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INVITED REVIEW / DAVETLİ DERLEME

Electrocardiogram and heart rate variability assessment in patients with common autoimmune diseases: a methodological review

Yaygın otoimmün hastalığı olan hastalarda elektrokardiyogram ve kalp hızı değişkenliği değerlendirmesi: Metodolojik bir inceleme

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Summary– The aim of this article was to summarize current knowledge about the potential clinical utility of electrocardiogram (ECG) and heart rate variability (HRV) measures in patients with 4 common autoimmune diseases (ADs): rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), Behcet's disease (BD), and systemic sclerosis (SSc). A search was conducted of the PubMed, Embase, and Scopus databases using terms and a controlled vocabulary associated with these ADs, ECG, and HRV. The available, full-text articles published in English were considered. In all, 20 publications that examined the direct effect of these diseases on the heart were selected according to a systematic review protocol. Time-frequency domain analysis revealed that HRV parameters were lower in patients with the selected ADs in comparison with control groups. An increased QT dispersion and heart rate corrected QT, which are well-known as risk factors for sudden cardiac death, were observed in the patient group. In some studies, a correlation was seen between the duration of the disease and its activity, while others did not report such an association. Heart rate turbulence parameters were also examined. Turbulence onset was increased in SLE and SSc patients, while the turbulence slope was decreased in SLE patients. There was no significant change in these parameters in BD patients. Patients with ADs demonstrate abnormal HRV and ECG parameters, which indicates an autonomic cardiac functional impairment. Measurement of these parameters can be a useful clinical tool in the diagnosis and prediction of some disorders in patients with ADs. Both of these signals can provide helpful information for physicians to trace the efficacy of prescribed medicines.

Özet– Bu makalenin amacı, dört yaygın otoimmün hastalığı olan hastalarda elektrokardiyogram (EKG) ve kalp hızı değişkenliği (HRV) ölçümlerinin potansiyel klinik faydası hakkında güncel bilgileri özetlemektir: Dahil edilen hastalıklar içerisinde romatoid artrit (RA), sistemik lupus eritematozus (SLE), Behçet hastalığı (BH) ve sistemik skleroz (SSc) yer almaktadır. Otoimmün hastalıklar, EKG, HRV ile ilişkili terimler kontrollü bir kelime haznesi kullanılarak PubMed, Embase ve Scopus veritabanlarında arama yapıldı. İngilizce olarak yayınlanan tam metin ve makaleler dikkate alındı. Hastalıkların kalp üzerindeki doğrudan etkisini inceleyen 20 yayının hepsi sistematik bir inceleme protokolüne göre seçildi. Zaman frekansı alan analizi, seçili otoimmün hastalığı olan hastalarda HRV parametrelerinin kontrol gruplarına göre daha düşük olduğunu ortaya koydu. Hasta grubunda, ani kardiyak ölüm için risk faktörleri olarak bilinen QT dispersiyonu ve kalp hızına göre düzeltilmiş QT (QTc) artışı gözlendi. Bazı çalışmalarda, hastalığın süresi ile aktivitesi arasında bir korelasyon görülürken, diğerleri için böyle bir ilişki rapor edilmedi. Kalp hızı türbülans parametreleri de incelendi. SLE ve SSc hastalarında türbülans başlangıcı yüksekken, SLE hastalarında türbülans eğimi azdı. BH hastalarında bu parametrelerde anlamlı bir değişiklik yoktu. Otoimmün hastalığı bulunanlar, otonomik kalp fonksiyon bozukluğunu gösteren anormal HRV ve EKG parametreleri gösterir. Bu parametrelerin ölçümü, otoimmün hastalığı olgularında, bazı bozuklukların tanı ve tahmininde faydalı bir klinik araç olabilir. Bu sinyallerin her ikisi de doktorlara reçeteli ilaçların etkinliğini izlemeleri için yardımcı bilgiler sağlayabilir.

The human immune system consists of complex and essential components designed to circulate throughout the body to defend against and eliminate harmful organisms and materials. Autoimmune diseases (ADs) occur when the body's immune system goes awry and mistakenly attacks organs, tissues, and

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joints. So far, more than 100 ADs have been identified. Some of these diseases, such as rheumatoid arthritis (RA), type 1 diabetes mellitus, multiple sclerosis, systemic lupus erythematosus (SLE), ulcerative colitis, Crohn's disease, and systemic sclerosis (SSc) are commonly known, but many others are less often seen and more challenging to diagnose.[1,2] The causes of ADs are mostly unknown. However, an interaction between genetic and environmental factors is evident in the occurrence of these diseases.[3–5]

There is significant behavioral variation among ADs. In general terms, ADs can be divided into 2 broad types: organ-specific and systemic. In organ-specific disorders, the autoimmune process primarily targets a single organ. Some of the disorders that fall into this category include Hashimoto's thyroiditis, type 1 diabetes, and pernicious anemia. In systemic diseases, the autoimmune activity is widely spread throughout the body. Examples include Behcet's disease (BD), SLE, RA, and dermatomyositis.[6] The classification of ADs and common diseases in each class are illustrated in Figure 1.

Cardiovascular disease (CVD) and ADs are among the most common causes of morbidity and mortality in developed countries.[7,8] Research has shown that the severity and probability of developing many CVDs, including atherosclerosis, myocardial infarction, myocarditis, cardiomyopathy, heart failure, and sudden cardiac death (SCD), was greater in patients with ADs.[9,10] There is substantial evidence that ADs play an essential role in the pathogenesis of inflammatory heart diseases, such as accelerated atherosclerosis, acute coronary syndromes, and myocarditis.[11–14]

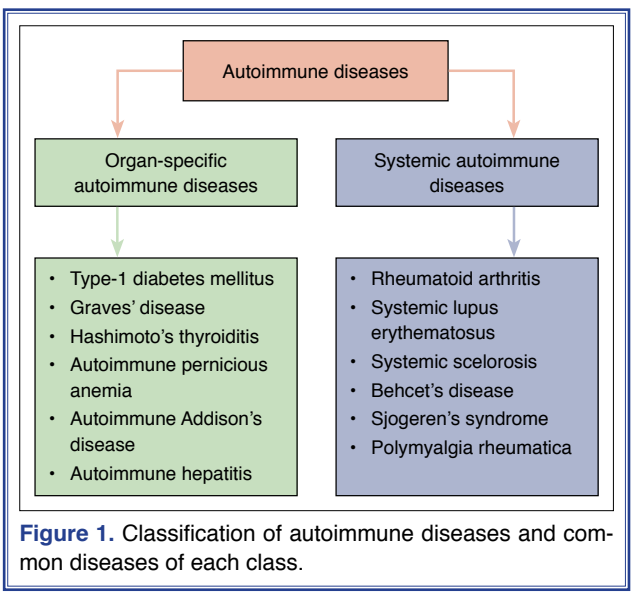

Figure 1. Classification of autoimmune diseases and common diseases of each class.

Abbreviations:

AD	*Autoimmune disease;*
ANS	*Autonomic nervous system;*
BD	*Behcet's disease*
CVD	*Cardiovascular disease*
ECG	*Electrocardiogram*
ESR	*Erythrocyte sedimentation rate*
HF	*High-frequency*
HRT	*Heart rate turbulence*
HRV	*Heart rate variability*
JTc	*Corrected JT interval*
JTc-d	*Corrected JTd*
JTd	*JT dispersion*
LF	*Low-frequency*
NN	*Normal-to-normal*
nU	*Normalized units*
PANS	*Parasympathetic nervous system*
pNN50	*Percentage of pairs of adjacent NN intervals differing by more than 50 milliseconds*
PVC	*Premature ventricular contraction*
QTc	*Corrected QT interval*
QTd	*QT dispersion*
RA	*Rheumatoid arthritis*
RMSSD	*Root mean square of the successive differences of NN intervals*
SAECG	*Signal averaged electrocardiography*
SANS	*Sympathetic autonomic nervous system*
SCD	*Sudden cardiac death*
SD	*Standard deviation*
SDNN	*Standard deviation of all NN intervals*
SDNNI	*Mean of the 5-minute standard deviations of NN intervals*
SDSD	*Standard deviation of differences between adjacent NN intervals*
SjS	*Sjögren's syndrome*
SLE	*Systemic lupus erythematosus*
SPECT	*Single-photon emission computed tomography*
SSc	*Systemic sclerosis*
Tc-99m MIBI	*Technetium sestamibi*
TO	*Turbulence onset*
TS	*Turbulence slope*
ULF	*Ultra-low-frequency*
VLF	*Very-low-frequency*

Cardiovascular and neurological manifestations can occur in patients with ADs. The autonomic nervous system (ANS) is mainly characterized by its regulatory role adjusting the function of different parts of the body. The ANS is divided into the sympathetic autonomic nervous system (SANS) and the parasympathetic nervous system (PANS), which control complementary activities. The ANS provides a connection between the brain and certain parts of the body, such as the heart, liver, sweat glands, skin, and even the interior muscles of the eye.[15] Leading causes of death in patients with ADs include an imbalance in the SANS, the PANS becoming overwhelmed or lost, and the increased risk of CVD.[16,17]

Rheumatological disorders can directly affect the myocardium, heart valves, pericardium, conduction, and vascular systems. While cardiovascular manifestations may be mild and clinical in patients with an AD, the same fact can significantly increase mortality.

Therefore, early diagnosis and treatment are important.[18]

Cardiac function and the progression or improvement of heart-related diseases are assessed using various methods of imaging and signal processing. A glimpse at the research on signal processing shows that behavioral and functional analysis of the heart is primarily based on electrocardiogram (ECG) and heart rate variability (HRV) signals. Each of these may be used individually, depending on the nature of the disease and the subject matter; however, the combined results can also be helpful. Examination of ECG morphology can reveal whether an increase in HRV values is due to a problem like atrial fibrillation.[19] ECG has the potential to detect cardiovascular involvement due to an AD, including rhythm disturbances and underlying repolarization abnormalities.[20–22]

Perhaps the simplest and most basic method of evaluating ECG and HRV is to extract their properties in the time domain. In a continuous ECG, each QRS complex is detected, and the normal-to-normal (NN) interval, which is a result of sinus node depolarization, is measured. Additional features based on the distance between other QRS complex waves, their amplitudes, and statistical characteristics can be used to obtain additional information from the ECG signal.[23]

The analysis of HRV is another non-invasive method to assess the function of the ANS used in various clinical conditions, such as stress recognition, heart attack, epileptic seizure classification and prediction, mortality prediction, etc.[24–30] HRV reflects the balance between the SANS and PANS.[31,32] HRV may be analyzed based on short-term (~5 minutes), ultra-short-term (<5 minutes), or long-term 24-hour recordings. Therefore, different tools, such as statistical analysis, time-domain analysis, frequency-domain analysis, nonlinear processes, and geometric characteristics, are used in various applications.[33–36]

Time-domain parameters extracted from HRV data quantify the variation in the period between successive heartbeats. Frequency-domain parameters estimate the distribution of absolute or relative power of 4 frequency bands: ultra-low-frequency (ULF), which is less than 0.003 Hz; very-low-frequency (VLF), which is limited to 0.0033–0.04 Hz; low-frequency (LF), which comprises the band of 0.04–0.15 Hz; and high-frequency (HF), which is the range of 0.15-0.40 Hz. Each of these frequency bands represents the performance of 1 or more activities controlled by the SANS, PANS, or both.[19]

To extract non-linear properties, one of the most commonly used methods in the analysis of HRV is the Poincaré plot. It is a geometric technique used to represent the dynamics of HRV. Each RR interval is plotted as a function of the previous RR interval, which makes it possible to evaluate the pattern of points qualitatively through the computation of SD indexes.[37] Usually, an ellipse can be fit to the scatterplot, and SD1 describes the variablility perpendicular to the line-of-identity, while SD2 represents the SD of the Poincaré plot points along the line-of-identity.[38] SD1 represents short-term HRV and long-term changes in the HRV are denoted by SD2.

Another indicator used to evaluate HRV is heart rate turbulence (HRT). HRT consists of 2 parameters: turbulence onset (TO), which reflects the immediate PANS-mediated response of the heart rate to the loss of cardiac output associated with a premature ventricular contraction (PVC), and turbulence slope (TS), which captures the slope of the return to baseline heart rate after a PVC, and is believed to reflect the baroreflex function.[19] This review is a summary of current knowledge about the scientific findings and methodological approaches to the diagnosis of ADs based on ECG and HRV measures.

METHODS

Study selection

Considering the broad behavioral patterns of ADs, 4 were chosen for this review from among the systemic diseases that have a greater history of affecting the heart and the ANS. Studies were selected that investigated ECG and HRV results in patients with the ADs of RA, SLE, BD, and SSc. Case series and letters to the editor were not included. A total of 497 records (including duplicates) were identified in the first step of the search. Several studies have investigated the effects of medicines, antibodies, and changes to lifestyle (smoking, exercise, etc.) on the ECG and HRV of AD patients. However, many of these articles were cross-sectional or longitudinal studies, which are not suited to the purpose of this article. Therefore, they were omitted. In all, 20 articles were summarized for

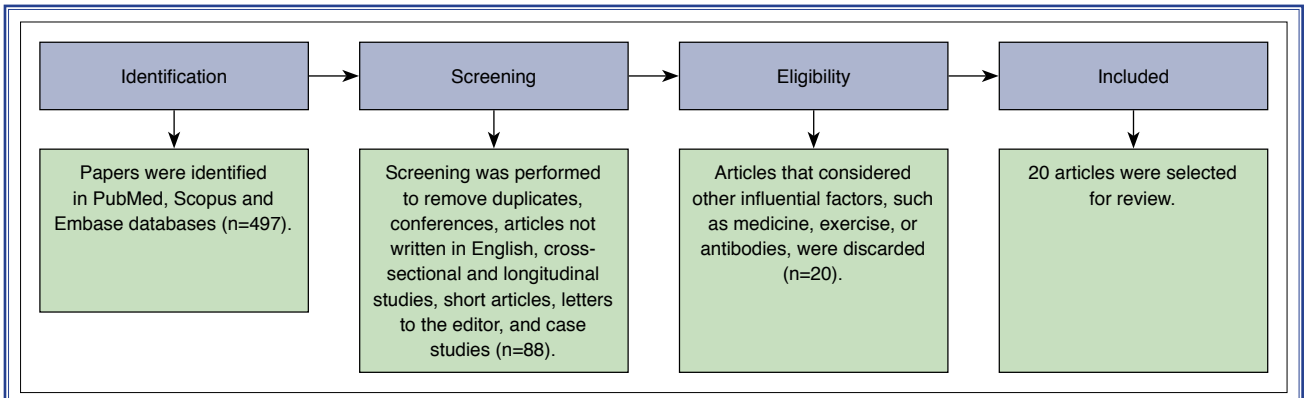

Figure 2. Flowchart of the method used to select articles for this review.

this review. Selected articles examined the direct effect of the AD on the heart.

Details of the information sources, search strategy, and methodology are shown in Figure 2. The length of the ECG recording and the number of leads used varied among the studies. While it is preferable to compare records using similar conditions, due to the limited number of articles for each of the ADs discussed, all of the cases were included.

The studies were organized under the following headings: study (first author and year of publication), group (characteristics of the patients and controls, if applicable), method (ECG, HRV, and HRT parameters assessed) and results (comparison of extracted features in patients and controls, relationships between HRV and other studied factors).

Data items and collection

Definitions for all ECG, HRV, and HRT measurements included in the review are shown in Table 1.

OVERVIEW OF SELECTED STUDIES

This section provides a brief explanation of each AD selected and a discussion of related articles examining changes in ECG, HRV, and HRT. A summary of the findings of the studies considered is presented in Table 2.

Rheumatoid arthritis

RA is a systemic AD known for inflammation and pain in the joints, but it can also affect other parts of the human body, including the eyes, heart, lungs, and brain. A large number of people around the world face a type of rheumatic disease like RA.[38] RA is a chronic, long-term illness that differs from 1 patient to another and has no specific pattern. The incidence varies and can be very unpredictable. The disease usually begins slowly, without any significant symptoms. It may take a few weeks or months before an immune rebound passes through the body without the individual being aware of it.

Patients with RA often have atherosclerosis, which leads to an increased risk of death. However, the mechanism of the complications of the disease on the heart, disorders, and arrhythmias of the heart is still not fully understood, and the processes that cause atherosclerosis in this case are mainly unknown. What is certain is that progression of the disease and its inflammatory nature lead to the formation of vascular plaques of atherosclerosis.[40–42]

Göldeli et al.[43] examined dispersion of ventricular repolarization values, which are utilized to assess the risk for ventricular arrhythmias in patients with RA. A total of 42 patients with RA and 42 healthy, age-matched control subjects were studied. ECG variables of QT, QTc, and QTd were calculated from 12-lead ECG recordings. The results showed that increases in QTd indicated regional inhomogeneity of ventricular repolarization in patients with RA.

Alkaabi et al.[44] measured the extent of subclinical atherosclerosis in patients with RA compared with controls to evaluate potential vascular risk factors. Forty RA patients were compared with an age- and sex-matched control group of the same size. The QTd was evaluated along with some other physiological traditional risk factors, such as high blood pressure, blood sugar, lipids, and steroid use. An increased QTd in RA patients indicated a greater risk of subclinical vascular disease.

Table 1. Electrocardiogram, heart rate variablility, and heart rate turbulence measurements and the physiological meaning

Variable	Definition and characteristics	Physiological meaning
Electrocardiogram		
QT interval	The time interval from the start of the Q wave to the end of the T wave	Shows the duration of ventricular depolarization and subsequent repolarization
QTc	Corrected QT interval Estimates the QT at a standardized heart rate of 60 bpm	Prolongation of QTc is known as a risk factor for SCD
QTd	QT dispersion Difference between the most extended (QTmax) and the shortest (QTmin) QT intervals	Reflects regional differences in ventricular repolarization. Increased QTd is known as a risk factor for SCD
QTc-d	Corrected QT dispersion QTc-d=Max QTc-Min QTc	Reflects inhomogeneity of repolarization and is a measurable index of ventricular arrhythmia risk
JT	The interval from the J point (i.e., the end of QRS) to the end of the T wave	Reflects the transmural dispersion of repolarization
JTc	Corrected JT interval JTc=QTc-QRS duration	Reflects the duration of ventricular repolarization
JTd	JT dispersion JTd=Max JT-Min JT	Prolonged JTd is a risk factor for arrhythmic cardiac death
JTc-d	Corrected JT dispersion JTc-d=Max JTc-Min JTc	Prolonged JTc-d is a risk factor for arrhythmic cardiac death
Heart rate variability		
SDNN (ms)	The SD of all NN intervals	An estimate of overall HRV
SDNNI (ms)	SDNN index The mean of the 5-minute SD of NN intervals calculated over 24 hours	Measures variability due to cycles shorter than 5 minutes
SDANN (ms)	The SD of the average NN intervals, measured for 5-minute segments during a 24-hour recording	Primarily reflects total circadian rhythms and physical activity
SDSD (SD) (ms)	The SD of differences between adjacent NN intervals	Reflects PANS activity
RMSSD (ms) (MSSD)	The root mean square of differences of successive NN intervals	Reflects PANS activity
pNN50 (%)	Percentage of pairs of adjacent NN intervals differing by more than 50 milliseconds	Reflects PANS activity
HRV triangular index	Total NN intervals number/height of the histogram of all NN intervals	An estimate of overall HRV without requiring detailed beat-by-beat scanning
TP $(ms)^2$	Total power Usually log-transformed for parametric statistical analysis	The variance of all NN intervals
ULF $(ms)^2$	Ultra-low-frequency power Usually log-transformed for parametric statistical analysis	Reflects circadian and ultradian rhythms
VLF $(ms)^2$	Very-low-frequency power Usually log-transformed for parametric statistical analysis	Reflects PANS activity and the effect of the renin-angiotensin system on heart rate. VLF power band represents HRV between 0.003 and 0.04 Hz

Table 1. Electrocardiogram, heart rate variablility, and heart rate turbulence measurements and the physiological meaning *(continuation)*

Variable	Definition and characteristics	Physiological meaning
LF $(ms)^2$	Low-frequency power Usually log-transformed for parametric statistical analysis	Often reflects the combination of SANS and PANS activity, including baroreflex functioning. LF power band represents HRV between 0.04 and 0.15 Hz
HF $(ms)^2$	High-frequency power Usually log-transformed for parametric statistical analysis	Reflects PNS activity. Reflects respiratory sinus arrhythmia-derived heart rate changes. HF power band represents HRV between 0.15 and 0.4 Hz. HF band is different in infants and children due to higher respiratory rates
LF/HF ratio	Low-frequency power/high-frequency power ratio	Often reported as reflecting the SANS/PANS or sympathovagal balance
LF (nU)	Normalized low-frequency power	Reflects SANS activity, but the interpretation of this index is controversial
HF (nU)	Normalized high-frequency power	Reflects PANS activity
SD1	Standard deviations of the Poincaré plot	Reflects an estimate of short-term HRV
SD2	Standard deviations of the Poincaré plot	Reflects an estimate of long-term HRV
Heart rate turbulence	Calculated from average of at least 5 PVCs; may be assumed to be healthy if <5 PVCs observed in 24-hour Holter monitoring	Based on heart rate responses to PVCs, which represent a sort of stress test for the cardiovascular system, as PVCs are associated with a fall in cardiac output for that beat
TO (%)	Turbulence onset Percentage change in the 2 normal NN intervals after a PVC when compared to the 2 immediately preceding NN intervals; normal if 0	Reflects the ability of the PNS to increase heart rate in immediate response to the loss of cardiac output with the PVC (sinus rhythm acceleration after PVC)
TS (ms/beat)	Turbulence slope The threshold for an abnormal value of TS, associated with increased risk of cardiovascular events, is population dependent (usually <2.5 ms/beat among cardiac patients).	Based on the slope of the recovery of heart rate to baseline and is believed to reflect slower-acting SNS (sinus rhythm deceleration after PVC)

NN: Normal-to-normal; nU: Normalized units; PANS: Parasympathetic nervous system; PVC: Premature ventricular contraction; SANS: Sympathetic autonomic nervous system; SCD: Sudden cardiac death.

Pirildar et al.[45] assessed the affect of secondary Sjögren's syndrome (SjS) on QTd and QTc in patients with RA. The study included 58 patients with RA divided into 2 groups according to the presence of secondary SjS and 29 healthy subjects as the controls. All of the patients demonstrated significantly longer QTd and QTc values, and those of RA patients with secondary SjS were substantially longer than those without SjS.

Evrengül et al.[46] examined the difference in HRV of patients with RA in comparison with the healthy population. They performed a short-term, time-frequency analysis of HRV in 42 patients with RA and 44 healthy, matched controls. Although the patients displayed a higher pNN50 and RMSSD than healthy individuals, the differences were not statistically significant. In the frequency-domain analysis, reduced HF and higher LF values were seen in the RA patients. Moreover, the LF/HF ratio, which represents sympathovagal modulation, was significantly increased in the patient group. Briefly, it could be concluded that an increase in sympathetic control of the heart rate is demonstrated in patients with RA.

Anichkov et al.[47] investigated HRV parameters in patients with RA and assessed their relationship to disease characteristics. Twenty-three female patients with RA and without CVD and 23 age- and gender-matched healthy controls were evaluated. The param-

Table 2. Electrocardiogram, heart rate variability, and heart rate turbulence findings in patients with autoimmune diseases in the studies reviewed

Study (type)	Group	The method, and ECG, HRV, and HRT parameters assessed	Results of measurements
Rheumatoid arthritis			
Göldeli et al.[43]	n=42 RA (32 F; age: 44±4.8 years) n=42 healthy (age-matched)	12-lead ECG and 24-h ambulatory ECG recordings: QT, QTc, JT, and JTc (QTd, QTc-d, JTd, and JTc-d)	↑QTd compared with healthy group
Alkaabi et al.[44]	n=40 RA n=42 healthy (age-matched)	ECG: QTd	↑QTd compared with healthy subjects
Pirildar et al.[45]	n=58 RA (divided into 2 groups according to presence of secondary SjS) n=29 healthy (age-matched)	ECG: QTd and QTc	↑QTd and QTc vs healthy group ↑QTd and QTc in RA patients with secondary SjS vs those without SjS
Evrengül et al.[46]	n=42 RA n=44 healthy (age-matched)	HRV parameters: pNN50, RMSSD, LF, HF, LF/HF ratio	↑pNN50 and RMSSD vs healthy subjects ↓HF, ↑LF, and ↑LF/HFin RA patients There was an increase in sympathetic control of the heart rate in patients with RA.
Anichkov et al.[47]	n=23 RA (all F; age: 48±7 years) n=23 healthy (age-matched)	24-h Holter ECG recordings HRV parameters: Mean NN, SDNN, RMSSD, SDANN, SD1, SD2, SD1/SD2 ratio	↓SD2 compared with healthy group SD1 significantly correlated only with disease duration. In RA patients, reduced HRV was independently associated with high disease activity and smoking.
Anichkov et al.[48]	n=90 RA (all F) n=30 healthy (age-matched)	5-min and 24-h ECG recordings HRV parameters: SDNN, RMSSD, pNN50 LF, HF, LF/HF ratio, SD1, SD2, SD1/SD2 ratio	↓HRV compared with healthy subjects ($p<0.05$) In 5-min ECG analysis: SDNN, RMSSD, pNN50), LF, HF, SD1, and SD2 negatively correlated with erythrocyte sedimentation rate ($p<0.05$). All HRV parameters except pNN50 had a strong negative correlation with disease activity score. LF and HF levels depended on age. In 24-h ECG analysis: SDNN, RMSSD, pNN50 showed a negative correlation with disease activity score and erythrocyte sedimentation rate.
Rensburg et al.[49]	n=45 RA (all F) n=39 healthy (age-matched)	HRV parameters: SDNN, pNN50 LF, HF, SD1, SD2	In the supine position, RMSSD, pNN50, SD1, and HF were significantly lower in the RA group. SD2 and LF were significantly lower in RA patients compared with controls.
Behcet's disease			
Kirimli et al.[57]	n=28 BD (12 F; age: 37±13 years) n=25 healthy (age-matched)	SAECG: QTd HRV parameters	↑QTd compared with healthy subjects HRV measures do not suggest a definite autonomic abnormality in BD.
Aytemir et al.[58]	n=71 BD n=26 healthy (age-matched)	HRV (supine and standing positions): LF, LF (nU), HF, HF(nU), and LF/HF	In supine position: ↑LF, LF (nU) and ↓HF, HF(Nu) compared with healthy controls ($p<0.05$). ↑LF/HF in both positions compared with healthy.
Akci et al.[59]	n=40 BD (20 F; age 40±9 years) n=20 healthy (all M; age 39±8 years)	24-h Holter ECG HRT parameters: TO and TS	There were no significant differences in HRT values between BD patients and the control subjects.
Systemic lupus erythematosus			
Lagana et al.[63]	n=20 SLE (all F) n=20 healthy (age-matched)	24-h ambulatory ECG recordings: HRV parameters: SDNN, pNN50, LF, HF	↓HRV parameters except ↑pNN50 compared with healthy group

Table 2. Electrocardiogram, heart rate variability, and heart rate turbulence findings in patients with autoimmune diseases in the studies reviewed *(continuation)*

Study (type)	Group	The method, and ECG, HRV, and HRT parameters assessed	Results of measurements
Huang et al.[65]	n=20 SLE n=20 healthy (all F; age-matched)	15-min ECG in supine left lateral, and right lateral positions HRV parameters: LF, LF (nU), HF, HF(nU), and LF/HF ratio	↓Indices of the time domain of HRV ↓LF, and HF (nU) compared with healthy group In the right lateral position: ↑HF, HF (nU), and ↓LF/HF ratio compared with supine position The lower the HF (nU) in the supine position, the greater the increase in HF (nU) when the position was changed from supine to the right lateral.
Milovanovic et al.[66]	n=52 SLE (46 F) n=36 RA (32 F) n=41 healthy (17 F)	24-h Holter ECG: QTc and HRV parameters: Poincare plot analysis	↑QTc in SLE ↓HRV in RA and SLE compared with healthy group. The reduction was greater in RA patients.
Aydemir et al.[67]	n=38 SLE n=26 RA n=40 healthy (age-matched)	6-channel ECG HRV parameters: LF, HF, and LF/HF ratio	No relationship between autonomic neuropathy and disease duration and disease activity
Yorgun et al.[68]	n=36 SLE (25 F; age 34.2±10.2 years) SLE duration (8.4±4.0 years) n=32 healthy (23 F; age 35±10.3 years)	24-h Holter ECG: QTd, HRV parameters: SDNN, SDANN, RMSSD, pNN50, LF, HF, LF/HF ratio HRT parameters: TO and TS	↓SDNN, SDANN, RMSSD, PNN50, HF, and ↑LF and LF/HF ratio compared with healthy group HRT onset and HRT slope significantly less negative in SLE ↑QTd in SLE
Poliwczak et al.[69]	n=26 SLE (all F; age 34.2±10.2 years) SLE duration: 11.52±7.42 years n=30 healthy (all F; age: 35±10.3 years)	24-h ambulatory ECG recordings HRT parameters: TO and TS	↑TO in SLE No differences in TS ↓SDANN, RMSSD, and pNN50 compared with healthy group The results were similar for the whole day. A positive correlation was seen between disease duration, SDNN, and SDANN. There was a negative correlation between LF/HF and RMSSD, pNN50, and HF values.
Systemic sclerosis			
Ferri et al.[75]	n=30 SSc (26 F; age: 45.2±9 years) n=30 healthy (age-matched)	24-h Holter ECG HRV parameters	↑Heart rate and ↓circadian and spectral parameters of HRV in SSc patients compared with controls
Othman et al.[76]	n=30 SSc n=15 healthy (age-matched)	24-h Holter ECG HRV parameters	Significant impairment of all HRV parameters in the SSc patients No correlation was seen between arrhythmia and HRV parameters and disease duration and type.
Bienias et al.[77]	n=46 SSc (40 F; age: 54.6±14.7 years) n=30 healthy (age-matched)	24-h Holter ECG, HRV parameters HRT parameters: TO and TS	↑Median TO and ↓median TS in SSc patients compared with controls 42% of SSc patients had abnormal HRT There was a negative correlation between disease duration and HRT values. ↓HRV parameters in SSc patients compared with controls. Significant correlations between HRT and HRV parameters.
Bienias et al.[78]	n=76 SSc (age: 51.9±13.1) n=70 SLE (age: 46.5±12.7) n=45 healthy (age-matched)	24-h Holter ECG, HRV parameters HRT parameters: TO and TS	Prolonged QTc intervals in SLE patients Significant correlations between QTc length and HRV indices. SSc and SLE subjects had impaired sympathetic cardiac autonomic modulation.

BD: Behcet's disease; ECG: Electrocardiogram; F: Female; HF: High-frequency; HRT: Heart rate turbulence; HRV: Heart rate variation; JTc: Corrected JT interval; JTc-d: Corrected JTd; JTd: JT dispersion; LF: Low-frequency; NN: Normal-to-normal; nU: Normalized units; PNN50: Percentage of pairs of adjacent NN intervals differing by more than 50 ms; QTc: Corrected QT interval; QTd: QT dispersion; RA: Rheumatoid arthritis; SAECG: Signal averaged electrocardiography; SjS: Sjögren's syndrome; SLE: Systemic lupus erythematosus; SSc: Systemic sclerosis; TO: Turbulence onset; TS: Turbulence slope.

eters used for the time-domain analysis were SDNN, SDANN, and RMSSD. The Poincaré plot parameters of SD1, SD2, and the ratio of SD1/SD2 were also measured to determine the short- and long-term changes in HRV. The HRV parameters, with the exception of SD2, were significantly lower in the RA patients compared with the control group.

Anichkov et al.[48] continued their research of HRV in RA patients with a study of 5-minute and 24-hour ECG recordings of 90 female patients with RA and 30 healthy subjects as the control group. The time-domain indices of SDNN, RMSSD, pNN50, and frequency-domain parameters of LF, HF, LF/HF ratio, and nonlinear indices such as SD1, SD2, SD21 extracted from 5-minute ECG recordings and the time-domain indices from 24-hour ECG recordings of both groups were compared. RA patients had a lower HRV in comparison with the control subjects. The LF and HF values depended on age. The authors reported that reduced HRV was associated with inflammation activity in RA patients.

Rensburg et al.[49] compared the autonomic cardiac control of women with RA with that of a healthy control group based on a time-frequency analysis and Poincaré plot analysis of HRV. The basal heart rate was significantly higher in the RA patients and significant differences were observed between RA patients and controls in the supine position ($p \leq 0.01$). The RMSSD, pNN50, SD1, and HF indicators of parasympathetic activity were significantly lower in the RA group. The indicators of sympathetic change of SD2 and LF were also considerably lower in the RA patients compared with the controls.

Behcet's disease

BD was named after the Turkish dermatologist Hulusi Behcet, who first described the disease in 1937. BD is a chronic inflammatory disease that can affect any organ system. BD is characterized by oral aphthous ulcers, mucosal lesions of the skin, joint and vessel involvement, uveitis, and epididymitis. The disease is more prevalent in areas along the ancient Silk Road extending from the Far East to the Middle East and the Mediterranean. BD is commonly seen in Turkey, Iran, China, North Korea, and Japan. Cardiac involvement is variable and seen in 7% to 46% of patients. It may lead to myocardial infarction, pericarditis, aneurysm, or congestive heart failure.[50–57]

Kirimli et al.[58] studied 33 patients with BD and 25 age- and sex-matched control subjects. Their goal was to evaluate myocardial involvement in patients with BD by measuring signal-averaged electrocardiography (SAECG), QTd, and HRV parameters. They focused on the PQRST complex and RR intervals. Their results revealed that patients with BD had significantly increased QTd and a high incidence of positive late potentials and more complex ventricular arrhythmias. The HRV measures did not suggest an apparent autonomic abnormality in BD.

Aksöyek et al.[59] evaluated ANS function in patients with BD. They used the time-frequency method and power spectral analysis to assess HRV. A total of 71 patients with BD and 26 healthy volunteers were studied. HRV was measured in the supine and standing position. In the supine position, BD patients had increased LF and LF normalized units (nU) but lower HF and HF (nU) values than the healthy group. In the standing position, BD patients had higher LF and LF (nU) values, but lower HF and HF (nU) values. The LF/HF ratio, which estimates the ratio between the SANS and PANS, was significantly higher in the BD patients in both the supine and standing positions. The authors concluded that patients with BD might have an asymptomatic ANS dysfunction.

Akci et al.[60] investigated the cardiac autonomic activity of 40 BD patients, and 20 gender- and age-matched healthy volunteers. The analysis was based on the HRT parameters of TO and TS, which are believed to be predictors of cardiac autonomic activity and mortality. All of the subjects underwent a 24-hour Holter ECG. No significant differences were seen in TO and TS values between the patients with BD and the control subjects.

Systemic lupus erythematosus

SLE is a systemic AD that can involve several organs, but in particular affects the skin, joints, blood, kidneys, and central nervous system. The disease appears to be more common in African-Americans, Spaniards, Asians, and Native Americans.[61,62] Pericarditis is the most common cardiac disorder in patients with SLE, but lesions of the valves, myocardium and coronary vessels may also occur.[63]

Laganà et al.[64] assessed the HRV of 20 patients with SLE and 20 age- and sex-matched healthy subjects using 24-hour ambulatory ECG monitoring. The

ECG and HRV measures of SDNN, LF, and HF power were significantly decreased in SLE patients when compared with healthy subjects. As a potential means of better evaluation of abnormal HRV in SLE patients, technetium sestamibi (Tc-99m MIBI) single-photon emission computed tomography (SPECT) imaging taken at rest and after dipyridamole infusion was analyzed. Abnormal Tc-99m MIBI SPECT results were observed in 15 of the 20 SLE patients. The authors hypothesized that Tc-99m MIBI SPECT could reveal microvascular disease or metabolic alterations in SLE patients with abnormal HRV, even if the patients do not show any symptoms of heart disease.

Huang et al.[65] assessed the ECG results of SLE patients according to the position used during examination. The study group consisted of 35 female SLE patients and 33 healthy, age-matched, female subjects. After a 5-minute rest, 15-minute ECG tracings were obtained in the supine, left lateral, and right lateral positions. The measured parameters were the SDNN, VLF power, LF power, HF power, LF/HF ratio, LF (nU), HF (nU), and VLF (nU). HRV parameters [VLF, LF, HF, VLF (nU) and LF (nU)] did not show any correlation with disease activity. The results demonstrated that patients with SLE had lower HF (nU) power and higher VLF (nU) in the supine position when compared with the controls. Also, HF power and HF (nU) power were more significant in SLE patients, while the LF/HF ratio was lower in the right lateral position than in the supine position.

Milovanović et al.[66] presented a time-frequency, non-linear analysis of HRV in 2 ADs, with 52 patients with SLE, 38 patients with RA, and 41 age-matched healthy subjects. The HRV was assessed using the 2 protocols of standard 12-lead ECG recordings (10 minutes, probably in supine position) and 24-hour ambulatory ECGs. Short-term analyses indicated that SDNN, pNN50, and RMSSD ECG parameters were lower in SLE and RA patients. Moreover, spectral parameters of VLF, LF, and HF were significantly different in patients with SLE or RA compared with controls. The LF values were higher in SLE patients compared with both the healthy subjects and RA patients. Non-linear analysis of the 10-minute HRV using Poincaré plot parameters showed that HRV values were dominant in SLE and RA patients compared with the controls. Long-term HRV analysis found that SDANN, RMSSD, LF, and the geometric parameter of the triangular index were different between SLE and RA patients and controls. In general, HRV values tended to be lower in the SLE patients when compared with the healthy control group. Similar results were reported for RA patients. RMSSD tended to be higher in RA patients than in the control group or SLE group.

Aydemir et al.[67] evaluated the HRV of 38 SLE patients, 36 RA patients, and 40 sex-matched healthy subjects based on 6-channel ECG recordings. The spectral analysis of HRV and related parameters of LF, HF, and the LF/HF ratio were measured. They evaluated the effect of body position on HRV using a tilt table test and the supine resting position. In the supine position, SLE and RA patients demonstrated lower LF values compared with the controls. HF power in the supine position did not differ significantly in either patient group when compared with the control group. The results obtained for the tilt position were similar to that of the supine position. In both patient groups, the HF value was lower in the tilt position compared with the control group. However, there was a significant decrease in LF power after the tilt position in SLE patients, while a substantial increase was reported in the LF of the controls. RA patient results did not show any significant difference in LF in the tilt position. There was a significant change in HF power after the tilt test in both SLE and RA patients, while no change was seen in the healthy subjects. In healthy subjects, the increase in LF/HF ratio with tilting was significant, while this parameter in SLE and RA patients demonstrated a smaller increase.

Yorgun et al.[68] investigated 36 patients with SLE and 32 individuals matched for age, sex, and body mass index using 24-hour ambulatory ECG recordings. Time-frequency analysis of HRV measures was performed. Several measures of HRV were decreased among patients compared with controls, including SDNN, SDANN, RMSSD, pNN50, and HF. The result showed that the LF value and the LF/HF ratio were significantly higher in SLE patients when compared with the controls. The results showed a positive correlation between the LF/HF ratio and disease duration ($p=0.06$) and activity ($p=0.07$). The authors also evaluated HRT parameters. A positive correlation of TO and disease activity ($p=0.054$) was seen, but not between TS and disease activity ($p=0.176$).

Poliwczak et al.[69] compared 26 SLE patients with 30 healthy age- and sex-matched subjects using

24-hour ambulatory ECG monitoring. The HRV and HRT analysis included 3 separate periods: a) entire day, b) daytime activity (between 8:00 am and 12:00 pm), and c) nighttime rest (between 12:00 and 4:00 am). In the 24-hour analysis, HRV parameters, with the exception of LF and the LF/HF ratio, were significantly lower in the SLE patients. Daytime and nighttime activities were similar for the entire period. The results revealed that although HRV parameters had a circadian pattern for both groups, circadian changes in the pNN50 and LF were not significant for the SLE patients.

Systemic sclerosis

SSc or systemic scleroderma is an AD of the connective tissue. The word "scleroderma" means "hard skin" in Greek, and this condition is characterized by tissue fibrosis in the skin and other organs. Thickening of the skin occurs due to the accumulation of collagen and damage to the small arteries. Fibrosis may also affect organs other than the skin.[70]

Cardiac involvement is one of the common complications of SSc, although it is often difficult to diagnose. If diagnosed promptly, these complications can often be controlled and even treated.[71] SSc can cause a variety of cardiac disorders, including coronary heart disease (associated with cardiac ischemia), myocardial fibrosis, left ventricular systolic dysfunction, left ventricular diastolic dysfunction, pericardial disorders, and conduction disorders. Such a variation in cardiac involvement leads to a high mortality risk in SSc patients.[72–74] Therefore, recognizing cardiac effects is very important in the treatment of SSc patients.

Ferri et al.[75] investigated the autonomic nervous control of the heart in patients with SSc. The HRV of 30 SSc patients (4 males; mean age: 45.2±9 years) and 30 healthy, age-matched subjects was analyzed using time-domain and spectrum analysis of 24-hour ECG ambulatory recordings. The results revealed a significantly higher heart rate and lower circadian and spectral parameters of HRV in SSc patients compared with controls.

Othman et al.[76] evaluated cardiac autonomic control and cardiac function in 30 SSc patients and 15 healthy, age- and sex-matched controls. The HRV of the patients was analyzed using 24-hour Holter monitoring results in time and frequency domains. The results revealed highly significant impairment in all HRV parameters of the SSc patients. No correlation was reported between arrhythmia and HRV parameters, SSc duration, or type.

Bienias et al.[77] focused on HRT evaluation of SSc patients to assess the cardiac autonomic nervous function. A total of 45 patients (40 women; mean age: 54.6±14.7 years) and 30 age- and sex-matched healthy controls underwent 24-hour Holter monitoring for HRT assessment and time- and frequency-domain HRV analysis. The reported results showed that the median TO was higher in SSc patients, and that the median TS was lower. In all, 42% of SSc patients had abnormal HRT findings. Moreover, disease duration had a negative correlation with HRT values. All of the HRV parameters were significantly lower in the SSc patients compared with the controls. There were significant correlations between the HRT and HRV parameters and the presence of SSc.

Bienias et al.[78] also examined 86 adult SSc patients, 76 patients with SLE, and 45 healthy controls using 24-hour Holter monitoring and time-domain analysis of HRV and HRT. There was a frequent incidence of various supraventricular and ventricular arrhythmias among the SSc patients. The SLE patients also demonstrated prolonged QTc intervals and significant correlations between QTc length and HRV indices. Both the SSc and SLE patients had impaired sympathetic cardiac autonomic modulation, while indices associated with PANS activity in SLE were not diminished.

DISCUSSION

Research about the effects of ADs on the heart can be divided into 2 broad categories: Studies that directly assessed the ECG as a benchmark, and other research that focused on HRV parameters. The results of most of the reviewed studies based on ECG analysis indicated that ADs are associated with increased QTd and QTc,[43–46,57,67] which is well-known as a risk factor of SCD.[79–81] It has been shown that the QTc interval is one of the main manifestations of cardiac autonomic neuropathy.

It is difficult to calculate the QT distance in normal conditions, as there may be confusion due to noise or other interference, given the small size of the wave. An error in the calculation of the QT interval can lead

to an incorrect interpretation of the results. If the patient has a CVD, this parameter may be even harder to calculate. However, when adequately determined, it can be an indicator of cardiac toxicity from many different medications, underlying cardiac conduction disease, or development of torsades de pointes, which is a potentially fatal cardiac dysrhythmia.[82,83]

More articles evaluated HRV than ECG findings. One reason for analysis of HRV is that it uses the RR intervals as the basis for the formation of time-series analysis and observation of the HRV signal. It is much easier to distinguish the R wave from the ECG signal than QT intervals, and the probability of mistakes and misinterpretations will be minimized.

In recent years, several parameters have been extracted from HRV analysis that describe the function of the ANS. In the reviewed studies, time-frequency domain analysis and non-linear analysis, such as Poincaré plots, were used to evaluate cardiac function. Regardless of the type of disease (AR, SLE, BD, SSc), all of the articles noted that HRV parameters were decreased in patients compared with a control group, due to sympathetic predominance or hyperactivity, or parasympathetic under-activity. Furthermore, studies confirmed that reduced HRV values and a depressed triangular index can lead to dangerous arrhythmias and SCD.[64,83] Therefore, the results obtained from patients with ADs reinforce the hypothesis that a significant reduction in the HRV of AD patients increases the risk of SCD.

HRV frequency-domain parameters of LF, HF, LF (nU), HF (nU), ULF, VLF, and LF/HF ratio have been analyzed several times with relation to other diseases, such as cardiac arrhythmias, stroke, and epilepsy.[84–88] The HF band indicates vagal activity, the LF/HF ratio indicates sympathetic activity, and the VLF band has a strong association with CVD prognosis in the study of ADs. Regardless of the concepts reflected by each of the frequency-domain parameters, significant changes in these parameters were reported related to position, which indicates the sensitivity of HRV to position and the potential for differentiation in various positions in AD patients. Two papers that examined HRV using frequency-domain analysis reported differences in the measured parameters in the supine and standing positions.[58,64]

Another factor discussed in some articles was the relationship between HRV and the duration of the disease, and 3 articles found no correlation between these 2 factors. Thus, although HRV can correctly characterize ANS dysfunction in ADs, it cannot necessarily illustrate the general activity of ADs on the body.[47,66,76]

In addition to the use of HRV parameters to explain non-specific ANS dysfunction-related symptoms, HRT parameters were also measured in some studies to complete the evaluation of the ANS. The question of which criteria can better describe ANS disorders is not yet well documented. Studies that have examined ANS function in different conditions have used HRV and HRT individually,[59] and sometimes, these criteria have been used in a complementary fashion.[68,77] HRT is less often used and therefore, comparison to HRV-based analyses is limited. HRT evaluation requires measurement of sinus rhythm and ventricular premature beats. Therefore, it cannot be calculated in patients with measurement of fewer than 5 baseline ventricular prognosis.

Three studies presented results based on HRT parameters.[68,77,78] Comparison of the ANS function of SLE and SSc patients with control groups revealed that the TO was increased in AD patients. The results suggested an increase of sinus acceleration following the ventricular premature complex. Also, TS, which is the rate of sinus deceleration, followed the sinus acceleration decrease in SSc patients. However, there were no significant differences in TS and TO in BD patients compared with the healthy control group.[59]

Several limitations were observed in the selected studies. The primary limitation was the small number of subjects examined (the most extensive research included 90 patients, the smallest study included 20). The writing teams of many of these papers are not known in terms of their expertise and the extent of their proficiency with HRV interpretation. The extracted ECG and HRV features can be compared with other research in signal processing. The only nonlinear features extracted were the Poincaré plot parameters,[47–49] while today, several ECG and HRV analyses can display the dynamics of these signals in greater detail.

Geometric features calculated based on the location of the points in the HRV time series relative to each other, energy, entropy, chaotic features, Lyapunov exponent, Hurst exponent, etc., which are com-

monly used in HRV analysis, were not utilized in any of these investigations.[32–33,35,89] Perhaps some of the limitations mentioned in this review, such as the lack of meaningful relationships between some factors, are due to the weakness of the features that were studied. Characteristics that show the complexity and dynamics within HRV may be the answer to the ambiguities of these articles.

In most of these studies, although the control groups were age- and gender-matched with the patient group, the gender balance was weak.[64–69,75,77] Research has repeatedly proven that gender has an impact on changes to the HRV signal,[25,89–91] and this imbalance may affect the quality of comparisons and outcomes. Also, in most of the reviewed articles, additional information regarding lifestyle factors that can affect the heart, such as prescribed drugs: other underlying conditions such as heart failure, diabetes, or untreated depression; and the duration of the disease was not known, which can play a key role in interpreting the results.

Conclusion

Patients with ADs demonstrated significant differences in ECG and HRV analysis, which indicates the presence of abnormalities of the cardiac ANS. Although in some cases, the HRV parameters showed a correlation with disease duration and activity, it cannot be stated that the severity of the disease can be definitively determined by HRV analysis. Nonetheless, it is useful, and due to the proven potential of HRV as a valuable clinical tool to monitor various dysfunction and progression of diseases in other research, it seems that all the capabilities of this signal have not yet sufficiently been used to diagnose and even predict some disorders in the context of ADs. Additional studies in the future should examine the ambiguities and target a more accurate analysis of the dynamics present in HRV.

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REFERENCES

1. Kim HY, Kim HR, Lee SH. Advances in Systems Biology Approaches for Autoimmune Diseases. Immune Netw 2014;14:73–80. [CrossRef]
2. Blumberg RS, Dittel B, Hafler D, von Herrath M, Nestle FO. Unraveling the autoimmune translational research process layer by layer. Nat Med 2012;18:35–41. [CrossRef]
3. Amaya-Amaya J, Montoya-Sánchez L, Rojas-Villarraga A. Cardiovascular Involvement in Autoimmune Diseases. Biomed Res Int 2014;2014:367359. [CrossRef]
4. Anaya JM, Castiblanco J, Rojas-Villarraga A, Pineda-Tamayo R, Levy RA, Gómez-Puerta J, et al. The multiple autoimmune syndromes. A clue for the autoimmune tautology. Clin Rev Allergy Immunol 2012;43:256–64. [CrossRef]
5. Anaya JM. The diagnosis and clinical significance of polyautoimmunity. Autoimmun Rev 2014;13:423–6. [CrossRef]
6. Fridkis-Hareli M. Immunogenetic mechanisms for the coexistence of organ-specific and systemic autoimmune diseases. J Autoimmune Dis 2008;5:1. [CrossRef]
7. Roger VL, Go AS, Lloyd-Jones DM, Adams RJ, Berry JD, Brown TM, et al. Heart disease and stroke statistics – 2011 update: a report from the American Heart Association. Circulation 2011;123:e18–e209.
8. Kurmann RD, Mankad R. Atherosclerotic vascular disease in the autoimmune rheumatologic woman. Clin Cardiol 2018;41:258–63. [CrossRef]
9. Abou-Raya S, Abou-Raya A, Naim A, Abuelkheir H. Chronic inflammatory autoimmune disorders and atherosclerosis. Ann N Y Acad Sci 2007;1107:56–67. [CrossRef]
10. Manzi S, Meilahn EN, Rairie JE, Conte CG, Medsger TA Jr, Jansen-McWilliams L, et al. Age-specific incidence rates of myocardial infarction and angina in women with systemic lupus erythematosus: comparison with the Framingham Study. Am J Epidemiol 1997;145:408–15. [CrossRef]
11. Nussinovitch U, Shoenfeld Y. Autoimmunity and heart diseases: pathogenesis and diagnostic criteria. Arch Immunol Ther Exp (Warsz) 2009;57:95–104. [CrossRef]
12. Sherer Y, Shoenfeld Y. Mechanisms of disease: atherosclerosis in autoimmune disease. Nat Clin Pract Rheumatol 2006;2:99–106. [CrossRef]
13. Lago F, Gómez R, Conde J, Scotece M, Gómez-Reino JJ, Gualillo O. Cardiometabolic comorbidities and rheumatic diseases: focus on the role of fat mass and adipokines. Arthritis Care Res (Hoboken) 2011;63:1083–90. [CrossRef]
14. Esdaile JM, Abrahamowicz M, Grodzicky T, Li Y, Panaritis C, du Berger R, et al. Traditional Framingham risk factors fail to account for accelerated atherosclerosis in systemic lupus erythematosus fully. Arthritis Rheum 2001;44:2331–7.
15. Stojanovich L. Autonomic dysfunction in autoimmune rheumatic disease. Autoimmun Rev 2009;8569–72.
16. Malpas SC. Sympathetic nervous system overactivity and its role in the development of the cardiovascular disease. Physiol

Rev 2010;90:513–57. [CrossRef]
17. Skamra C, Ramsey-Goldman R. Management of cardiovascular complications in systemic lupus erythematosus. Int J Clin Rheumtol 2010;5:75–100. [CrossRef]
18. Kitas G, Banks MJ, Bacon PA. Cardiac involvement in rheumatoid disease. Clin Med (Lond) 2001;1:18–21. [CrossRef]
19. Shaffer F, Ginsberg JP. An Overview of Heart Rate Variability Metrics and Norms. Front Public Health 2017;5:258.
20. Fisch C. Centennial of the string galvanometer and the electrocardiogram. J Am Coll Cardiol 2000;36:1737–45. [CrossRef]
21. Lamberts RJ, Blom MT, Novy J, Belluzzo M, Seldenrijk A, Penninx BW, et al. Increased prevalence of ECG markers for sudden cardiac arrest in refractory epilepsy. J Neurol Neurosurg Psychiatry 2015;86:309–13. [CrossRef]
22. Maršánová L, Ronzhina M, Smíšek R, Vítek M, Němcová A, Smital L, et al. ECG features and methods for automatic classification of ventricular premature and ischemic heartbeats: A comprehensive experimental study. Sci Rep 2017;7:11239.
23. Anuradha B, Suresh Kumar K, Veera Reddy VC. Classification of Cardiac Signals Using Time Domain Methods. ARPN Journal of Engineering and Applied Sciences 2008;3:7–12.
24. Behbahani S, Dabanloo NJ, Nasrabadi AM, Attarodi GA, Teixeira CA, Dourado A. Epileptic Seizure Behaviour from the Perspective of Heart Rate Variability. Computing in Cardiology 2012;117–20.
25. Behbahani S, Jafarnia Dabanloo N, Motie Nasrabadi A, Dourado A. Gender-related differences in heart rate variability of epileptic patients. Am J Mens Health 2018;12:117–25.
26. Chattipakorn N, Incharoen T, Kanlop N, Chattipakorn S. Heart rate variability in myocardial infarction and heart failure. Int J Cardiol 2007;120:289–96. [CrossRef]
27. Oliveira NL, Ribeiro F, Alves AJ, Teixeira M, Miranda F, Oliveira J. Heart rate variability in myocardial infarction patients: effects of exercise training. Rev Port Cardiol 2013;32:687–700. [CrossRef]
28. Kim HG, Cheon EJ, Bai DS, Lee YH, Koo BH. Stress and Heart Rate Variability: A Meta-Analysis and Review of the Literature. Psychiatry Investig 2018;15:235–45. [CrossRef]
29. Behbahani S, Dabanloo NJ, Nasrabadi AM, Dourado A. Classification of ictal and seizure-free HRV signals with focus on lateralization of epilepsy. Technol Health Care 2016;24:43–56. [CrossRef]
30. Moridani MK, Setarehdan SK, Nasrabadi AM, Hajinasrollah E. Analysis of heart rate variability as a predictor of mortality in cardiovascular patients of intensive care unit. Biocybernetics and Biomedical Engineering 2015;35:217–26. [CrossRef]
31. Stein PK, Pu Y. Heart rate variability, sleep, and sleep disorders. Sleep Med Rev 2012;16:47–66. [CrossRef]
32. Rajendra Acharya U, Paul Joseph K, Kannathal N, Lim CM, Suri JS. Heart rate variability: a review. Med Biol Eng Comput 2006;44:1031–51. [CrossRef]
33. Karimi Moridani M, Haghighi Bardineh Y. Presenting an efficient approach based on novel mapping for mortality prediction in intensive care unit cardiovascular patients. MethodsX 2018;5:1291–8. [CrossRef]
34. Behbahani S, Dabanloo NJ, Nasrabadi AM, Teixeira CA, Dourado A. Pre-ictal heart rate variability assessment of epileptic seizures using linear and non-linear analyses. Anadolu Kardiyol Derg 2013;13:797–803. [CrossRef]
35. Jovic A, Bogunovic N. Electrocardiogram analysis using a combination of statistical, geometric, and nonlinear heart rate variability features. Artif Intell Med 2011;51:175–86. [CrossRef]
36. Dabanloo NJ, Moharreri S, Parvaneh S, Nasrabadi AM. New representation of heart rate and evaluation of extracted geometric features. In Proceedings of Computing in Cardiology 2010;77–80.
37. Woo MA, Stevenson WG, Moser DK, Trelease RB, Harper RM. Patterns of beat-to-beat heart rate variability in advanced heart failure. Am Heart J 1992;123:704–10. [CrossRef]
38. Melillo P, Bracale M, Pecchia L. Nonlinear Heart Rate Variability features for real-life stress detection. Case study: students under stress due to university examination. Biomed Eng Online 2011;10:96. [CrossRef]
39. Barbour KE, Helmick CG, Boring M, Brady TJ. Vital Signs: Prevalence of Doctor-Diagnosed Arthritis and Arthritis-Attributable Activity Limitation – United States MMWR2017 2013–2015;. MMWR Morb Mortal Wkly Rep 2017;66:246–53. [CrossRef]
40. Ku IA, Imboden JB, Hsue PY, Ganz P. Rheumatoid arthritis: a model of systemic inflammation is driving atherosclerosis. Circ J 2009;73:977–85. [CrossRef]
41. Full LE, Ruisanchez C, Monaco C. The inextricable link between atherosclerosis and prototypical inflammatory diseases rheumatoid arthritis and systemic lupus erythematosus. A Arthritis Res Ther 2009;11:217. [CrossRef]
42. Bartoloni E, Shoenfeld Y, Gerli R. Inflammatory and autoimmune mechanisms in the induction of atherosclerotic damage in systemic rheumatic diseases: two faces of the same coin. Arthritis Care Res (Hoboken) 2011;63:178–83. [CrossRef]
43. Göldeli O, Dursun E, Komsuoglu B. Dispersion of ventricular repolarization: a new marker of ventricular arrhythmias in patients with rheumatoid arthritis. J Rheumatol 1998;25:447–50.
44. Alkaabi JK, Ho M, Levison R, Pullar T, Belch JJ. Rheumatoid arthritis and macrovascular disease. Rheumatology (Oxford) 2003;42:292–7. [CrossRef]
45. Pirildar T, Sekuri C, Utük O, Tezcan UK. QT dispersion in rheumatoid arthritis patients with and without Sjögren's syndrome. Clin Rheumatol 2003;22:225–8. [CrossRef]
46. Evrengül H, Dursunoglu D, Cobankara V, Polat B, Seleci D, Kabukçu S, et al. Heart rate variability in patients with rheumatoid arthritis. Rheumatol Int 2004;24:198–202. [CrossRef]
47. Anichkov DA, Shostak NA, Ivanov DS. Heart rate variability is related to disease activity and smoking in rheumatoid arthritis patients. Int J Clin Pract 2007;61:777–83. [CrossRef]
48. Anichkov DA, Platonova AA. Clinical Significance of Heart

Rate Variability Indexes Derived from 5-Minute and 24-Hour ECG Recordings in Patients with Rheumatoid Arthritis. Rational Pharmacotherapy in Cardiology 2009;5:77–82. [CrossRef]
49. Rensburg DC JV, Ker JA, Grant CC, Fletcher L. Autonomic impairment in rheumatoid arthritis. Int J Rheum Dis 2012;15:419–26. [CrossRef]
50. Aslam F, Bandeali SJ, Crowson C, Alam M. Cardiac Function, and Diastolic Dysfunction in Behcet's Disease: A Systematic Review and Meta-Analysis. Int J Rheumatol 2016;2016:9837184. [CrossRef]
51. Davatchi F, Shahram F, Chams-Davatchi C, Shams H, Abdolahi BS, Nadji A, et al. Behcet's Disease in Iran; Analysis of 7641 Cases. Mod Rheumatol 2019;29:1023–30. [CrossRef]
52. Mazzoccoli G, Matarangolo A, Rubino R, Inglese M, De Cata A. Behcet syndrome: from pathogenesis to novel therapies. Clin Exp Med 2016;16:1–12. [CrossRef]
53. Mat MC, Sevim A, Fresko I, Tüzün Y. Behcet's disease as a systemic disease. Clin Dermatol 2014;32:435–42. [CrossRef]
54. Davatchi F, Jamshidi AR, Banihashemi AT, Gholami J, Forouzanfar MH, Akhlaghi M, et al. WHO-ILAR COPCORD Study (Stage 1, Urban Study) in Iran. J Rheumatol 2008;35:1384.
55. Palizgir M, Mahmoudi M, Qorbani M, Djalalinia S, Mostafaei S, Shahram F. Prevalence and Clinical Investigation of the Behcet's Disease in Middle East and North Africa: A Systematic Review and Meta-Analysis. Iran Red Crescent Med J 2017;19:e43313. [CrossRef]
56. Gül A. Pathogenesis of Behcet's disease: autoinflammatory features and beyond. Semin Immunopathol 2015;37:413–8.
57. Palizgir MT, Akhtari M, Mahmoudi M, Mostafaei S, Rezaeimanesh A, Akhlaghi M, et al. Macrophages from Behcet's Disease Patients Express Decreased Level of Aryl Hydrocarbon Receptor (AHR) Mrna. Iran J Allergy Asthma Immunol 2017;16:418–24.
58. Kirimli O, Aslan O, Göldeli O, Güneri S, Badak O, Fetil E, et al. Heart rate variability, late potentials and QT dispersion as markers of myocardial involvement in patients with Behçet's disease. Can J Cardiol 2000;16:345–51.
59. Aksöyek S, Aytemir K, Ozer N, Ozcebe O, Oto A. Assessment of autonomic nervous system function in patients with Behcet's disease by spectral analysis of heart rate variability. J Auton Nerv Syst 1999;77:190–4. [CrossRef]
60. Akci O, Aldemir M, Yaman F, Solak O, Emren SV, Onrat E, et al. Assessment of Cardiac Autonomic Function by Using Heart Rate Turbulence in Behcet's Disease. World Journal of Cardiovascular Surgery 2014;4:193–9. [CrossRef]
61. Rees F, Doherty M, Grainge MJ, Lanyon P, Zhang W. The worldwide incidence and prevalence of systemic lupus erythematosus: a systematic review of epidemiological studies. Rheumatology (Oxford) 2017;56:1945–61. [CrossRef]
62. Akbarian M, Faezi ST, Gharibdoost F, Shahram F, Nadji A, Jamshidi AR, et al. Systemic lupus erythematosus in Iran: a study of 2280 patients over 33 years. Int J Rheum Dis 2010;13:374–9. [CrossRef]
63. Doria A, Iaccarino L, Sarzi-Puttini P, Atzeni F, Turriel M, Petri M. Cardiac involvement in systemic lupus erythematosus. Lupus 2005;14:683–6. [CrossRef]
64. Laganà B, Schillaci O, Tubani L, Gentile R, Danieli R, Coviello R, et al. Lupus carditis: evaluation with technetium-99m MIBI myocardial SPECT and heart rate variability. Angiology 1999;50:143–8. [CrossRef]
65. Huang ST, Chen GY, Wu CH, Kuo CD. Effect of disease activity and position on autonomic nervous modulation in patients with systemic lupus erythematosus. Clin Rheumatol 2008;27:295–300. [CrossRef]
66. Milovanović B, Stojanović L, Milićevik N, Vasić K, Bjelaković B, Krotin M. Cardiac autonomic dysfunction in patients with systemic lupus, rheumatoid arthritis, and sudden death risk. Srp Arh Celok Lek 2010;138:26–32. [CrossRef]
67. Aydemir M, Yazisiz V, Basarici I, Avci AB, Erbasan F, Belgi A, et al. Cardiac autonomic profile in rheumatoid arthritis and systemic lupus erythematosus. Lupus 2010;19:255–61.
68. Yorgun H, Canpolat U, Aytemir K, Ateş AH, Kaya EB, Akdoğan A, et al. Evaluation of cardiac autonomic functions in patients with systemic lupus erythematosus. Lupus 2012;21:373–9. [CrossRef]
69. Poliwczak AR, Waszczykowska E, Dziankowska-Bartkowiak B, Koziróg M, Dworniak K. The use of heart rate turbulence and heart rate variability in the assessment of autonomic regulation and circadian rhythm in patients with systemic lupus erythematosus without apparent heart disease. Lupus 2018;27):436–44. [CrossRef]
70. Pieroni M, De Santis M, Zizzo G, Bosello S, Smaldone C, Campioni M, et al. Recognizing and treating myocarditis in recent-onset systemic sclerosis heart disease: potential utility of immunosuppressive therapy in cardiac damage progression. Semin Arthritis Rheum 2014;43:526–35. [CrossRef]
71. Faludi R, Költő G, Bartos B, Csima G, Czirják L, Komócsi A. Five-year follow-up of left ventricular diastolic function in systemic sclerosis patients: determinants of mortality and disease progression. Semin Arthritis Rheum 2014;44:220–7.
72. Meune C, Vignaux O, Kahan A, Allanore Y. Heart involvement in systemic sclerosis: evolving concept and diagnostic methodologies. Arch Cardiovasc Dis 2010;103:46–52.
73. Kahan A, Coghlan G, McLaughlin V. Cardiac complications of systemic sclerosis. Rheumatology (Oxford) 2009;48:iii45–8. [CrossRef]
74. Champion HC. The heart in scleroderma. Rheum Dis Clin North Am 2008;34:181–90. [CrossRef]
75. Ferri C, Emdin M, Giuggioli D, Carpeggiani C, Maielli M, Varga A, et al. Autonomic Dysfunction in Systemic Sclerosis: Time and Frequency Domain 24 Hour Heart Rate Variability Analysis. Br J Rheumatol 1997;36:669–76. [CrossRef]
76. Othman KM, Assaf NY, Farouk HM, Aly Hassan IM. Autonomic Dysfunction Predicts Early Cardiac Affection in Patients with Systemic Sclerosis. Clin Med Insights Arthritis

Musculoskelet Disord 2010;3:43–54. [CrossRef]
77. Bienias P, Ciurzyński M, Glińska-Wielochowska M, Szewczyk A, Korczak D, Kalińska-Bienias A, et al. Heart rate turbulence assessment in systemic sclerosis: the role for the detection of cardiac autonomic nervous system dysfunction. Rheumatology (Oxford) 2010;49:355–60. [CrossRef]
78. Bienias P, Ciurzyński M, Kisiel B, Chrzanowska A, Ciesielska K, Siwicka M, et al. Comparison of non-invasive assessment of arrhythmias, conduction disturbances and cardiac autonomic tone in systemic sclerosis and systemic lupus erythematosus. Rheumatol Int 2019;39:301–10. [CrossRef]
79. DE Maria E, Curnis A, Garyfallidis P, Mascioli G, Santangelo L, Calabrò R, et al. QT dispersion on ECG Holter monitoring and risk of ventricular arrhythmias in patients with dilated cardiomyopathy. Heart Int 2006;2:33. [CrossRef]
80. Youssef OI, Farid SM. QTc and QTd in Children with Type 1 Diabetes Mellitus during Diabetic Ketoacidosis. ISRN Pediatr 2012;2012:619107. [CrossRef]
81. Neki NS, Kaur J. A study of QTc-Prolongation and QT Dispersion (QTd) as an indicator of Cardiac Autonomic Neuropathy (CAN) in type 2 Diabetes Mellitus Patients. JIMSA 2014;27:195–6.
82. Matthew Li, Ramos LG. Drug-Induced QT Prolongation and Torsades de Pointes. P T 2017;42:473–7.
83. Roden DM. Drug-induced prolongation of the QT interval. N Engl J Med 2004;350:1013–22. [CrossRef]
84. Stein PK, Barzilay JI. Relationship of abnormal heart rate turbulence and elevated CRP to cardiac mortality in low, intermediate, and high-risk older adults. J Cardiovasc Electrophysiol 2011;22:122–7. [CrossRef]
85. Assoumou HG, Pichot V, Barthelemy JC, Dauphinot V, Celle S, Gosse P, et al. Metabolic syndrome and short-term and long-term heart rate variability in elderly free of clinical cardiovascular disease: The PROOF study. Rejuvenation Res 2010;13:653–63. [CrossRef]
86. Usui H, Nishida Y. Relationship between Physical Activity and the Very Low-Frequency Component of Heart Rate Variability after Stroke. J Stroke Cerebrovasc Dis 2015;24:840–3.
87. Calandra-Buonaura G, Toschi N, Provini F, Corazza I, Bisulli F, Barletta G, et al. Physiologic autonomic arousal heralds motor manifestations of seizures in nocturnal frontal lobe epilepsy: implications for pathophysiology. Sleep Med 2012;13:252–62. [CrossRef]
88. Romigi A, Albanese M, Placidi F, Izzi F, Mercuri NB, Marchi A, et al. Heart rate variability in untreated newly diagnosed temporal lobe epilepsy: Evidence for ictal sympathetic dysregulation. Epilepsia 2016;57:418–26. [CrossRef]
89. Karimi Moridani M, Setarehdan SK, Motie Nasrabadi A, Hajinasrollah E. Non-Linear Feature Extraction from HRV Signal for Mortality Prediction of ICU Cardiovascular Patient. J Med Eng Technol 2016;40:87–98. [CrossRef]
90. Ramalho ESV, Souza-Junior EL, Magnani M, Braga VA. Gender Differences in Heart Rate Variability Among Individuals Undergoing Regular Resistance Training Preliminary observations. Sultan Qaboos Univ Med J 2017;17:e209–e12.
91. Lutfi MF, Sukkar MY. The effect of gender on heart rate variability in asthmatic and normal healthy adults. Int J Health Sci (Qassim) 2011;5:146–54.
92. Voss A, Schroeder R, Heitmann A, Peters A, Perz S. Short-Term Heart Rate Variability—Influence of Gender and Age in Healthy Subjects. PLoS One 2015;10:e0118308. [CrossRef]

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