-hospital mortality	Increased SDNN, RMSSD, NN50, pNN50, TINN, HF (nu), SD1, and decreased LF (nu) in 30 day in-hospital mortality group.
Prabhakar et al. (2019) [39]	343	50.7	67.5 ± 15.6	Emergency Department	1. Survivor 2. Non-survivor	Increased SDNN, RMSSD, TINN, HFnu, SD1 and decreased LF/HF, DFAα1, DFAα2, LF nu in non-survivors group.
Samsudin et al. (2018) [40]	214	50.5	66.9 ± 15.6	Emergency Department	1. Survivor 2. Non-survivor	Increased SDNN, RMSSD, TINN HF (nu), SD1 and decreased DFAα1, DFAα2 and LF (nu) in non-survivors.
Tang et al. (2009) [41]	34	Not provided	52.9	Emergency Department	1. Systemic inflammatory response syndrome (SIRS) 2. Severe Sepsis 3. Healthy volunteers.	LF (nu) was decreased in severe sepsis patients.

Table 2.							
	Survivors			**Non-Survivors**			
	Mean	**SD**	**n**	**Mean**	**SD**	**n**	**P Value**
LF (nu)	43,2864	24,63906	847	33,09029	24,7233	206	**0,02443**
HF (nu)	45,20782	24,23509	847	63,38981	24,4311	206	**0,02402**
LF/HF	2,762645	3,785706	673	1,521084	4,33735	166	**0,01041**
RMSSD	24,3383	33,82116	847	43,07961	49,0573	206	**0,02492**
SDNN	21,38553	22,22373	847	32,16214	32,9631	206	**0,02048**
HTI	4,8	2,7	21	6,5	3,15714	39	**0,01142**
SD1	19,34021	27,3337	746	27,45447	30,9277	235	**0,02506**
SD2	25,7	26,7	174	9,287356	37,1	40	**0,00154**
DFAα1	0,683993	0,389328	551	0,517949	0,28654	156	**0,00561**
DFAα2	0,955724	0,40811	725	0,683163	0,40357	196	**0,03295**

The importance of the autonomic nervous system in the complicated mechanisms involved in sepsis physiopathology has piqued researchers' curiosity. Vagus nerve stimulation, for example, is known to stimulate cortisol hormone release [48]. And the primary vagal neurotransmitter, acetylcholine, has an anti-inflammatory impact, reducing the release of cytokines including TNF, IL-1beta, IL-6, and IL-18 and preventing cytokine storm and septic shock [49].

Based on our findings, some studies evaluated if the HRV analysis, a noninvasive method to evaluate the autonomic function could be useful to predict outcome in septic patients. And the findings of these studies suggest that HRV monitoring may be beneficial, especially when combined with the frequently used scoring systems such as Sequential Organ Failure Assessment (SOFA), Quick SOFA (qSOFA), modified SOFA (mSOFA) and Acute Physiology and Chronic Health Evaluation (APACHE) II scores. HRV analysis can be performed using simple and non-invasive methods even with the smart watches available on the market. So, these features of HRV analysis makes HRV one of the most widely used methods and it is appropriate for use in emergency departments, general wards, and ICU settings.

In this present review we found that non-survivors have significantly lower LF (nu), LF/HF ratio, SD2, DFAα_1, and higher DFAα_2 and HF (nu), RMSSD, SDNN, HTI and SD1. Hatsy et al. (2021) conducted a study in to determine whether decreases in SDNN predict elevations in CRP in COVID-19 patients [12]. They found with a 90.9 percent positive predictive value, significant declines in SDNN predicted increases of CRP in the following 72 hours. Natarajan et al. (2020) found that RMSSD was decreased significantly before the onset of COVID-19 symptoms [50]. Aragón-Benedí et al. (2021) found that lower SDNN and HF (nu) are associated with a poor prognosis, higher mortality, and higher IL-6 levels in COVID-19 patients [51]. Similarly, Krishnan et al. (2021) found that SDNN, RMSSD, LF, HF, and DFA parameters were associated with Sepsis-related acute respiratory failure patients [52]. Kenig and Ilan (2019) study on sepsis treatment proposed a predictive model for severe sepsis that included mean RR interval and DFAα_2 alongside other clinical parameters [53]. This model aimed to enhance the efficacy of sepsis treatment by incorporating DFA analysis as a predictive component. Furthermore, a case report monitoring HRV in a patient with terminal phase sepsis observed a reduction in LF and HF prior to death, indicating HRV alterations in the progression of sepsis [54]. Even though the studies with experimental animals are not included in this review, SDNN and RMSSD replicates decreasing trends previously observed for a peritonitis-induced sepsis model in pigs [55].

HRV has emerged as a potential marker for monitoring sepsis progression. Brown et al. (2013) have shown that changes in HRV, such as loss of complexity or alterations in sympathovagal balance, can herald the onset of sepsis and predict the development of shock and organ dysfunction in patients with severe sepsis [56]. Additionally, continuous monitoring of HRV in adult patients has been associated with reduced HRV coinciding with the onset of sepsis [57].

Several HRV parameters have been reported to be lower in non-surviving septic patients among all HRV parameters investigated to predict risk of mortality in sepsis. More research is needed to determine which HRV parameters are most beneficial in predicting mortality in sepsis and what cut-off values should be employed for each parameter. In the a few studies on predictive value of HRV analysis in sepsis cases SDNN stood out in them along with RMSSD and HF (nu).

Sepsis can be predicted using longitudinally collected HRV data from a regularly used commercial wearable devices such as Apple Watch, FitBit, and Polar. Significant changes in HRV parameters, especially RMSSD, SDNN, HTI, LF (nu), HF (nu), LF/HF ratio, SD1, SD2, DFAα_1, and DFAα_2 are candidate parameters for the identification of sepsis. More studies need to evaluate the predictive power of these parameters by confirming the cases with laboratory tests.

Conclusion

In the studies included in this review, several HRV values are altered in non-surviving septic patients. SDNN, RMSSD, SDNN, HTI, LF (nu), HF (nu), LF/HF ratio, SD1, SD2, DFAα_1, and DFAα_2 appear to be related with mortality in patients with sepsis outcome. Therefore, it can be concluded that monitoring these parameters for the early detection of sepsis may be beneficial. Larger and well-designed research are needed to corroborate on these conclusions.

Limitations

The low quantity and quality of papers included in this systematic review are the primary limitations. Thus, although it may be concluded that monitoring the reduction of HRV and these stood out parameters may be linked to sepsis detection and severity more studies are need to determine the best methodology and cutoff points that can be used.

Ethics

Authorship Contributions

Concept: H.K., Data Collection and Process: H.K., Analysis or Interpretation: H.K., H.F.M., Literature Search: H.K., H.F.M., Writing: H.K., H.F.M.,

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