

Heart rate variability as predictive factor for sudden cardiac death

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ABSTRACT

Sudden cardiac death (SCD) represents about 25% of deaths in clinical cardiology. The identification of risk factors for SCD is the philosopher's stone of cardiology and the identification of non-invasive markers of risk of SCD remains one of the most important goals for the scientific community.

The aim of this review is to analyze the state of the art around the heart rate variability (HRV) as a predictor factor for SCD.

HRV is probably the most analyzed index in cardiovascular risk stratification technical literature, therefore an important number of models and methods have been developed.

Nowadays, low HRV has been shown to be independently predictive of increased mortality in post-myocardial infarction patients, heart failure patients, in contrast with the data of the general population.

Contrariwise, the relationship between HRV and SCD has received scarce attention in low-risk cohorts. Furthermore, in general population the attributable risk is modest and the cost/benefit ratio is not always convenient.

The HRV evaluation could become an important tool for health status in risks population, even though the use of HRV alone for risk stratification of SCD is limited and further studies are needed.

INTRODUCTION

In the past decades, in high-income countries, thanks to the adoption of preventive measures, cardiovascular mortality was significantly reduced [1]. Nonetheless, cardiovascular diseases (CVD) are a leading cause of morbidity and mortality worldwide [2-5]. In developing countries, CVDs are responsible for approximately 17

million deaths every year. Sudden cardiac death (SCD) represent about 25% of these deaths, one of the most important and unresolved problems in clinical cardiology [6].

SCD in young people has an estimated incidence of 0.46-3.7 events per 100000 person-years and it is more frequent in men than women as summarized in Table 1

Table 1. SCD rate estimated per 100000 person-years: the risk of SCD is higher in men than in women [7].

	MEN	WOMEN
SCD rate estimated per 100000 person-years	6.68 (95% CI - 6.24, 7.14)	1,46 (95% CI - 0.95, 1.98)

[8, 9]. In young people it relates to channelopathies and cardiomyopathies [10-14], myocarditis and substance abuse [15-20]. The risk of SCD increases with age due to the higher prevalence of coronary artery disease (CAD), valvular heart diseases and heart failure (HF) in older age [7]. To ascertain the cause of the death in young people, the autopsy remains the main procedure, along with histological, immunohistochemical, toxicological, and genetic examinations; nonetheless, about 48% of these deaths result unexplained [10].

The identification of risk factors for SCD is the philosopher's stone of cardiology. In the major number of cases (>90%), the victim has previously known or unrecognized cardiac abnormality [21, 22]. To date, this field of research is full of difficulties because the phenomenon of SCD originates as a 'perfect storm', interacting with a vulnerable substrate (genetic or acquired changes in the electrical or mechanical properties of the heart) with multiple transient factors that participate in triggering the fatal event [23].

Several studies have provided evidence that the predisposition to die suddenly can be traced in the genes, even in absence of a Mendelian disease, and encourages molecular investigations to identify DNA markers to predict SCD in the general population [24, 25].

In the last decades, researchers throughout the world tried to identify a broad range of 'markers' for SCD. Besides utilizing public access defibrillation (PAD) procedure to rescue impending death patient after collapse, the better way is to prevent onset SCD by adopting medical aid prior to collapse [26]. For patients with myocardial ischemia, more "indicators" have been proposed, such as programmed ventricular stimulation (PVS), late potentials, heart rate variability (HRV), baroreflex sensitivity, QT interval dispersion, microvolt T-wave alternans and heart rate turbulence [27].

Among these, HRV proved to be the most interesting marker. It is considered, indeed, a standard noninvasive method for evaluating Autonomic Nervous System

(ANS) function [28]. Previous studies have shown that HRV is a powerful prognostic indicator of arrhythmic events following myocardial infarction [29, 30]. Sympathetic activity is associated with the low frequency range (LF, 0.04–0.15 Hz) while parasympathetic activity is associated with the higher frequency range (HF, 0.15–0.4 Hz) of modulation frequencies of the heart rate [31]. This frequency range difference represents an important marker to identify the contribution of sympathetic and parasympathetic systems. As well described in literature, lower HRV is frequently related to a poorer autonomic function [32, 33], and this parameter is the most extensively studied among all arrhythmia risk markers.

ECG

The detection of electrocardiographic (ECG) and echocardiographic signs for the identification of SCD represents an essential part of clinical practice and it is at the base of the identification of patients at risk of SCD. In ECG continuous, each QRS complex is recorded: all intervals between adjacent QRS complexes, resulting from sinus node depolarization, named normal to normal (NN) intervals, determined the instantaneous heart rate.

An important question for the scientific community remains if these techniques must be used as mass screening in populations at risk of sudden death. For example, Italy and Japan have implemented ECG screening systems, with the aim to identify asymptomatic patients with inheritable arrhythmogenic diseases [34-36]. The evaluation of the cost/benefit profile of performing ECG screening in different populations and in different healthcare systems and settings should be carried out. Notwithstanding the recent studies, there is no clear data supporting the benefit of broad screening programs in the general population [37, 38]. Nonetheless, for what concerns the inclusion of ECG as an essential technique for the prevention of SCD in adolescent athletes, the European Society of Cardiology suggests the incorporation [39, 40], while the American Heart Association considers

Table 2. Parameters utilized for HRV analysis [49].

MEASUREMENT OF HRV		SPECTRAL COMPONENTS	
TIME DOMAIN METHODS	FREQUENCY DOMAIN METHODS	SHORT TERM RECORDING (2-5 minutes)	LONG-TERM RECORDING (24 hour)
Standard deviation of the NN intervals (SDNN)	Power spectral density (PSD)	Very Low Frequency (VLF) (Milliseconds squared)	Very Low Frequency (VLF)
Standard deviation of the average NN intervals (SDANN)	PSD parametric	Low Frequency (LF) (Milliseconds squared)	Low Frequency (LF)
Root mean square of difference of successive RR intervals (RMSSD)	PSD non parametric	High Frequency (HF) (Milliseconds squared)	High Frequency (HF)

more important personal/family history and physical examination [41].

However, a standard resting 12-lead ECG can identify the principal inherited disorders associated with ventricular arrhythmias (VAs) and SCD such as channelopathies (Long Q-T Syndrome, Short Q-T Syndrome, Brugada syndrome, Catecholaminergic polymorphic ventricular tachycardia) and cardiomyopathies (Arrhythmogenic right ventricular dysplasia and Hypertrophic cardiomyopathy). Furthermore, the ECG techniques can contribute identifying structural disease including bundle branch block, atrioventricular (AV) block, ventricular hypertrophy and Q waves consistent with ischemic heart disease or infiltrative cardiomyopathy. Electrolyte disturbances and the effects of various drugs may result in the repolarization of abnormalities and/or in the prolongation of the QRS duration. Exercise stress testing combined with ECG testing has been used for the detection of silent ischemia in adult patients with VAs. Exercise-induced non-sustained ventricular tachycardia (V-tach or VT) was reported in nearly 4% of asymptomatic middle-aged adults and was not associated with an increased risk of total mortality [42].

Heart rate (HR) and HR variability (HRV)

HR and HRV provide a measure of how the organism reacts and adapts itself to stress, physical fatigue and metabolic-request changes [43].

The intrinsic HR generated by the sinoatrial node (SA node) in the absence of any neural or hormonal influence is about 100 to 120 beats per minute (BPM). However, in healthy individual, resting HR would never be that high. The normal resting adult human heart rate ranges from 70–75 bpm, but this value decreased in

trained people (around 60 bpm). The exercise training influences the parasympathetic tone, reducing HR [44]. In fact, practicing endurance sport can lead to slow heart rate below 60 bpm at rest, so-called "bradycardia", and it is considered a training status index [45]. Several studies, on the other hand, indicate that the normal resting adult heart rate is probably closer to a range between 50 and 90 bpm. During sleep a slow heartbeat with rates around 40–50 bpm is common and is considered normal. When the heart is not beating in a regular pattern, this is referred to as an arrhythmia [46, 47].

The period of time between two consecutive beats is called cardiac period (CP); the duration time is not the same generating the HRV, defined as the fluctuation degree of HR around its mean value [48]. HRV is mirroring the regularity of heart beats: bigger regularity - lowers HRV (and vice versa). Regularity of heartbeats is derived from a quantity of values; equal to the times elapsed between successive heartbeats. They are named R-R intervals and are measured in millisecond (ms). R-R intervals are obtained from ECG or tachograph. The physiological origins of HRV are the fluctuations of the activity of cardiovascular vasoconstrictor and vasodilator centres in brain. Normally these fluctuations are a result of blood pressure oscillation (baroreflex modulated), respiration, thermoregulation, and circadian biorhythm. All these factors can influence the length of beat-to-beat intervals, named R-R intervals.

Politano et al. [49] described different methods to determine HRV: time domain methods, frequency domain methods, short-term recording and long-term recording. Analyzing the differences among HRV measures, the SDNN (Standard Deviation of Normal-to-Normal R-R intervals) is not a well statistically method because it is related to the recording period. The

SDANN (Standard Deviation of the 5-minute Average NN intervals) represents an estimate of the heart changes in two periods with a duration of 5 minutes. Frequently, the measure of the root-mean-square of the difference of successive R-R intervals (RMSSD) was used. As a frequency domain method, the power spectral density (PSD) analyzes the relationship between power and frequency. In the category of short-term recording (2-5 minutes) Very Low Frequency (VLF), Low Frequency (LF) and High Frequency (HF) are analyzed. In the category of long-term recordings, the same parameters are evaluated in the 24-hour period (Table 2).

The HRV is related to a wide broad spectrum of disease or symptoms [26, 50-75], as illustrated in Figure 1.

The clinical use of HRV was described for the first time in 1963 [76], but it became a strong and important factor in the death cases after heart failure during the 90s [77-79]. Thanks to studies on animal models the true nature of HRV was discovered: the lower frequencies of the power spectrum of HRV are under control of the sympathetic nervous system directed to the heart, whereas higher frequencies are regulated by vagal activity modulated by respiration and depict respiratory sine arrhythmia [80, 81]. On the other hand, thanks to HRV power spectral analysis, several studies described that a lower respiratory sinus arrhythmia

connected with deep breathing tests are related to cardiac vagal dysfunction in obese adolescents [28]. Moreover, the HRV marker was frequently investigated in women with the aim to identify the relationship among obesity (analyzing lean and obese groups) and menopausal age (premenopausal and postmenopausal group). The power spectral analysis of HRV highlighted a significant reduction in LF and HF both in obesity group and in postmenopausal group. These findings are related to a reduction of sympathetic and parasympathetic activities: the reduction of the sympathetic branch is directly linked to obesity [31]. On the other hand, a reduction of the parasympathetic activity is associated with different conditions related to higher rate of morbidity and mortality [28].

In elderly individuals, the HR spectrum was observed lower because respiratory sine arrhythmia is lost with ageing [82]. In diseased individuals with heart failure, reduced or abnormal HRV are indicators of an increased risk of mortality [83-85]. HRV has proved to be useful in predicting SCD in patients suffering from non-cardiac causes [86, 87].

To date, even though both HR and HRV are related with cardiovascular risk and SCD, not always they have been used to evaluate the health conditions of athletes [88-92].

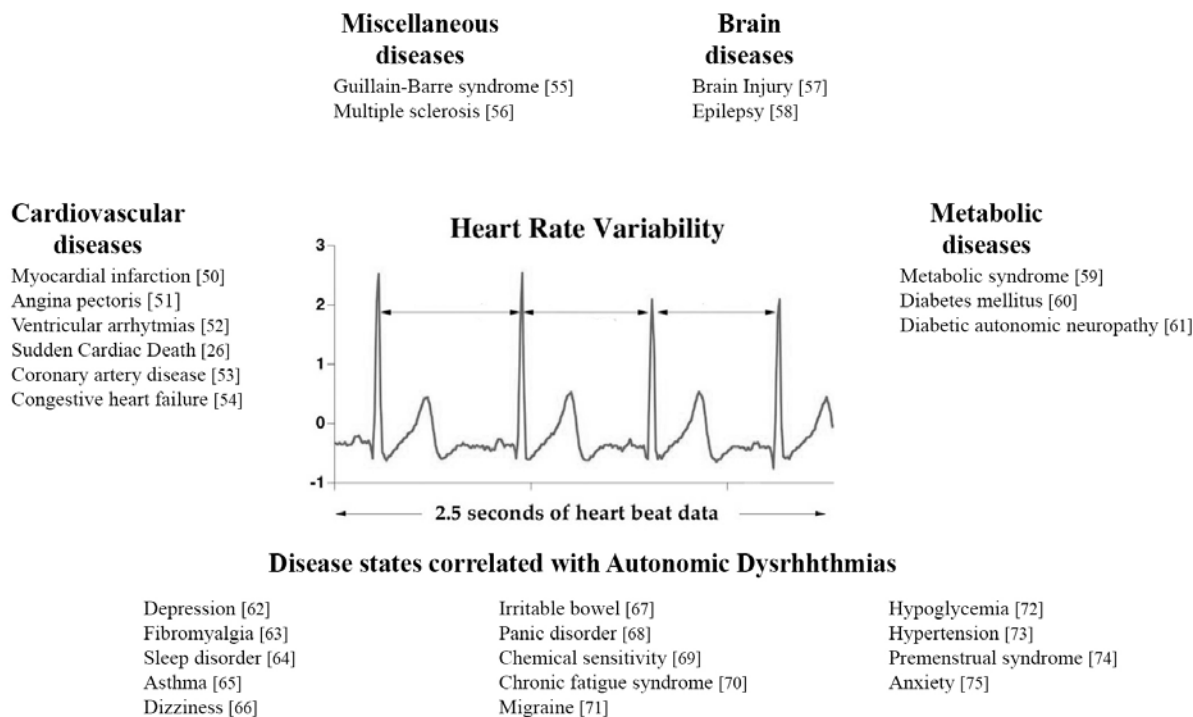


Figure 1. Principal diseases related to HRV.

It is very interesting that athletes appear at excessive risk of SCD compared with similar-aged non-athletes [93]; the annual incidence of SCD in young athletes (<35 years) is estimated to range from 0.7 to 3.0 per 100 000 athletes [94]. In older athletes, the incidence is higher and is expected to increase with age [95]. The intensity of the activity and the age of the athlete are core risk factors.

It is well known that an intense training forces the entire body to adapt to this condition through the development of morphological and functional changes [96-98]. These adjustments mean that the heart of an athlete appears different from that of a sedentary subject [99]. Typically, SCD occurs in athletes when pathological hypertrophic enlargement of the heart went undetected or it was incorrectly attributed to benign athletic adaptations. Other alternative causes of SCD are: episodes of isolated arrhythmias which degenerated into lethal ventricular fibrillation and asystole, and undetected asymptomatic congenital defects of the cardiac valves. For these reasons, coaches and staff at sporting facilities are trained to face emergency situations, perform cardiopulmonary resuscitation and use automatic external defibrillators [100, 101].

In 2001, Lombardi et al. examined the role of HRV for identifying patients at risk of SCD, concluding that the measurement of HRV represents a useful research tool for documenting events in various clinical settings, even if the specificity and predictive accuracy of imminent or future fatal arrhythmia events have been relatively low yet. Another study [102] suggests that short-term HRV recordings should be routine in chronic heart failure (CHF) patients. In CHF, markedly reduced HRV has been demonstrated to coincide with the severity of CHF, as well as being an independent marker of sympatho-excitation. On the other hand, after acute myocardial infarction, depressed HRV predicts cardiac mortality and malignant arrhythmias [103, 104]. In 2007 Kiviniemi et al [105]. demonstrated that HRV spectral parameters (Table 2), had a strong prognostic power as predictor factors of SCD.

Ebrahimzadeh et al. [26] stated that the four-minute interval before SCD contains more information related to the SCD which can be used for prediction. They further specified that the first one-minute interval before SCD contains much more precious information for prediction of SCD in comparison with other intervals.

Finally, Maranesi et al. [43] described an innovative low-cost, large-scale procedure for HR and HRV monitoring from signals obtained using comfortable

wearable sensors in order to evaluate the health status of an athlete besides his/her performance levels. Thanks to tachograph, they have monitored 10 amateur athletes in contrast with 10 sedentary subjects, with no differences in term of age, weight and height. They acquired tachogram at resting phase, during exercise and in the recovery phase. Their results suggest that physical activity has a beneficial effect on health status (RMSSD lower than normal, HR lower and HRV higher at resting phase).

DISCUSSION AND CONCLUSION

The SNA controls every aspect of cardiac activity. It is well described that autonomic instability and CNS disorders can lead to cardiovascular diseases. As previously analyzed, the autonomic cardiac innervations are involved in SCD. Their role is important in cardiac excitability and propagation [106].

HRV is probably the most analyzed index in the cardiovascular risk stratification technical literature, and an important number of models and methods have been developed for this purpose. As previously described, the HRV represent an accessible technique for evaluating the risks of SCD. There are several open questions for the scientific community related to use of HR and HRV as predictor factors of SCD, such as economic feasibility, applicability in mass screening and comfort of the measurements.

Nowadays, low HRV has been shown to be independently predictive of increased mortality in post-myocardial infarction patients, CHF patients, in contrast with the data of the general population.

Contrariwise, the relationship between HRV and SCD has received limited evaluation in low-risk cohorts. Furthermore, in general population the attributable risk is modest and the cost/benefit ratio is not always convenient. The HRV evaluation could be an important tool for health status in risks population, such as athletes, subject with familiarity, etc. For example, SCD remains the leading medical cause of death in athletes, even if, the precise causes are unclear. To date, the prevention of the SCD represents a broad ethical challenge, as it requires balancing the benefits and risks of an inappropriate decision for an athlete [107].

In this scenario, further studies are required to determine if the inclusion of HRV in a multi-marker approach would improve risk prediction of SCD in the general population. To date, the use of HRV alone for risk stratification of SCD is limited.

CONFLICTS OF INTEREST

The authors declare that there are no conflict of interests, financial or otherwise, regarding the publication of this paper.

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