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REVIEW

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Myocardial determinants in regulation of the heart rate

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Abstract Heart rate is a function of at least three factors located in the sinus node, including the pacemaker and the activity of the sympathetic and vagal pathways. Heart rate varies during breathing and exercising. The is far from being a purely academic question because, after myocardial infarction or in cardiac insufficiency, reduced heart rate variability (HRV) represents the most valuable prognostic factor. HRV is usually considered index of the sympathovagal balance and is explored using time domain analysis, such as spectral analysis. Nevertheless, methods such as the Fast Fourier Transformation are not applicable to small rodents which have an unstable heart rate with asymmetric oscillations. Nonlinear methods show chaotic behavior under some conditions. A time and frequency domain method of analysis, the Wigner-Villé Transform, has been proposed for the study of HRV in both humans and small rodents, as a compromise between linear and nonlinear methods. We developed a method to quantify both arrhythmias and HRV in unanesthetized rodents. Such a method allows study of the relationship between the physiological parameters and the myocardial phenotype. Ventricular premature beats are more frequent in 16-month-old spontaneously hypertensive rats than in age-matched controls. In addition, HRV is attenuated in spontaneously hypertensive rats, as in compensatory cardiac hypertrophy in humans, and such attenuation is considered a prognostic index. Converting enzyme inhibition reduces in parallel arterial hypertension, cardiac hypertrophy, and ventricular fibrosis; it prevents ventricular premature beats and normalizes heart rate variability. It can be demonstrated that the incidence of ventricular premature beats is linked to the myocardial phenotype in terms of both cardiac hypertrophy and fibrosis. The two factors act as independent variables. HRV is correlated with the incidence of arrhythmias, suggesting that the beneficial effects of converting enzyme inhibition are related to prevention of arrhythmias.

Key words Heart rate variability · Chaos · Transgenic mice · Adrenergic receptors · Arrhythmias

Abbreviations *HRV* Heart rate variability · *SHR* Spontaneously hypertensive rats

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Introduction

Heart rate variability (HRV) depends upon various reflex arcs, including baroreflex, and respiration. Experimental studies on HRV and myocardial adrenergic and muscarinic transduction systems suggest that the myocardial phenotype, in terms of adrenergic and muscarinic receptor density, play an additional role. A transgenic strain of mice with atrial overexpression of the β_1-adrenergic receptors was generated. HRV is attenuated in this particular transgenic strain compared to controls. Nevertheless, such mice have a normal lifespan, which demonstrates both that alterations in the myocardial phenotype, without any changes in baroreflex, are determinants of heart rate varibility, and that HRV has a prognostic value only on a diseased heart.

Heart rate and HRV are not only determined by various reflex arcs but also by the myocardial phenotype, and it is suggested that the modifications of this phenotype, in terms of adrenergic/muscarinic receptor density

participates in the well-known attenuation of HRV in cardiac hypertrophy and failure.

Heart rate accelerates or decelerates during breathing and exercising and after stress. In man, when the heart is denervated during cardiac transplantation, the heart rate is more rapid than before transplantation, and the heart beats at 90 bpm instead of 70 [1–3]. The same result is obtained pharmacologically with a combination of atropine and β-blocker. The pace-maker frequency in humans is therefore 90 bpm. The activity of the pace-maker depends on the specific equipment of the sinusal node, namely a particular calcium current called I_{CaT}, which is not inhibited by the calcium blockers, a specific Na-K current called I_f, which is the main determinant of the slow diastolic depolarization, and lack of sodium current [4–5]. There are specific inhibitors of I_f which induces bradycardia [5]. The oscillator from which the spontaneous depolarization results is unknown. Other factors may include angiotensin II since there are some angiotensin II receptors around the sinus node (unpublished data from this laboratory).

Heart rate reflects the balance between the two components of the autonomous nervous system [6]. In situ in humans the frequency of 70 bpm is obtained because of the vagal influence on heart rate, called the vagal tone, and, accordingly, atropine accelerates heart rate. Nevertheless, the situation is somewhat more complex since a β-blocker also has an effect and slows the heart rate. Therefore it is more accurate to say that the normal heart rate in human is under a dominant vagal influence. This situation is species specific, and differs in mice. Mouse have no vagal tone, and atropine injection does not result increase heart rate as it does in humans (unpublished data from this laboratory). Nevertheless, in mouse atropine reduces HRV, i.e., the standard deviation (SD) of heart rate, which means that the lack of vagal tone is not due to the absence of muscarinic receptors or vagal innervation of the myocardium.

The oscillatory variations of the heart rate are more easily measured by quantifying the SD of the mean heart rate which allows exploration of the activity of the autonomous nervous system [7, 8], although there are indications that intrinsic variations of the pace-maker exist in denervated hearts [1]. This is far from being a purely academic matter because reduced SD of the heart rate, i.e., reduced HRV has a better prognostic value than any other prognostic criteria than myocardial infarction and cardiac insufficiency for both sudden death and ventricular arrhythmias [9–11]. Nevertheless, the significance of these changes needs to be interpreted with caution. HRV attenuation can also be due, for example, to decreased activity of autonomous nervous sytem or to a saturation process occurring in extreme situations which renders these oscillations insensitive to specific stimuli [12] or an excessive inbalance between the two components of autonomous nervous system [13].

Surprisingly, in spite of its major prognostic significance HRV has not yet been studied in experimental models of cardiac failure or hypertrophy, nor has it been a target of pharmacological screening. This review summarizes our present knowledge concerning the biological determinants of HRV and relates HRV to the new myocardial phenotype which appears during cardiac hypertrophy.

Linear versus nonlinear analysis of HRV

Presently available data favor the idea that regulation of the heart rate can be either linear, nonlinear, or even chaotic, depending on the physiological conditions. The subject is controversial, and up to now there are good arguments which favor both a linear and a chaotic organization of such a biological oscillator. The discussion has a broader interest and also concerns other biological rhythms including respiration, nonconscious motricity, vasomotricity, and electroencephalogram [23, 24, 26].

Chaos is a new discipline based on the mathematics of nonlinear dynamics which has been widely applied to many areas of physics, biology, sociology, and weather forecasting. Chaotic behavior is deterministic as periodicity and appears disorganized, random. Chaotic systems are characterized mainly by their sensitive dependence on initial conditions, as initially shown by Poincaré 90 years ago, and can be quantified using several techniques, including graphic methods such as phase plane plot, and calculations of the Lyapunov exponents and fractal dimension (reviewed in [14, 23, 24]).

It is possible noninvasively to record heart rate in humans using Holter monitoring. Techniques have also been developed to both record and analyze heart rate during the day-and-night cycle in small rodents [13, 19]. Such techniques allow us to study HRV in experimental models, including transgenic mice. Several methods are now available for analyzing the cardiac signal, depending on the stationary assumption which is made, and such an assumption may vary from one animal species to the other. Schematically heart rate in human or dog is stable enough to be analyzed using linear methods including spectral analysis. In contrast, the spectral power of the oscillations in heart rate is remarkably high in both normal or transgenic mice, which renders difficult any analysis of the cardiac function based on linear methods. In such animal species Time and Frequency domain and nonlinear methods of analysis are a necessary tool. The Time and Frequency instant method of analysis offers something of an alternative between linearity and chaotic behavior and is applicable to both groups of animal species.

Linear methods

Time domain methods of analysis include measurement of the SD [16] and spectral methods. The spectral method of HRV analysis, initially proposed by Akselrod et al. [15], consists of a Fast Fourier Transformation which allows decomposition of the complex pat-

tern of oscillations into two main components in the HRV: High Frequency oscillations which have a vagal origin and the same period as the respiratory oscillations, and the Low Frequency oscillations which are both of sympathetic and vagal origin. In addition, there are oscillations with a very low frequency due to circadian and ultradian rhythms. The Fourier transform is independent of time and is based on two assumptions, namely that the signal is symmetric and stationary. Biological signals rarely satisfy these requirements, especially for long periods. The asymmetry of the peaks may result in artifacts during the transformation, and the existence of frequent sudden changes in heart rate create wideband noise [16, 17]. The spectral power is normally equal to the SD in a sine function which returns to zero. However, most of the biological oscillators including the tachogram are not a sine function which returns to zero, and other methods must be used to analyze this oscillatory system (see further Time and Frequency domain analysis).

The nonspectral methods of analysis include the peak and trough method, initially proposed by Coumel [17, 18]. This method consists in recording the number of heart rate oscillations per hour, which are composed of decelerations of N (2–30) consecutive R-R intervals surrounded by accelerations of N/2 R-R intervals as well as the mean gradient or amplitude, A (milliseconds), of the deceleration. The product (N×A) has a physiological significance and is correlated with heart rate in both human and rats [19]. With this technique two groups of oscillations similar to those found with the Fourier transform are also found in humans as in rats [18, 19].

Time and Frequency domain analysis

Time and Frequency methods are free from the stationary assumption underlying spectral analysis and therefore applicable to the analysis of unstable cardiac rhythms such as heart rate in mice. They provide an instant analysis of the spectrum every 0.5 s over moving windows, which attributes a value of the spectrum power to each point in time and to each frequency and produces instant, or evolutionary, spectra. The Wigner-Villé Transform, which has already been applied to biological signals [13, 20–22], allows such a dynamic study of the spectral power in three dimensions (time, spectral power, and frequency) and cross-analysis of various biological rhythms. This technique shows the instant variations of the oscillations in heart rate and distinguishes, as the Fast Fourier Transform, two groups of oscillations, those of low and those of high frequency. Nevertheless, it allows one to see that, in humans as well as mice, the oscillations in the heart rate are much more pronounced when plotted against time rather than against frequency. The Wigner-Villé method of analysis is therefore better considered as a spectral method which provides nonlinear results when plotted against time.

Nonlinear methods

From a dynamic point of view a discrete time series, such as the RR series, is seen as the projection on a line of the trajectory of an unknown discrete, deterministic, dynamic system in m-dimensional space. If this evolution is not subjected to sudden changes induced by external factors, such a trajectory will converge to an attractor, i.e., to a closed set of points in m-dimensional space which is a limit set for all trajectories of the system, and is supposed to cover the entire data if the time series is long enough [14].

A chaotic attractor is, by definition, sensitive to initial conditions. When it is a fractal object with a noninteger dimension, it becomes a strange attractor and displays no simple geometric structure [23, 24]. The Lyapunov exponents allows quantification of the sensitive dependence on initial conditions, and the first exponent, λ_1, must be positive for the system to be chaotic. The Lyapunov exponents quantify the complexity of a dynamic system, not its variability, and there are experimental conditions in which variability is diminished and complexity is increased. For example, after atropine injection in the mouse, the spectral power of heart rate oscillations diminishes as measured by the Wigner-Villé Transform (Table 1). In a normal mouse the first Lyapunov exponent is positive, and the sum of the various exponents is negative, which favors a deterministic dissipative chaotic system. Atropine increases both exponents, which indicates an increased complexity. There are several other techniques for providing evidence of such nonlinearity which result in the same conclusion [25].

Although numerous other algorithms have been applied to chaotic analysis, biological chaos still remains an interesting working hypothesis. Investigations using such a tool are rare, and there is a need for new algorithms or new approaches to study biological rhythms more specifically.

Table 1 Nonlinear analysis of HRV: normal mice and mice after atropine injection (recalculated data from [14, 25]). Atropine attenuated the indexes of variability of the heart rate; in contrast, the drug augmented the complexity of the system, which suggests that complexity can be a mode of physiological regulation

	Control	Atropine
Indexes of variability		
RR interval, SD (ms)	9.56	4.40
Tachogram	Variable	Flat
Spectral analysis (Fourier)	Irregular	Irregular
Peaks (Hz)	2.5, 0.02–0.7	0.02–0.8
Spectral analysis (Wigner-Ville) spectral power (ms^2/Hz)	24|106	15|200
Recurrence map	Torpedo aspect	Small circle
Indexes of complexity		
Lyapunov exponent (in dimension 3)	0.86	0.97
Correlation dimension for m=3	1.4	2.2
Approximate entropy	0.03	0.10

HRV in cardiac hypertrophy in rats: effects of regression of hypertrophy

HRV is now a pharmacological target and needs to be explored experimentally. It is possible to monitor ECG permanently in unanesthesized small rodents by Holter monitoring or telemetry. Analysis of the signal is more difficult since the heart rate of rats is around 350 bpm and that of mice around 500 bpm, and most computer programs are adapted to humans. We have solved this by using a modified Holter monitoring connected to subcutaneous electrodes [26] and more recently a telemetry system whose signal is recorded directly on computer disk [13].

Both thyrotoxicosis and abdominal aortic stenosis result in augmentation of the left ventricular weight/body weight ratio, which is more pronounced after banding aorta (53%) than during cardiotoxicosis (20%) [19]. Thyroxine accelerates the heart rate and attenuates the Low-Frequency oscillations, but the effect on HRV is specific and independent of tachycardia. Abdominal aortic stenosis results in compensatory cardiac hypertrophy within 4 weeks with no failure after even 1 year. The cardiac hypertrophy has no effect on HRV, indicating a good adaptation of the autonomous nervous system. Nevertheless, in this case heart rate is not correlated with the amplitude of the variations as it normally is [19].

Studies on the regression of myocardial hypertrophy

Sixteen-month-old spontaneously hypertensive rats (SHR) are equivalent to 65-year-old hypertensive men in that they have marked arterial hypertensiona biventricular cardiac hypertrophy, and both perivascular and interstitial cardiac fibrosis. Cardiac hypertrophy is strongly linked to myocardial fibrosis, and when the animals start to fail at the age of 18 months, the main biological marker of the myocardial deterioration is fibrosis [27].

Holter monitoring demonstrates an increased number of ventricular premature beats, a slow heart rate (Table 2), and a lower spectral power of the Low-Frequency oscillations than inage-matched Wistars [28, 29]. Heart rate is correlated with the two components of HRV in every experimental group, including SHRs. Multivariate analysis shows a strong correlation between arrhythmias, fibrosis, and cardiac hypertrophy. Nevertheless, as demonstrated by correspondence analysis, these two factors are independently linked to ventricular premature beats, suggesting that the new membrane phenotype also plays a role in the genesis of arrhythmias. In addition, linear discriminant analysis with treated and nontreated SHRs successfully discriminates 83% of the rats, with a positive correlation coefficient of 0.55 for the ventricular premature beats and a negative coefficient of –0.64 for the HRV, strongly suggesting that these two parameters are negatively correlated to each other [28]. In other words, by using such a statistical analysis, we can directly observe in vivo what epidemiological studies have suggested, i.e., a causal relationship between the incidence of arrhythmias and disorders of the autonous nervous system.

Changes in HRV in relation to the cardiac phenotype

HRV is one of the most easily accessible biological systems since it can be noninvasively and directly monitored in man. These oscillations have various origins: (a) the intrinsic variability of the sinusal node is for the moment a controversial issue which could reflect the chaotic behavior of the activation-inactivation process responsible for the nodal ionic channels gating; (b) the various determinants of the vagal and sympathetic tones: central influences (emotion, stress, anticipated exercise), baro, and respiratory reflexes [6, 8]; (c) thermoregulation and circadian variations of various plasma hormones and peptides (catecholamines, angiotensin II) [30]; (d) the myocardial phenotype, which includes the β_1-adrenergic receptor and M_2 muscarinic receptor density, the concentraion in α and αs subunits of the G proteins ($G_{\alpha s}$, G_{α}), the content in adenylate cyclases isoforms [13]; (e) several other receptors, including the angiotensin II receptors which are present in or around the sinusal node, suggesting that they

Table 2 Effects of the regression of cardiac hypertrophy on arrhythmias and HRV (data from [28, 29]): 16-month-old SHR compared to age-matched Wistars and treated for 3 months with a converting enzyme inhibitor. The treatment had no effect in Wistars; converting enzyme inhibition prevented cardiac hypertrophy, fibrosis, arrhythmias, and the diminution of HRV

	Wistars	SHRs	Treated SHRs
Morphological data			
Heart weight/body weight (mg/g)	1.98±0.04	4.70±0.16[a]	3.49±0.07[b]
Macroscopic collagen density (×100)	0.89±0.25	2.2±0.35[a]	1.35±0.27[b]
Electrophysiological data			
Supraventricular premature beats per 24 h	130±77	419±129	250±70
Ventricular premature beats per 24 h	2±0.6	128±60[a]	14±6[b]
HRV at rest (ms^2 per Hz/1|000)			
Frequency component	29±3	24±2	28±2
Frequency component	57±9	29±4[a]	44±5[b]

[a] Effect of strain
[b] Effect of treatment

play a direct role in the regulation of heart rate; and (f) genetic components, such as the per gene which is partly responsible for circadian rhythms [31]. Determinants of heart rate and HRV include [6, 8, 12]:
– Pacemaker activity [4, 5]: the chaotic behavior of the activation/inactivation gating of I_{CaL} or $_T$, I_f, I_K (?)
– Reflex arcs (respiration, Bainbridge, carotid sinus) and central nervous system connections to autonomous nervous system [6, 47, 48]
– Genetics [30, 31]
– Circadian oscillations in plasma hormones (e.g., cortisol) and thermoregulation
– Myocardial phenotype in terms of β-adrenergic and muscarinic receptors, G proteins and adenylate cyclases isoforms [13]
– Other receptors located in the sinusal node including angiotensin II, dopamine, and adenosine receptors [49]

Experimental models of cardiac hypertrophy

Changes in HRV can result from a modification occurring at any level. Changes in HRV have been well-documented in conditions such as cardiac failure, baroreflex, and central nervous system dysfunction, and various disorders in plasma content of hormones and regulatory peptides [32]. At the level of the myocardium β_1-adrenergic receptor downregulation and an enhanced intracellular content in the Gα proteins are also well-established findings [33, 34]. Indeed, in addition to the well-known homologous downregulation due to the increased plasma content in catecholamines, the β_1-adrenergic receptor downregulation is likely to have a second origin. It has indeed been demonstrated that the β_1-adrenergic receptor density, both in terms of protein [35] and mRNA [36], is diminished in compensatory cardiac hypertrophy (Table 3) while plasma and myocardial catecholamines [37] are unchanged. The β_1-adrenergic receptor gene belongs to the same family as that of the SERCA gene [38], a group of genes that are not activated by mechanical overload.

The incidence of arrhythmias increases with aging and is associated with a progressive attenuation of HRV [39], which is more pronounced for the High Frequency component in rats [29]. The myocardial phenotype is deeply altered during senescence, and among the better documented modifications are diminution of the sensitivity of the aged myocardium to isoproterenol and impaired exercise-induced tachycardia [40]. In senescent 24-month-old rats the β-adrenergic receptors density diminishes, the muscarinic receptor density is also altered, but the diminution in the muscarinic receptors is more pronounced, and consequently the muscarinic/β-adrenergic receptor density ratio is lowered [41] (Table 3).

Experimentally induced thyrotoxicosis is associated with tachycardia and various types of arrhythmia, and it is well-known that the β-adrenergic myocardial receptor density nearly doubles. By contrast, and less well known, the muscarinic receptor density is halved, and several modifications in the G proteins isoforms occur [42, 43]. As a consequence there is a pronounced imbalance between the two components of the autonous nervous system and the muscarinic/β-adrenergic receptor density ratio is strongly modified, suggesting a causal relationship with the diminution of the low-frequency oscillations.

Table 3 The β-adrenergic/muscarinic system of the overloaded hypertrophied young adult rat heart: myocardial adrenergic and muscarinic receptors density (B_{max}) and the corresponding mRNAs concentrations (in G proteins subunits mRNA; data from this laboratory [35, 36, 41])

	Controls	Overloaded
β_1-Adrenergic system		
Receptors		
B_{max} (fmol/mg)	27±2	19±2*
mRNA (pg mRNA/mg RNA)	4.3±0.8	2.2±0.2*
$G_{\alpha s}$ mRNA (pg mRNA/mg RNA)	55±4.5	49±5.4
Muscarinic system		
Receptors		
B_{max} (fmol/mg)	100±6	78±2**
mRNA (pg mRNA/mg RNA)	3.1±0.4	1.7±0.3**
$G_{\alpha i2}$ mRNA (pg mRNA/mg RNA)	13+2.8	12±1.7
β_1-Adrenergic/muscarinic receptor ratios		
B_{max}	0.27±0.2	0.22±0.2
mRNA	1.4±0.3	1.5±0.2

*, $P<0.05$; **, $P<0.01$

By contrast, after banding aorta in the rats the density of the two types of receptors decreases in parallel [35], and the muscarinic/β-adrenergic receptor densities ratio remained unchanged, which may explain why the HRV was unchanged. The situation may not be the same in other species [43]. By contrast, in this model HRV and heart rate are not correlated as they normally are, which indicates the limits of the biological adaptation [35].

Transgenic models overexpressing the β-adrenergic receptors

Several determinants of HRV are usually altered in experimental models of cardiac disease. Most of these have additional effects on the reflex arcs, for example, aortic stenosis which influences the baroreflex, and cardiac failure, as explained above. Therefore we need to design experiments in which the modifications of the myocardial phenotype in terms of receptors or transduction system are not accompanied by hemodynamic changes.

Transgenic mice were designated with a targeted β_1-atrial overexpression of β_1-adrenergic receptors [44]. Their heart rate was analyzed using the time and frequency method described by Wigner and Villé. In addition, studies on atrial contractility changes in the presence of β-adrenergic agonists were performed in vitro. The transgenic manipulation resulted in decreased HRV, showing that the myocardial phenotype is indeed one of the determinants of HRV. Nevertheless, these mice have

no arrhythmias and a normal lifespan, which indicates that HRV is of no pronostic significance in the absence of cardiac disease [13]. The atrial strips of these mice have an increased basal contractility, but contractility, heart rate, and HRV are insensitive to propranolol [13]. Further experiments can be suggested to resolve this issue, including transgenic models with a more targeted overexpression by using sinus or specific promoters.

Similar results were obtained more recently by Milano and Lefkowitz [45] by using the promotor of the α myosin heavy chain gene and the coding part of the β_2-adrenergic receptors. By doing so the β_2-adrenergic receptors was overexpressed in the ventricles by nearly 200% which also results in an enhanced basal contractility and abolition of the sensitivity to isoproterenol.

Therefore an overexpression of β-adrenergic receptors, whatever the level, has the same effect on contractility both in atria and ventricles. It enhances the basal contractility and attenuates the effects of β-adrenergic agonists. It also attenuates the effects of β-agonists on heart rate and HRV. Recent concepts in receptology suggest that a certain amount of receptors exists in an active state even in the absence of agonists [46]. Therefore a good explanation of these data would be that the overexpression of the β-adrenergic receptors will result in an increased number of such active receptors. Consequently even in the absence of agonists these active receptors will maximally activate the cells at the level of the downstream effectors. The resulting physiological phenotype is an increased basal contractility and an abolition of isoproterenol sensitivity (discussed in [13, 45]).

To conclude, HRV is determined not only by the well-known neural factors but also by the myocardial phenotype. It is proposed that in cardiac failure the attenuation of the HRV depends not only upon central sympathetic outflow [47, 48] but is also a consequence of the phenotypic modifications of the myocardium at the level of the adrenergic and muscarinic transduction system [33, 34, 35] and possibly at that of the renin-angiotensin system since the sinusal node area is particularly rich in angiotensin II receptors [49].

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