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13

Electrocardiographic Analysis of Heart Rate Variability in Aging Heart

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1. Introduction

Heart rate variability (HRV) is a non-invasive and quantitative marker of cardiac autonomic function that reflects the regulation of the sinoatrial node by the sympathetic and parasympathetic branches of the autonomic system (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996).
The clinical importance of autonomic function became evident when HRV was confirmed to be strong and independent predictor of mortality after acute myocardial infarction (Kleiger RE et al., 1987; Bigger JT et al., 1993; Huikuri HV, 1995; Bigger JT et al., 1997). Recently, in addition to the well-accepted application in cardiology, heart rate variability has also drawn attention in other important application fields as geriatric medicine.
Aim of the chapter is to illustrate the usefulness of electrocardiographic analysis of heart rate variability, focusing on senescent heart. The number of elderly people in western developed countries is rapidly growing-up.
Currently, 31 million people are older than 65 years in the United States, representing 12% of the global population. By 2025 a percentage of 20% of the population will be older than 65 years. The prognostic significance of conventional risk factors applicable to younger ages tends to disappear in old age (Anderson KM et al., 1987; Harris T et al., 1988). So it is important to find prognostic and diagnostic markers to define the risk of death among elderly subjects.
HRV analysis is able to give prognostic information beyond that obtained by traditional risk markers in populations of elderly subjects (Heikki V et al., 1998). Assessment of heart rate variability in older subjects is, however, complicated by changes in the autonomic nervous system that occur with advancing age (O'Brien IAD & O'Hare P, 1986).

2. Measurement of heart rate variability

The employ of high frequency 24-h electrocardiographic Holter recorders for analysis of HRV has provided helpful insight into physiological and pathological conditions and risk stratification in different cardiac diseases.
There are many commercial accessible automated HRV measurement devices utilizing variety of methods, providing cardiologists, internists and geriatricians with a seemingly simple tool for both research and clinical studies.

In 1996, time and frequency domain parameters for the assessment of the autonomic regulation was established (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996). Variations in heart rate may be evaluated by a number of methods including:

- time-domain analysis,
- frequency domain analysis
- non linear analysis

2.1 Time-domain analysis

When heart rate variability is assessed by time-domain indices (Table 1), in a continuous electrocardiographic record, each QRS complex is detected, and the so-called normal-to-normal (NN) intervals (that is all intervals between adjacent QRS complexes resulting from sinus node depolarizations), or the instantaneous heart rate is calculated (Figure 1, Figure 2). Simple time–domain variables that can be obtained include the mean NN interval, the mean heart rate, the difference between the longest and shortest NN interval, the difference between night and day heart rate, etc.

Other time–domain measurements that can be used are: variations in instantaneous heart rate secondary to respiration, tilt, Valsalva manoeuvre, or secondary to phenylephrine infusion. These differences can be described as either differences in heart rate or cycle length. Time-domain analysis of HRV can be performed using both statistical and

Time-Domain Measures of HRV			
Statistical Measures		*Geometric Measures*	
SDNN	Standard deviation of all NN intervals.	**HRV triangular index**	Total number of all NN intervals divided by the height of the histogram of NN intervals measured on a discrete scale with bins of 7·8125 ms (1/128 s).
SDANN	Standard deviation of the averages of NN intervals in all 5 min segments of the entire recording.		
RMSSD	The square root of the mean of the sum of the squares of differences between adjacent NN intervals.	**TINN**	Baseline width of the minimum square difference of the triangular interpolation of the highest peak of the histogram of all NN intervals.
SDNN index	Mean of the standard deviations of all NN intervals for all 5 min segments of entire recording.		
SDSD	Standard deviation of differences between adjacent NN intervals.	**Differential index**	Difference between the widths of the histograms of differences between adjacent NN intervals measured at selected heights.
NN50 count	Number of pairs of adjacent NN intervals differing by more than 50 ms in the entire recording.		
pNN50	NN50 count divided by the total number of all NN intervals.	**Logarithmic index**	Coefficient φ of the negative exponential curve $k \cdot e^{-\varphi t}$ which is the best approximation of the histogram of absolute differences between adjacent NN intervals.

Table 1. Time-Domain measures of HRV

geometrical methods. From a series of instantaneous heart rates or cycle intervals, particularly those recorded over longer periods, traditionally 24 h, complex statistical time-domain measures can be calculated. Few studies have fully used the main 4 statistical time domain measures of heart rate variability (HRV):

- the root mean square of the successive normal sinus RR interval difference (rMSSD)
- percentage of successive normal sinus RR intervals >50 ms (pNN50)
- standard deviation of all normal sinus RR intervals during a 24-hour period (SDNN)
- standard deviation of the averaged normal sinus RR intervals for all 5-minute segments (SDANN)

The series of NN intervals can also be converted into a geometric pattern (Figure 3, Figure 4) such as the sample density distribution of NN interval durations, sample density distribution of differences between adjacent NN intervals, Lorenz plot of NN or RR intervals, etc.

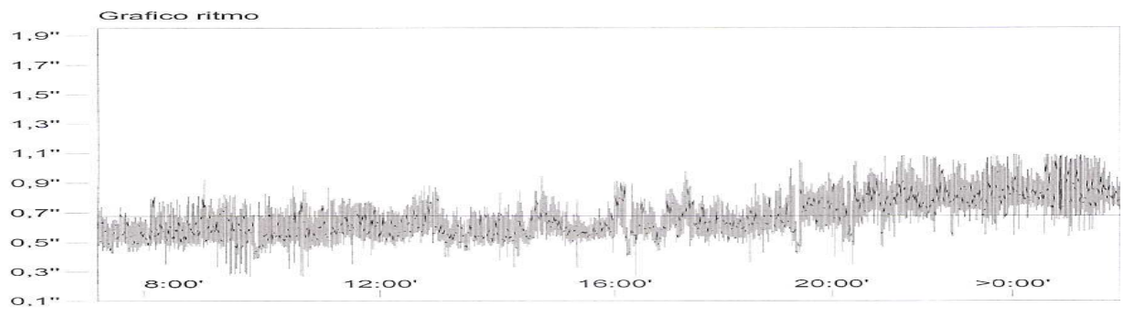

Fig. 1. NN sequences tachogram in a young healthy subject

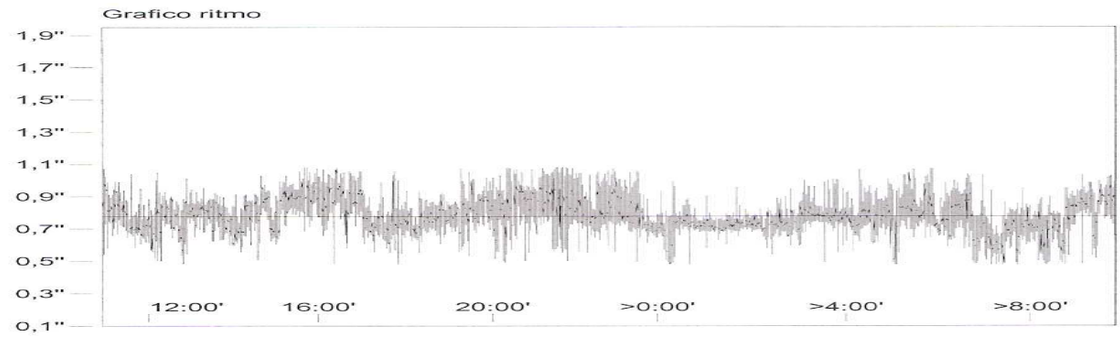

Fig. 2. NN sequences tachogram in an old healthy subject

2.2 Frequency domain analysis

Frequency domain measures of HRV (Table 2) provide information about the frequency distribution of the components of HRV using Power Spectral Density analysis (PSD) (Malliani A et al., 1994). PSD analysis provides the basic information of how power (i.e. variance) distributes as a function of frequency (Figure 5) (Akselrod S et al. 1981). Independent of the method employed, only an estimate of the true PSD of the signals can be obtained by proper mathematical algorithms. Fast Fourier transform, point process, and autoregressive procedures quantify components of HRV that are expressed in 2 main frequency regions or bands (Hz):

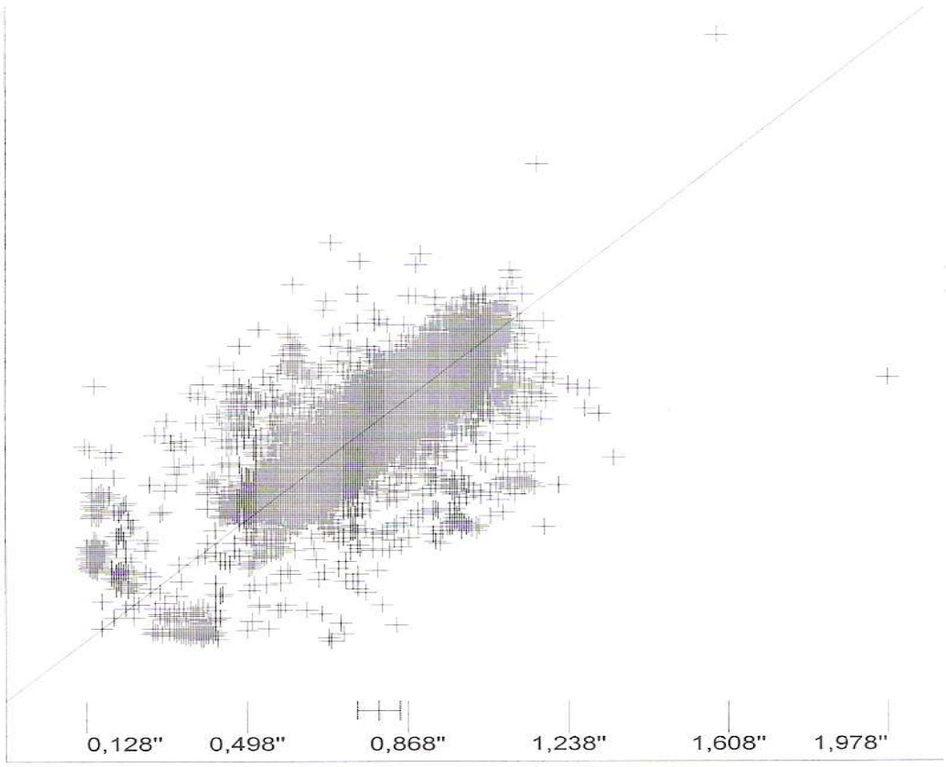

Fig. 3. Scattergram representation of HRV: on X axis the duration of RR sequence, on Y axis the duration of the precedent RR sequence

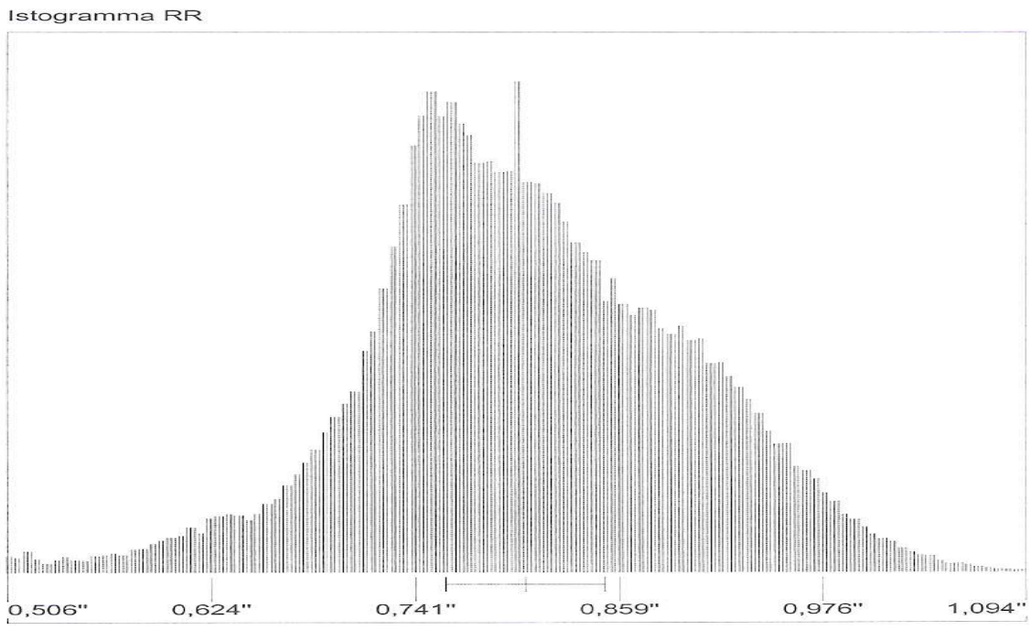

Fig. 4. Histogram representation of HRV: graphic shows the distribution of duration of RR sequences

high-frequency (HF) and low-frequency (LF) power. HF power primarily reflects respiratory-modulated parasympathetic outflow, whereas LF power is subject to both substantial sympathetic influence and varying amounts of parasympathetic contribution. The LF/HF ratio has been proposed, by some investigators, as an index of relative balance of sympathovagal influences on the heart, with higher LF/HF ratios reflecting increased sympathetic activity and/or decreased parasympathetic tone. The origin of very low frequency (VLF) oscillations in the power spectra of HRV is controversial with possible mechanisms involving thermoregulation and/or renin-angiotensin-aldosterone system. When spectral analysis is used to analyse the sequence of NN intervals in the entire 24-h period the result include an ultra-low frequency component (ULF), in addition to VLF, LF and HF components. Methods for the calculation of PSD are generally classified as non-parametric and parametric.

Frequency-Domain Measures of HRV			
Short-term recordings		***Analysis of 24 hh***	
Variable	**Description**	**Variable**	**Description**
5 min total power (ms^2)	The power of NN intervals over the temporal segment	**Total power (ms^2)**	Variance of all NN intervals
VLF (ms^2)	Power in very low frequency range	**ULF (ms^2)**	Power in ultra low frequency range
LF (ms^2)	Power in low frequency range	**VLF (ms^2)**	Power in very low frequency range
LF norm	LF power in normalised units LF/(Total Power-VLF)X100	**LF (ms^2)**	Power in low frequency range
HF (ms^2)	Power in high frequency range	**HF (ms^2)**	Power in high frequency range
HF norm	HF power in normalised units HF/(Total Power-VLF)X100	**α**	Slope in the linear interpolation of the spectrum in a log-log scale
LF/HF	Ratio LF [ms^2]/HF [ms^2]		

Table 2. Frequency-Domain measures of HRV

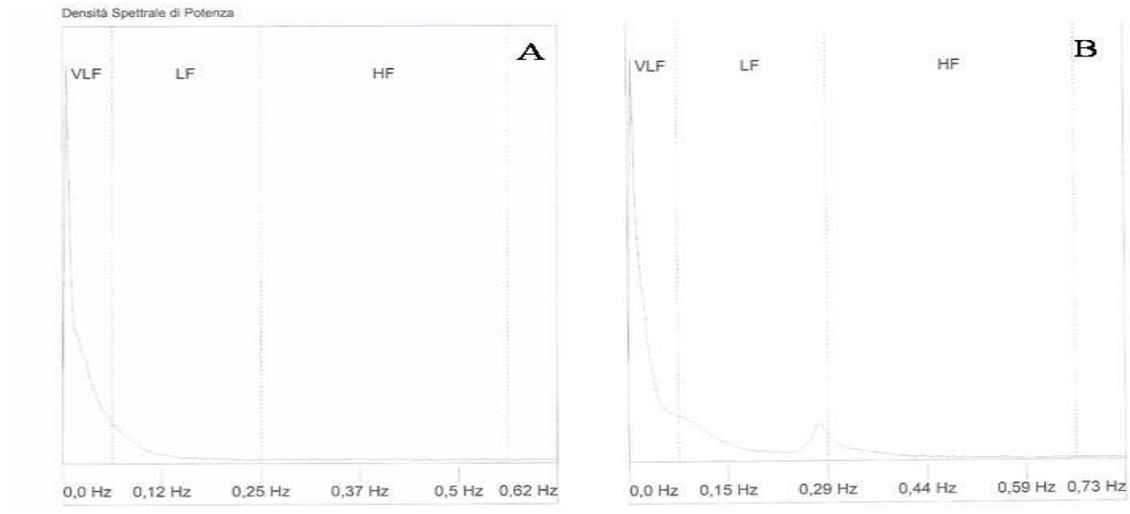

Fig. 5. Power spectral density analysis (A) in an old and (B) in a young subject

2.3 Non linear analysis

Cardiovascular signals have been largely analyzed using traditional time and frequency domain measures. However, such measures fail to account for important properties related to multi-scale organization and nonequilibrium dynamics.

In recent years there has been increasing evidence that HRV may reflect a much more complex phenomenon representing the nonlinear fluctuations of cardiac-autonomic outflows in a fractal or entropic, perhaps chaotic way (Perkiomaki JS et al., 2005). The chaotic vs. fractal/entropic/stochastic descriptions of HRV present a dilemma in interpreting its power spectrum (Watanabe MA, 2003). Definitive testing of these divergent characterizations is key to unrevealing the physiologic mechanisms underlying HRV, which is critical to its proper use as a noninvasive marker for cardiac mortality risk assessment and stratification in chronic heart failure and other cardiac diseases (Mäkikallio TH et al., 2002).

Non-linear phenomena are determined by complex interactions of haemodynamic, electrophysiological and humoral variables, as well as by autonomic and central nervous regulations. It has been speculated that analysis of HRV based on the methods of non-linear dynamics might elicit valuable information for the physiological interpretation of HRV and for the assessment of the risk of sudden death (Mansier P et al., 1996).

3. Heart rate turbolence

In 1999, the analysis of the heart rate turbulence (HRT) was introduced. Heart rate turbolence describes the fluctuations of the RR interval after ventricular premature beats expressing the residual ability of the sympathetic nervous system to adapt itself to instantaneous pressure variations and to adjust cardiac frequency to sudden and unexpected flow reductions (Francis J et al., 2005; Klingenheben T et al., 2008). Ventricular extrasystole induces a modification of the ventricular contraction axis, causing a reduction of the cardiac flow which is proportional to the previous beat and to its point of origin.

A reduction of the cardiac flow brings about an immediate decrease of the cerebral flow, followed in a few seconds by a stimulation of the aortic baroreceptors and a subsequent neurovegetative cardiac stimulation according with a frequency reduction. However, this reflex occurs in patients with a normal sympathetic-vagal balance.

HRT is usually expressed by two parameters, the turbulence onset and the turbulence slope. The turbulence onset describes the difference between the mean of the two sinus RR intervals before and the first two sinus RR intervals after the ventricular premature depolarization divided by the mean of the last two sinus RR intervals before the ventricular premature depolarization. The turbulence slope is defined as the highest slope of the regression line over any of the five successive sinus beat RR intervals during first 20 sinus beat RR intervals after a ventricular premature depolarization.

4. Autonomic regulation in senescent heart

It is well known that the anatomy, histology and physiology of the heart changes with age (Klausner SC & Schwartz AB, 1995). Together, age-related structural and functional changes reduce the complexity of physiologic heart rate control, impairing the individual's ability to adapt to stresses such as hypotension.

Aging heart is characterised by peculiar biophysical properties such as increased deposition of collagen and fat. On the electrophysiological level in senescent heart several alterations

have been described such as a progressive prolongation of the action potential (explained by a decreasing density of the transient outward potassium current, and a prolongation of the decay time of the L-type calcium current) (Salameh A et al., 2010). Interestingly beat-to-beat fluctuation of heart rate, commonly known as heart rate variability declines steadily with age (Colosimo A et al., 1997). Reduced intrinsic heart rate were also observed in older individuals (Fleg JL & Kennedy HL, 1982). Furthermore it has been described an age-related decline in parasympathetic regulation and greater sympathetic modulation (De Meersman RE & Stein PK, 2007). Studies have demonstrated a decline in sino-atrial node parasympathetic activity and an increase in sympathetic activity in the heart with aging (Eckberg DL et al., 1971). The impairment of cardiac-vagal neurons appears to be the major determinant of changes in the control of heart rate that come with aging, since aging reduces the tachycardia that may be induced by atropine in humans and animals (Ferrari AU et al., 1991). The age-related increases in sympathetic nervous system activity under resting conditions seem to be related mainly to a primary increase in central sympathetic nerve discharge (Esler M et al., 2002).

Functional changes in elderly populations include a gradual increase in basal and stimulated plasma noradrenaline concentrations, altered adrenoceptor function and diminished responsiveness to adrenergic agonists and antagonists (Rubin PC et al., 1982; Xiao RP et al., 1998).

5. Frailty and heart rate variability

The age-related changes in the "complexity" of cardiovascular dynamics reflect the breakdown and decoupling of integrated physiologic regulatory systems occurring with senescence (Goldberger AL, 1996) .

Results from the Cardiovascular Health Study (CHS), confirmed an impairment in cardiovascular ability to adapt to external and internal perturbations with advancing age. The Cardiovascular Health Study (CHS) was a population based study of risk factors for cardiovascular disease (CVD) and stroke, enrolling 5,888 community-dwelling subjects aged ≥65 years. Authors found that cardiac autonomic function, assessed by frequency-domain HRV, declines most at 65–70 and levels off at age >75. The decline was independent of CVD risk or change in CVD risk (Stein PK et al., 2009).

Frailty is a biological syndrome typical of old persons, characterized by low reserve and resistance to stressors. It has been suggested that frailty may result from cumulative declines across multiple physiological systems that cause vulnerability to adverse outcomes. Fried et al. proposed a phenotype of frailty involving at least three of five components: unintentional weight loss, self-reported low energy level, weak grip strength, slow walking speed and low level of physical energy (Fried LP et al., 2001). Using a frailty index based on this phenotype, researchers have reported its association with falls, hospitalization, disability and death (Bandeen-Roche K et al., 2006; Boyd CM et al., 2005; Cawthon PM et al., 2007; Ensrud KE, et al., 2008). Recently a study showed that in old women, decreased HRV indices were associated with an increased risk of frailty (Varadhan et al., 2009). Similarly in Women's Health and Aging Study I, a community-based observational study that enrolled 389 community-dwelling women aged 65 years and older with moderate to severe disability, frailty was consistently associated with lower HRV as assessed using time and frequency-domain indices (Chaves PHM et al., 2008).

Both studies supports the notion that less physiological complexity marks frailty and provides an empirical basis to the concept of frailty as a syndrome of homeostatic impairment.
Congruent with this theory are the results of a cross-sectional study of HRV of 344 healthy subjects, (10 to 99 years old) which assessed the relation between autonomic function and longevity. Authors evidenced that a persistently high HRV in the elderly represents a marker predictive of longevity (Zulfiqar U et al., 2010). Another study (Chiang JK et al., 2011) evaluated the association between frequency domain heart rate variability and the risk of unplanned readmission in hospital in total of 78 geriatric patients. Frequency domain heart rate variability indices measured on admission were significantly associated with increased risk of unplanned readmission that was significantly higher in patients with lower levels of total power, LF power and HF power.
All these evidences suggest that healthy longevity could depend on preservation of autonomic function, in particular, HRV parasympathetic function, despite the early age-related decrease.

6. Heart rate variability and mortality in elderlies

Reduced HRV variability is commonly found in older people (Colosimo A et al., 1997) and has been linked to increased risk for morbid and fatal outcomes (Tsuji H et al., 1996).
Framingham Heart Study participants, in a closely monitored community-based study, underwent a routine biennial examination including 2-hour ambulatory ECG recordings to evaluate the prognostic implications of heart rate variability. Results, based on 2-hour monitoring, demonstrated that reduced heart rate variability predicts mortality in a population based sample of elderly subjects (Tsuji H et al., 1994).
UK-HEART, a prospective study powered for mortality, examined the value of heart rate variability measures as independent predictors of death in old patients with heart failure. In UK-HEART study were recruited 433 outpatients 62±9.6 years old with heart failure. Concordant to the above, a reduced HRV identified patients at high risk of death. Interestingly reduced HRV was a better predictor of death due to progressive heart failure than other conventional clinical measurements (Nolan J et al., 1998).
In another study of 347 subjects of ≥65 years of age (mean, 73± 6 years) HRV gave prognostic information beyond that obtained by traditional risk markers (Heikki V et al., 1998). In particular, after a 10-year follow-up, among all analyzed variables, a steep slope of the power-law regression line of HRV was the best predictor of all-cause mortality.
Interestingly in the Rotterdam Study, a population-based cohort study of 2,088 men and 3,184 women aged ≥55 years (mean follow-up: 4 years), increased heart rate variability resulted an even stronger indicator of cardiac mortality than decreased heart rate variability (de Bruyne MC et al., 1999). The authors examined the association between heart rate variability on a standard 10-second electrocardiogram and cardiac and all-cause mortality. In subjects in the highest quartile of SDNN (a time-domain measure of HRV), a more pronounced risk for cardiac mortality was present. In the Zutphen Study an association of increased HRV with all-cause mortality was observed only in elderly men (Dekker JM et al., 1997). Similarly, in the Bronx Aging Study (Bernstein JM et al., 1997), among men and women aged 75-85 years, no association was found between decreased HRV and cardiac or all-cause mortality, but an association of increased HRV with cardiac events was present in women.

It has been suggested that, increased HRV, unlike decreased HRV, is hardly influenced by the autonomic nervous system. The risk of mortality presumably associated with increased HRV has been reported to sinus node dysfunction.
More recently LILAC study examined 298 people older than 75 years (average age: 79.6 years). One hour of ambulatory ECG recording was obtained during routine medical examination conducted each year in July (mean follow-up time of 1152 days). Authors evidenced that an intermediate-term fractal-like scaling exponent of RR intervals is a better predictor of death than the traditional measures of HRV in elderly community-dwelling people (Hotta N et al., 2005).
Taken together the above data indicate that analysis of heart rate variability can be used to identify older men and women with an increased risk for cardiac mortality.

7. Influences on heart rate variability

Biologically, the physiological outputs of the human body, including heart rate variability, emerge from interactions among a variety of factors, ranging from genes to organs to the environment.
Heart rate variability analysis in elderlies, is influenced by various physiological factors including gender, postural changes, ventilation and time of day. Pathological conditions such as congestive heart failure and diabetic diabetic neuropathy are associated with alterations in heart rate variability.

7.1 Genetic influences on heart rate variability

Recent evidence suggests that genetic factors may contribute to the beat-to-beat variability in heart rate (Singh JP et al., 1999).
Analysis from Framingham study suggested there may be influential genetic regions contributing to HRV on chromosome 15 at 62 cM and on chromosome 2 at 153 cM (Singh JP et al., 2002).
Another study in an Asian population showed genes located on 216 cM region at chromosomes 5 and on 77 cM region at chromosome 18 may be involved in the regulation of heart rate (Gombojav B et al., 2008).
The apolipoprotein-E (APOE) gene has been studied extensively in regard to its relationship to aging-associated medical illness including cardiovascular disease, geriatric cognitive decline and late-onset Alzheimer's disease.
It has been hypothesized that diminished physiological complexity, as measured by heart rate variability, is influenced by polymorphisms in the APOE allele among elderly individuals. In a study, multi-scale entropy (MSE), an analysis used in quantifying complexity for nonlinear time series, was employed to analyze heart-rate dynamics. Reduced physiological complexity, as measured by MSE, was significantly associated with the presence of the APOE ε4 allele in healthy elderly subjects, as compared to APOE ε4 allele non-carriers (Cheng D et al., 2009). This finding suggests a role for the APOE gene in the diminished physiological complexity seen in elderly populations.
Variants in transcription factor 7-like 2 (TCF7L2) gene have been found strongly associated with an increased risk of type 2 diabetes, as well as with an impairment of glucagon-like peptide-1 (GLP-1) signalling chain. It has been shown that TT genotype of rs12255372 and rs7903146 TCF7L2 gene variants are associated with lower insulin secretion and higher

cardiosympathetic activity (Boccardi V et al., 2010). Moreover, such effect is independent of GLP-1 and insulin plasma concentrations suggesting a potential role of such gene variants in increasing cardiovascular risk through enhanced sympathetic nervous system activity.
It has been demonstrated that AKAP10 Val allele, the dual-specific A kinase-anchoring protein 2, predicted greater resting heart rate and diminished HRV suggesting that this variant may modulate the sensitivity of cardiac pacemaker cells to autonomic inputs, possibly conferring risk for arrhythmias and sudden cardiac death (Neumann SA et. al., 2009).
Other evidences support that variation in the choline transporter gene (CHT1), which encodes the choline transporter, may conceivably also account for some portion of interindividual variability in cholinergic transmission, as reflected in HRV phenotypes (Neumann SA et al., 2005). These findings show that polymorphic variation in the CHT1 gene is associated significantly with interindividual variability in HRV indices related to parasympathetic (cholinergic) activity.
All these studies strongly indicate that heart rate is controlled by genes mapped to several loci.

7.2 Environmental and behavioural influences on heart rate variability

Results of several studies support a potential benefit of increasing or maintaining fitness in order to slow the decline of parasympathetic control of heart rate with normal aging.
In a meta-analysis of 13 studies exercise training results in significant increases in RR interval and HF power. These changes are influenced by study population age (Sandercock GR et al., 2005). Other studies have provided inconclusive results regarding the effects of aerobic training on HRV in elderly subjects. The different results from these studies may be due to the different exercise loads (Wichi RB et al., 2009). It is well known that exercise training has direct and reflex sympathoinhibitory beneficial effects in chronic heart failure. The mechanism by which exercise training normalizes autonomic derangement and neurohumoral activation is to elucidate for further development of chronic heart failure-related training programs aimed at maximizing efficacy while minimizing workload.
Animal data support the hypothesis of the alteration of the autonomic nervous system by air pollution. Clinical exposure studies also support these findings (Schneider A et al., 2010). It has been reported that elderly subjects experienced significant decreases in HRV immediately following exposure to concentrated air pollution particles persisting at least 24 hours after exposure for some HRV parameters (Devlin RB et al., 2003).
Various studies with different recording lengths of ECG and different populations evidenced a negative association of smoking with measures of HRV, although significant effects were not always observed for all HRV measures determined or for both sexes, or were not confirmed in multivariable analyses (Hayano J et al., 1990; Kobayashi F et al., 2005).
A recent report from the Whitehall Study (Chandola T et al., 2008) has shown that work stress is associated with decreased heart rate variability. Dietary pattern also could influence HRV.
It has been suggested that higher intake of green leafy vegetables may reduce the risk of cardiovascular disease through favorable changes in cardiac autonomic function in aging heart (Park SK et al., 2009).
Moderate alcohol assumption and intake of omega-3 fatty acids and vitamin D through fish or nut consumption seem also effective approaches for which there is some suggestive evidence linking them to increased HRV (Mozaffarian D et al., 2008).

7.3 Physiologic influences on heart rate variability

Gender is one of the factors that influence HRV (Kuo TB et al., 1999; Ryan SM et al. 1994). Studies involving models of linear analysis showed that women presented higher HRV in the supine position than men of a similar age, indicating that the female population has a higher cardiac vagal modulation and a lower cardiac sympathetic modulation.

Women demonstrate a more appropriate response to a postural change than the men even though women are postmenopausal, suggesting that autonomic heart rate modulation is better preserved in the women's group (Perseguini NM et al., 2011).

Several studies have described a circadian pattern of cardiac autonomic modulation (Malpas SC & Purdie GL, 1990), which can be quantified with a cosine periodic regression model consisting of three cosine function parameters: mean (M), amplitude (Â), and acrophase (θ) (Rodríguez-Colón SM et al., 2010). The cosine function parameter M measures the overall average of a HRV index, the Â measures the amplitude of the oscillation of a HRV index, and the θ measures the clock time when the highest oscillation (amplitude) is reached. Lack of circadian variation of HRV is associated with increased vulnerability to cardiovascular events.

Aging is commonly associated with decreased sleep quality and increased periodic breathing that can influence heart rate variability (Brandenberger G. et al. 2003). Two distinct features depending on respiratory pattern characterize HRV in the elderly during sleep: (1) during periods of normal breathing, there is a large fall in absolute values of HRV indices without any significant sleepstage dependent variation, and a relative increase in sympathetic activity associated with decreased sleep quality, and (2) periodic breathing, that often interrupts normal respiratory patterns in most of the elderly, induces substantial modification in HRV by triggering important oscillations in the VLF range via autonomic efferents. So it is clear that respiration must be considered to correctly interpret HRV in the elderly (Schäfer C et al., 1998).

It is likely that several mechanisms are contributing at some level to the HRV that is observed with respiration (Shields RW, 2009).

Recent studies have shown that ormonal factors such as sex steroid levels, may also influence autonomic functions (Moss AJ, 2004). While physiological levels of androgens seem to be positively related with parasympathetic activity, estrogens appear positively related with sympathetic activity in men. In contrast, decreased androgen levels in aging males have controversial effects on autonomic function (Tolga Doğru M et al., 2010). Adrenal androgens seem to be more important for cardiac autonomic control.

7.4 Pathologic influences on heart rate variability

Many studies have shown decreased HRV in patients with congestive heart failure. Several reports suggested that the withdrawal of parasympathetic activity and the concomitant increase of sympathetic activity lead to decreased HRV in heart failure patients (Mark AL, 1995; Chattipakorn N et al., 2007). Measures of heart rate variability have been shown to provide independent prognostic information in congestive heart failure patients (Galinier M et al., 2000; La Rovere MT et al., 2003; Sandercock GR & Brodie DA, 2006).

Findings from large, epidemiological studies provide strong evidence that vagal tone, as measured by HRV, is lower in persons with hypertension than in normotensives even after adjustment for a range of covariates. Importantly, these studies suggest that decreases in vagal tone may precede the development of this critical risk factor for cardiovascular disease (Singh JP et al. 1998; Schroeder EB et al. 2003).

The association between diabetes and autonomic nervous system dysfunction is well known to clinicians caring for patients with clinically manifest autonomic neuropathy (Lefrandt JD et al., 2010). Recently it has been documented that even minor degrees of glucose intolerance are associated with abnormalities of autonomic balance. Homeostasis model assessment of insuline-resistance (HOMA-IR) has been applied to quantify insuline-resistance in people with or without glucose intolerance, and it has been a reliable tool in the evaluation of insuline-resistance, especially before the clinical diagnosis of type 2 diabetes. Several epidemiological studies have shown that individuals with insuline-resistance, hyperinsulinemia or increased fasting glucose have increased heart rate and reduced HRV (Galinier M et al., 1999).

In communities study, a consistent association between, metabolic syndrome and impaired cardiac autonomic modulation has been reported (Liao D et al., 1998; Park SK et al., 2006). People with metabolic syndrome tend to have a greater percentage of adipose, atherogenic dyslipidemia, hypertension, and a higher proinflammatory and prothrombotic state, all of which are associated with decreased parasympathetic and increased sympathetic tone.

In chronic obstructive pulmonary disease (COPD) patients, functional and structural changes of the respiratory system deeply influence cardiovascular function. Cardiac autonomic dysfunction, in COPD patients, is important in the development of arrhythmias.

It has been suggested that in COPD patients, combination of HRV and HRT analysis may improve risk stratification leading to a more accurate identification of high risk patients, more aggressive treatment toward preventing sudden death and/or preventing progression of disease to mortality (Gunduz H et al., 2009).

A study in COPD patients (Antonelli-Incalzi R et al., 2009) found that autonomic control deteriorates as COPD worsens. It would be plausible that the diffuse cerebral metabolic impairment well documented in COPD patients, might induce, among others, lesions to functional connection of the insular cortex. The right anterior insula has a role in modulation of sympathetic tone and is implicated in the sympathetic arousal associated with mental tasks.

Major depression and depressive symptoms are associated with decreased HRV, both in patients with coronary heart disease (Carney et al., 2001; Vigo et al., 2004) and in community subjects (Udupa et al., 2007; van der Kooy et al., 2006). Depression has been associated with increased risk of morbidity and mortality in patients with coronary artery disease (Lett et al., 2004). Dysregulation of the autonomic nervous system has been proposed as a plausible explanation (Carney et al., 2005). Results from a recent study (Kop WJ et al., 2010) confirmed that the long-term adverse cardiovascular consequences of depression may be partially explained by autonomic nervous system dysfunction and inflammation. In particular depression was associated with selected indices of autonomic nervous system dysfunction and inflammation markers (white blood cell count and fibrinogen) in individuals >65 years of age free of clinical cardiovascular diseases.

Recently authors have suggested that association between depressive symptoms with decreased HRV is due, in large part, to a shared genetic effect (Su S et al., 2010).

Autonomic dysfunction can occur in all common dementias in older people, but is a particularly common feature of Lewy body dementia and Parkinson disease dementia (Allan LM et al., 2007). Cholinergic dysfunction has been discussed as a potential cause of autonomic failure in patients with dementia, and may be particularly important in Lewy body dementia and Parkinson disease dementia, where cholinergic deficits are especially pronounced, and where the disease pathology involves the dorsal vagal nucleus.

8. Conclusions

Since reduced HRV is associated with higher cardiovascular morbidity and mortality rates, it has an important clinical impact on the elderly. The age-related changes in HRV and their implications for mortality suggest that periodic HRV monitoring of the elderly could help predict and promote longevity. Further studies are needed to clarify what different HRV measures reflect physiologically and which measure of HRV is more useful. Identifying HRV abnormalities in subjects free from clinically evident mechanical and arrhythmic problems might be a clue to detect timely patients at risk of such diseases. Recognition of the genetic determinants of HRV may provide additional insights into the pathophysiology of the autonomic nervous system and offer clues to its modulation.

The intensified research about correlations between heart rate variability and pathologies with a variety of methods (in particular from nonlinear dynamics) will not only increase our knowledge about the complex autonomic regulation but will lead us to an enhanced diagnostics and therapy for older patients. Future research will determine whether noninvasive measures of physiological complexity underlying heart rate dynamics might be useful for screening and monitoring of clinical vulnerability in older adults. Research will be needed also to identify behavioural strategies of favorably modulating autonomic function that improve outcomes in the clinic and among large populations.

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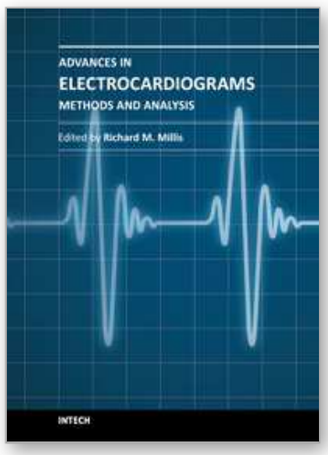

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Electrocardiograms are one of the most widely used methods for evaluating the structure-function relationships of the heart in health and disease. This book is the first of two volumes which reviews recent advancements in electrocardiography. This volume lays the groundwork for understanding the technical aspects of these advancements. The five sections of this volume, Cardiac Anatomy, ECG Technique, ECG Features, Heart Rate Variability and ECG Data Management, provide comprehensive reviews of advancements in the technical and analytical methods for interpreting and evaluating electrocardiograms. This volume is complemented with anatomical diagrams, electrocardiogram recordings, flow diagrams and algorithms which demonstrate the most modern principles of electrocardiography. The chapters which form this volume describe how the technical impediments inherent to instrument-patient interfacing, recording and interpreting variations in electrocardiogram time intervals and morphologies, as well as electrocardiogram data sharing have been effectively overcome. The advent of novel detection, filtering and testing devices are described. Foremost, among these devices are innovative algorithms for automating the evaluation of electrocardiograms.

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