Review

Aging and cardiac autonomic control in chronic heart failure: methods and clinical implications

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A large body of evidence has been provided that cardiac autonomic control is deranged in heart failure. It is also commonly accepted that aging is characterized by several molecular and structural changes in organs and tissues, and *per se* affects cardiac autonomic control. Hence, as far as we are concerned with heart failure in the elderly, both cardiac diseases and age are likely to contribute to the autonomic dysfunction of these patients.
In the first part a brief review to the methods currently used to assess the autonomic control of the cardiovascular function in human subjects is reported. Then, major findings on the relationship between aging and cardiac autonomic indexes in normal subjects are presented. In the third part, main concept and experimental observations on autonomic dysfunction in heart failure are reviewed. Finally, some basic considerations on the relationship between aging, cardiac autonomic function and heart failure are introduced.
1. A brief review to the methods currently used to assess the autonomic control of the cardiovascular function in human subjects is reported
2. The relationship between aging and cardiac autonomic indexes in normal subjects are presented
3. Main concept and experimental observations on autonomic dysfunction in heart failure are reviewed

Key words: HRV, Poincarè analysis, Fractal analysis

INTRODUCTION

A large body of evidence has been provided that cardiac autonomic control is deranged in heart failure [1]. It is also commonly accepted that aging is characterized by several molecular and structural changes [2] in organs and tissues that *per se* affect cardiac autonomic control [3-6]. Hence, both cardiac diseases and aging are likely to contribute to the autonomic dysfunction of elderly patients with heart failure.
In the first part a brief review of the methods currently used in the autonomic control assessment of the cardiovascular function in human subjects is reported. Then, major findings on the relationship between aging and cardiac autonomic indexes in normal subjects are presented. In the third part, main concept and experimental observations on autonomic dysfunction in heart failure are reviewed. Finally, some basic considerations on the relationship between aging, cardiac autonomic function and heart failure are introduced and results from a previous study described.

METHODS OF AUTONOMIC FUNCTION INVESTIGATION IN HUMANS

Since changes in sympathetic and vagal traffic to the sinoatrial node alter the natural frequency of the cardiac

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pacemaker inducing a corresponding change in heart rate, the measurement of the latter would be the simplest way of appraising the heart autonomic control and, more specifically, the sympatho-vagal balance. The interaction among heart rate, intrinsic frequency of the pacemaker and the levels of vagal and sympathetic outflows to the heart has been model as a multiplicative relationship [7] and could be conditioned by several different factors [8-11]. Hence, given the intrinsic frequency, the net effect of the sympatho-vagal balance is expressed by the current heart rate. Unfortunately the intrinsic frequency changes between individuals and its measurement require a complete autonomic blockade. As a consequence, the measurement of heart rate provides only an uncalibrated quantification of the sympatho-vagal balance.

Beat-to-beat spontaneous fluctuations of heart rate do occur continuously in every human subject with a healthy heart and reflect corresponding fluctuations in neural traffic of efferent vagal and sympathetic nerves. The fluctuation of heart rate around its mean has commonly referred as heart rate variability (HRV). Several time- and frequency-domain indexes have been extracted in the last two decades from the HRV signal using digital signal processing techniques, and experimental evidence have been provided that known changes in sympathetic and vagal outflows to the heart, associated with physiological manoeuvres, drug administration, disease or increased risk for lethal arrhythmias, are accompanied by well-defined changes in HRV parameters [12]. It has been thus hypothesized that spontaneous cardiovascular fluctuations can be exploited to provide quantitative indexes of cardiac autonomic control mechanisms.

Time-domain HRV indexes are basically derived from direct measurement of normal-to-normal (NN) RR intervals or from the differences between them. The most common parameters obtained are the standard deviation of NN intervals (SDNN) and the root square of the mean successive squared difference of successive NN intervals (RMSSD) (task force), respectively. These measurements can be performed either on long-term (24-h) ambulatory recordings or on short-term (< 10 min) laboratory recordings. Long-term indexes, in turn, may be derived from the analysis of the overall recording, or may be calculated segmenting the entire 24-h period into consecutive small epochs (typically 5') and then averaging results over pre-defined periods of time, e.g. night and day. A depressed SDNN has consistently been found in patients after myocardial infarction (MI) and interpreted as the effect of a reduced vagal activity directed to the heart [13]. In the acute phase of a myocardial infarction the 24-h SDNN is related to left ventricular dysfunction, peak creatine kinase and Killip class [13]. Large-scale studies have shown that a depressed SDNN is also a powerful predictor of mortality and arrhythmic complications in post-MI patients, independently of other well-established risk stratification markers such as left ventricular ejection fraction, ventricular ectopic activity and presence of late potentials [13].

Frequency-domain methods aim to identify and estimate major rhythms hidden into the apparently erratic behaviour of the HRV signal. These methods are mostly used in short-term recordings, typically ranging from 2 to 5 min [7 12-14]. Three rhythms or spectral components are commonly detected: the very low frequency (VLF) rhythm in the range: 0.01-0.04 Hz, the low frequency (LF) rhythm in the range 0.04-0.15 Hz and the high frequency (HF) or respiratory rhythm in the range 0.15-0.4 Hz. Automatic signal processing procedures provide both the central frequency and power of these spectral components [15]. Graded orthostatic tilt, which is known to be associated with sympathetic activation, typically causes an increase of the LF component and a simultaneous decrease of the HF component. This displacement of power from one component to the other is well correlated with the angle of tilt [16]. Pharmacological blockade of beta-adrenergic receptors causes an unbalance of the power content in favour of the HF component, whereas muscarinic receptor blockade causes a prevalence of the LF over the HF component [12]. These findings, together with several experimental observations from animal studies, led to the conclusion that in spontaneous rhythms the analysis of the HRV signal, more appropriately, the relative power of the LF and HF components expressed as normalized powers or LF/HF power ratio, are capable of providing quantitative markers of the sympatho-vagal balance [12]. More recently, several investigators have shown that heart rate fluctuations share some basic properties with nonlinear dynamics and chaotic determinism [16-19].

Complex interactions of hemodynamic, electrophysiological and humoral variables as well as reflex and central regulatory mechanisms involved in cardiovascular function [20-23] are thought to determin Nonlinear phenomena involved in the genesis of HRV.

It has been speculated that the HRV analysis based on methods of nonlinear dynamics may provide valuable information for the physiological interpretation of HRV and for prognostic stratification of cardiac disease patients [24-26].

The parameters most often used to measure nonlinear properties of HRV include 1/f scaling of Fourier spectra, D_2 correlation dimension, Lyapunov exponent, Kolmogorov entropy, H scaling exponent and Coarse Graining Spectral Analysis. For data representation, Poincarè plots, low dimension attractor plot, singular

value decomposition, and attractor trajectories have been used. Although all these techniques are in theory powerful tool for the analysis of HRV, their practical usefulness is still controversial. Indeed, most attempts to apply nonlinear dynamics techniques to real data have provided either trivial results or intriguing speculations. Moreover, some basic methodological issues, such as the confounding effect of non-stationarity in the observed HRV time series, still need to be solved. Finally, the general requirement of long-term recordings for these methods prevents their application to laboratory data [27].

Two nonlinear techniques have recently gained great interest due to remarkable results in clinical studies: the 1/f scaling of Fourier spectra and Poincarè plots [28].

The former method has recently been applied in the prognostic assessment of patients with recent myocardial infarction and patients with heart transplants, and it has been shown that power law regression parameters are excellent predictors of death of any cause or arrhythmic death and predict these outcomes better than the traditional power spectral bands [29 30].

The Poincarè plot method has been used by some investigators in patients with mild to moderate chronic heart failure, showing an independent prognostic value and identifying increased risk for all-cause cardiac death [31]. This method consists in constructing HRV maps by plot of each RR interval against the subsequent one. These maps allow detecting patterns resulting from non-linear processes that may not be detectable by other classical methods of analysis. A simple example is given by sudden changes in the RR interval, which would appear in the power spectrum as wide-band noise. The major limitation of the traditional approach to the analysis of Poincarè plots is the visual classification of plot shapes and the manual measurement of the maps. To overcome this limitation our group has developed new algorithms for automatic morphological quantification of the plots [32 33], which allows to extract relevant parameters like length, wideness and area of the bi-dimensional plots and number of peaks and radii of inertia of the three-dimensional maps (Fig. 1).

Arterial baroreceptors play a major role in controlling the cardiac autonomic nerves activity through quick adaptation to changes in pressure and tissue perfusion in response to daily activities. The evaluation of baroreflex sensitivity has become a widely used clinical tool since it has been recognized that vagal and sympathetic control is deeply deranged in several cardiac diseases, and that changes in sensitivity of heart baroreflex control may be highly relevant for the outcome of these patients [34].

Among the various quantitative methods developed to estimate baroreflex sensitivity, the most widely used technique is the measure of the heart rate response to the injection of a vasoactive drug free of cardiac action. Baroreceptors stimulation with the vasoconstrictor agent phenylephrine has become the reference for the clinical evaluation of baroreflex sensitivity. However, other techniques such as the neck chamber have been largely used, mainly for research purposes [35]. More recently, several methods have been devised to estimate

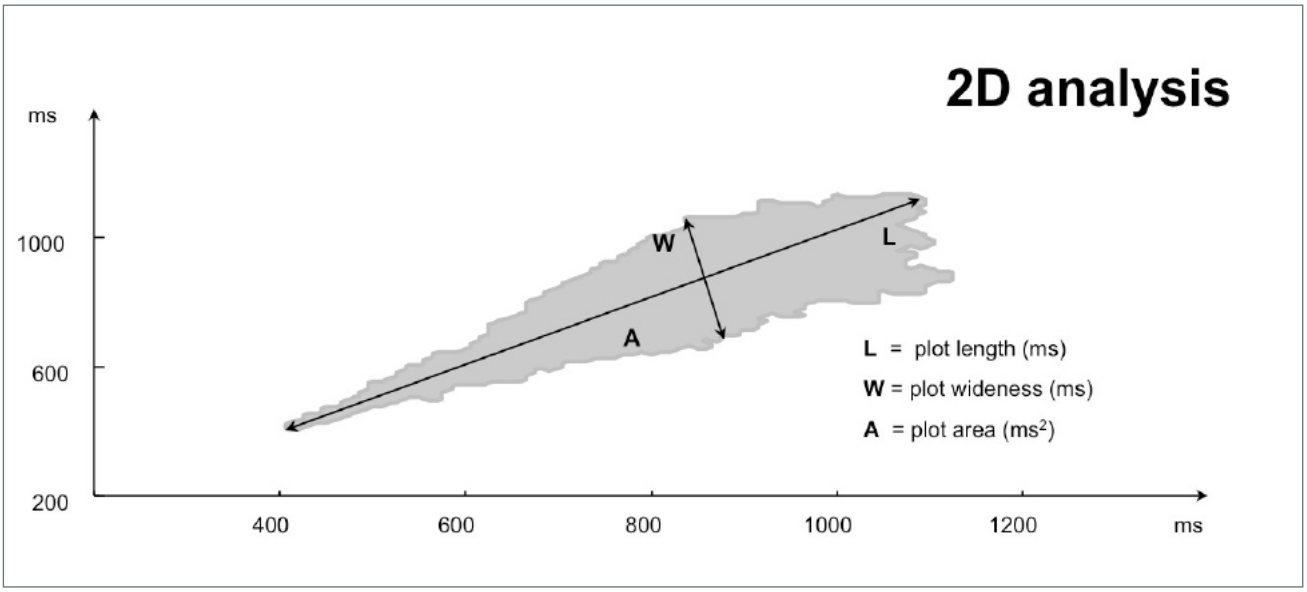

Figure 1. New algorithms for automatic morphological quantification of the plots, which allows to extract relevant parameters like length, wideness and area of the bi-dimensional plots and number of peaks and radii of inertia of the three-dimensional maps.

the baroreflex gain by the analysis of spontaneous beat-to-beat fluctuations of systolic arterial pressure and of related changes in the RR interval, thus avoiding the need of drug injection. Two basic approaches have been proposed and validated: the time-domain approach, better known as the sequence method, and the frequency domain approach, which exploits LF and HF oscillatory components in arterial pressure as "stimuli" for the baroreceptors**,** and measures related changes in corresponding oscillatory components of the RR interval [35 36].

AGING AND THE AUTONOMIC NERVOUS SYSTEM

A full knowledge of age-related changes of the autonomic nervous system in humans is still lacking. There is general consensus that aging is accompanied by increased plasma norepinephrine concentration and decrease of a) cardiac norepinephrine stores, b) affinity of beta-receptors stores, c) inotropic and chronotropic response to beta-agonists and d) baroreflex sensitivity [37]. Supine resting heart rate does not change significantly with age, whereas a significant lengthening of the RR interval has been observed both in the seated and in the standing posture of elderly [3 38]. HRV has consistently been found to decrease with age, independently of aerobic capacity and body mass index [3 38-40]. Time indexes of HRV show a pattern of change with age, which is a dependent measure. SDNN, for instance, decreases very gradually with aging with a quadratic regression pattern and a 40% reduction between 20 and 95 years [40]. Conversely, RMSSD decreases in the same length of time by about 60% [40]. The presence of a blunted baroreflex response together with a decreased HRV and a reduced heart response to atropine have been interpreted as evidence of decreased parasympathetic activity in elderly people. Postural change from supine to standing produces significant variations in heart rate and HRV, but this effect is blunted in elderly with respect to young people [38]. Since aging makes an increase in peripheral vascular resistance and a decrease in peripheral vascular capacitance, it is likely that baroreceptor-mediated modifications in HRV in response to posture-induced changes in vascular dynamics are reduced in elderly persons as a consequence of reduced demand made upon baroreceptors. Some investigators have shown that elderly people have less movement of thoracic blood into lower extremities in response to lower body negative pressure, suggesting that during postural change a similar phenomenon could occur, thus reducing the need for baroreceptor-mediated pressure regulation [41 42]. However, a reduction of the sensitivity of the baroreflex arc *per se* with aging cannot be excluded, contributing both to the reduced response of heart rate and HRV to postural change as well as to the reduced supine resting HRV.

Using spectral indexes of HRV, absolute powers in the LF and HF bands have been found to be significantly and negatively correlated with ageing [43]. Among all variables the ln(LF) parameter is the best correlated with age with a coefficient of determination which explain more than 15% of variability by aging [43]. The normalized LF power and LF/HF power ratio, but not the normalized HF power, were found to correlate with age. However, no significant changes were detected, especially in men, until age 60 years [43]. Although the age-related decrease in HRV has been commonly attributed to a decline in parasympathetic activity, the reduction in normalized LF power with increasing age suggests that sympathetic activity may also drop with age. Conversely, the fall in absolute LF power might simply reflect the decline of baroreflex sensitivity.

As depressed HRV has been proposed as a marker of a number of pathological conditions and of increased risk of mortality in cardiac patients, the use of HRV for predictive purposes must take in account the confounding effect of age. Umetani et al. [40], analysing 24-h HRV time-domain indexes in 260 healthy subjects, found that either the SDNN or RMSSD of subjects > 65 years old fell below published cut-points for increased risk of mortality in respectively 25% and 12% of them. In the same study the range of variation of all HRV measures, defined as 95% confidence limits, was wider in young subjects and narrows with increasing age, reflecting a decrease in interindividual differences over time.

AUTONOMIC DYSFUNCTION IN HEART FAILURE

Heart failure is commonly characterized by a prominent neurohormonal excitation which appears as increased sympathetic activity, increased circulating levels of norepinephrine, vasopressin and renin, withdrawal of parasympathetic activity and impaired baroreflex gain [1 44-46]. Evidence of increased central sympathetic outflow has been provided by direct recording of nerve firing in sympathetic nerves innervating muscular or cutaneous vascular beds, and by correlating the level of this firing with plasma norepinephrine levels [47]. Caution, however, should be exerted in interpreting plasma norepinephrine concentrations as measure of sympathetic nerve traffic in humans, since it actually represents the balance between norepinephrine spillover (i.e. the neurally released norepinephrine) and its clearance. When plasma norepinephrine spillover is measured separately from norepinephrine clearance, the former is on average double in heart failure patients compared to control

subjects and the latter is reduced by about a third [48]. Indirect evidences of generalized sympathoneural activation in decompensated congestive heart failure are represented by clinical observation of tachycardia, tachypnea, diaphoresis, pallor, agitation and renal sodium retention [49 50].

In a similar way only indirect evidence has been provided on parasympathetic withdrawal in heart failure. Besides the original demonstration by Eckberg et al. of a defective parasympathetic control of heart rate [51], the observation of a reduced bradycardic response to the pressor stimulus of phenylephrine has been interpreted as the effect of reduced vagal outflow to the heart. However, as increased sympathetic activity may interfere with the ability to increase vagal activity, a more realistic interpretation of depressed baroreflex gain in heart failure is to be secondary to a concomitant and opposite alteration in the activity of the two autonomic limbs [52].

The generalized sympathetic activation and parasympathetic withdrawal in heart failure have been attributed to alterations in inhibitory and excitatory influences on vasomotor neurons. In normal subjects afferent inputs from arterial baroreceptors as well as from cardiopulmonary mechanoreceptors exert a major inhibitory influence on sympathetic outflow, whereas discharge from muscle metaboreceptors are major excitatory inputs [53 54]. The vagal limb of the baroreceptor heart rate reflex is also responsive to arterial baroreceptor afferent input. At rest the net effect of these competing influences is characterized by a relatively low sympathetic activity. In heart failure the principal stimuli to baroreceptors (mean pressure, pulse pressure and rate of increase of blood pressure) are blunted and the sensitivity of cardiopulmonary mechanoreceptors diminishes, reducing inhibitory input. Moreover, excitatory input may originate from arterial chemoreceptors and skeletal metaboreceptors. The net response to this shift in balance between inhibitory and excitatory afferent inputs is a generalized increase in basal sympathetic outflow, parasympathetic withdrawal and impaired regulation of heart rate and vascular resistance.

Several investigators have attempted to assess the autonomic dysfunction of heart failure patients through analysis of HRV [55 56].

A consistent finding has been that HRV measured either in the time or frequency domain, in short-term or long-term recordings, is markedly depressed in heart failure [1 57 58], a finding, which has been interpreted as the effect of impaired parasympathetic control of heart rate. The amount of heart rate variability is closely and negatively related to the degree of sympathoexcitation as expressed by muscle sympathetic nerve activity and plasma norepinephrine [59]. When HRV in heart failure patients is assessed through spectral methods and compared to normal subjects, the distribution of the variability over frequency invariably shows a shift from the LF and HF band to the VLF band [57]. Hence, all oscillatory components of HRV in heart failure are depressed with respect to normal controls but, at the same time, VLF oscillations are proportionally much higher then the other spectral components. The presence of a reduced HF component supports the notion of parasympathetic withdrawal in heart failure patients, as this component is almost entirely vagal-mediated. The LF component shows two typical patterns. In some patients it is predominant over the HF component, suggesting, as expected, a shift of the sympathovagal balance in favor of sympathetic activation [60]. In other patients the HF component is still low but the LF component has almost disappeared [57]. These patients are characterized by a greater severity of the disease, including a higher NYHA class, a more depressed left ventricular function and a higher degree of sympathoexcitation as evidenced by higher levels of plasma noradrenaline. This paradoxically low LF component in presence of a pronounced sympathetic activity has been explained by the concept that in the more severe stages of the disease an abnormally high sympathetic tone may be capable of "saturating" the sinus node response, making it almost insensitive to modulations of this tone [60]. However, in chronic heart failure patients, spectral analysis of resting muscle sympathetic nerve activity and RR interval has recently shown a close coherence between the variability patterns of the two signals [61]. A consistent finding of this and other studies is that patients with very depressed or absent LF component have the worse prognosis [60 61].

In recent years, the increasing evidence of association between various respiratory and cardiovascular diseases [59], and the simultaneous recording of cardiovascular (ECG, arterial blood pressure) [62] and respiratory (lung volume, SaO_2) signals in patients with heart failure has disclosed new important information on respiratory abnormalities of these patients and on related implications on cardiovascular regulation [63-71]. These respiratory abnormalities are typically characterized by a smooth rise and fall in ventilation with cycle lengths ranging from about 25 s to 100 s (0.01¸0.04 Hz) and are commonly referred to as periodic breathing, or, usually when separated by apnea, Cheyne-Stokes respiration. Although the phenomenon of periodic breathing has been studied mostly during sleep, recent investigations have shown that it has a high prevalence in awake patients, ranging from 25% to 66% during recordings in controlled laboratory conditions in patients with mild to moderate severity of the disease (New York Heart Association class I to III) [72 73]. The ventilatory oscillation is

accompanied by a synchronous oscillation of arterial O_2 saturation, which, especially in the more accentuated forms of periodic breathing, brings about marked cyclic desaturations. As a consequence, a chemoreceptor-induced sympathetic excitation results, which adds to an already existing condition of sympathetic predominance [61 74]. Moreover, the cyclic change in ventilation is also accompanied by a phase-linked oscillation of heart rate and arterial blood pressure in the VLF band, which dominates the overall fluctuating pattern of these signals [75]. These findings clearly indicate that during periodic breathing a deep simultaneous involvement of the respiratory and cardiovascular systems does take place. Moreover, they also point out that the use of HRV for the assessment of autonomic cardiovascular regulation and for prognostic evaluation in heart failure patients must take into account the confounding effect of periodic breathing [73].

Evidence has been provided that alterations in sympathetic and parasympathetic outflows to the sinoatrial node in heart failure can be identified by analysis of Poincarè plots shape from 24-h heart variability recordings [76]. While normal subject typically show a comet-shaped pattern, indicating an increasing variability at lower heart rates, heart failure patients show three main patterns: 1) a contraction in the plot's length with a torpedo-shaped pattern, resulting in a reduced distribution of the whole heart rate dispersion, 2) a fan-shaped pattern, with a great dispersion on a narrow range of frequencies and 3) a complex-shaped pattern, consisting of a thin core area and several clusters of points (Fig. 2).

The mechanisms responsible for these strikingly different patterns are not entirely clear and are currently under investigation in our laboratory. It has been suggested that the core of the pattern is the result of sympathetic influences, whereas the increased dispersion at longer RR intervals reflects parasympathetic

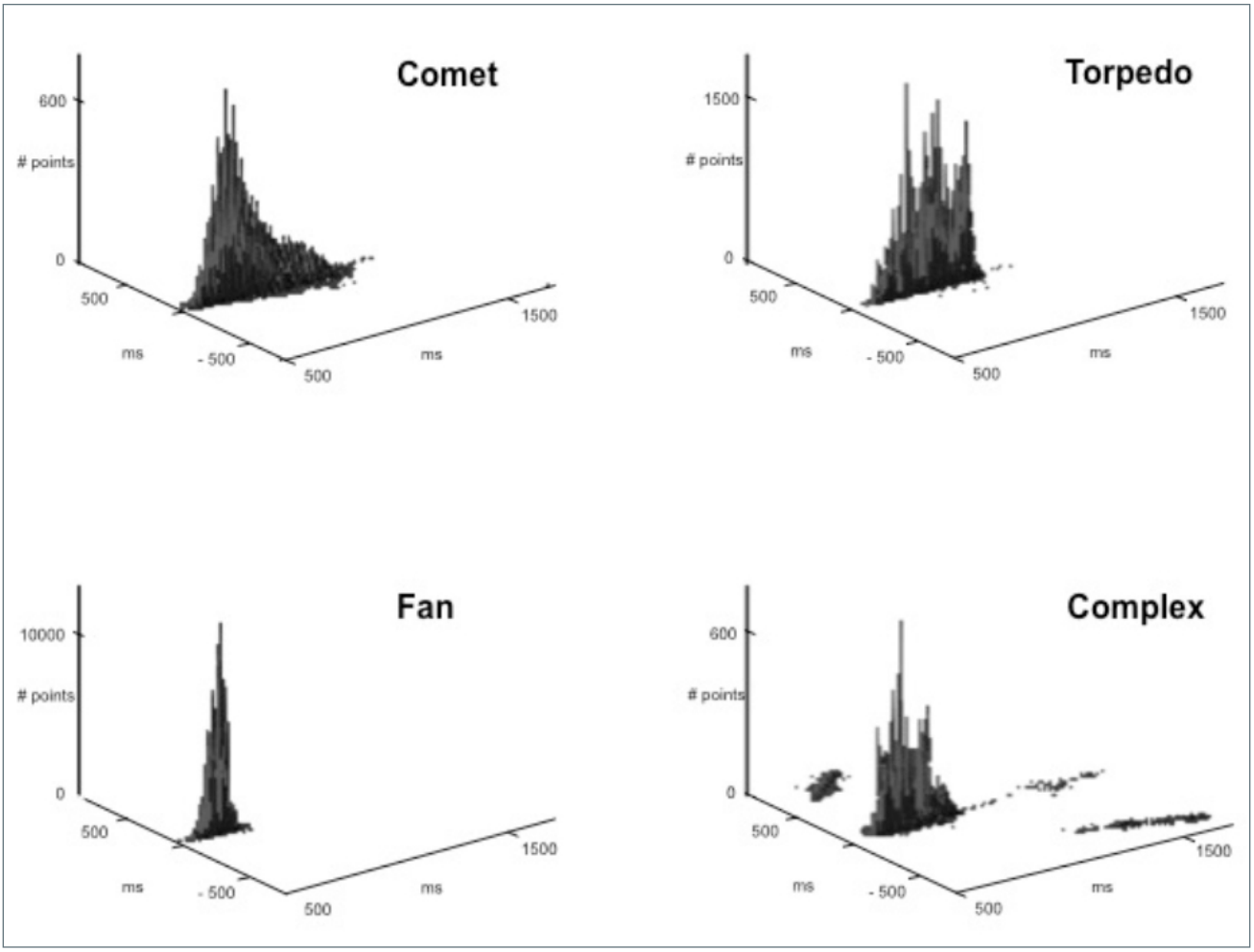

Figure 2. Alterations in sympathetic and parasympathetic outflows to the sinoatrial node in heart failure identified by analysis of Poincarè plots shape from 24-h heart variability recordings.

activity, respiratory sinus arrhythmia or sleep state. The torpedo-shaped pattern seems the one closer to the normal pattern, whereas the complex- and fan-shaped pattern reflect a greater disturbance in autonomic cardiac regulation. We have developed a set of morphological quantification indexes in order to provide an objective assessment of Poincarè maps. These indexes are characterized by an excellent short- and long-term reproducibility in stable chronic heart failure patients, indicating that they constitute reliable measures suitable to be used in the clinical setting [33]. Among the overall set of 2-dimensional and 3-dimensional indexes, the latter are closely and independently related to plasma norepinephrine levels in patients with advance heart failure [77 78].

AGING AND AUTONOMIC FUNCTION IN HEART FAILURE

We have seen so far that that both aging and heart failure affect the autonomic regulation of the cardiovascular system and that marked changes in heart rate variability follow the progression of age and of disease severity. It thus appears that when heart failure develops or progresses in the elderly both factors contribute concurrently to the deterioration of the autonomic function and their effects tend to be confounded. Although intuitively the effect of aging and heart failure would sum each other, there are no definite proofs that they are additive. In general, studies on the relationship between aging and heart failure are scanty. It is well known that impaired cardiac beta-adrenergic receptor (beta-AR) signalling and function represents a hallmark underlying mechanism of chronic heart failure (HF) pathophysiology, characterized by a beta-AR downregulation and desensitization of both beta-AR and beta-AR subtypes [79 80].

We recently analyzed time- and frequency-domain as well as Poincarè plot indexes of HRV from 24-h ambulatory recordings of 41 chronic heart failure patients (NYHA class III-IV) and compared the results with those from 59 patients with coronary artery disease without signs or symptoms of heart failure. Patients were divided according to the standard cut-off age of 65 years. Results are given in Table I. It can be noticed that in subjects under 65 years with the exception of the HF power (in absolute units) and the Width parameter of Poincarè plots, all indexes of heart rate variability are significantly reduced in HF compared to CAD patients, in agreement with the notion of depressed variability in heart failure. In patients over 65 years almost all heart rate variability indexes except the LF power in normalized units do not change significantly with respect to younger subjects in both groups. Peak number and mean peak distance of Poincarè plots are the only variability indexes, which differentiate heart failure patients from CAD patients in both age groups. These results suggest that cardiac autonomic regulation in chronic heart failure and CAD patients over 65 years does not change in a clearly detectable way with respect to the same patients under 65 years old. As expected, chronic heart failure patients

Table I. Relationship between age and major time-domain (Mean RR, SDNN), frequency-domain (lnLF, lnHF, LF_{NU}) and Poincarè plot (Length, Width, 3D peak number, Mean peak distance) indexes of heart rate variability from 41 chronic heart failure patients and 59 patients with coronary artery disease without sign or symptoms of heart failure.

	Age < 65 years		Age ≥ 65 anni	
	CHF	CAD	CHF	CAD
N	22	35	19	24
Age (years)	57 ± 6	37 ± 15**	70 ± 4 ††	73 ± 6 ††
EF (%)	24 ± 7	63 ± 5**	26 ± 6	55 ± 7** ††
Mean RR (ms)	790 ± 119	833 ± 168	834 ± 198	985 ± 157* ††
SDNN (ms)	102 ± 31	143 ± 40**	110 ± 63	133 ± 41
lnLF (ln(ms^2))	5.93 ± 0.46	6.38 ± 0.37*	5.8 ± 0.8	5.97 ± 0.53
lnHF (ln(ms^2))	5.47 ± 0.44	5.7 ± 0.4	5.49 ± 0.94	5.56 ± 0.5
LF_{NU} (%)	60 ± 19	65 ± 15**	57 ± 36	59 ± 32 ††
Length (ms)	139 ± 43	228 ± 58**	145 ± 81	193 ± 50
Width (ms)	28 ± 15	32 ± 9	45 ± 45	31 ± 12
Peak number	18 ± 8	30 ± 12**	16 ± 6	25 ± 6**
Mean peak distance (ms)	4.5 ± 4.2	12.7 ± 6.9**	3.94 ± 4.02	8.34 ± 6.8**

Results are expressed as meanSD. EF: ejection fraction; SDNN: standard deviation of normal-to-normal RR intervals; LF: absolute power in the LF band; HF: absolute power in the HF band; LF_{NU}: LF power in normalized units; ln: natural logarithm.f

* $p < 0.01$ *vs* CHF; ** $p < 0.001$ *vs* CHF

† $p < 0.05$ *vs* < 65 years; †† $p < 0.001$ *vs* < 65 years

have depressed variability compared to CAD patients that is most consistently described by the peak number and mean peak distance of the Poincarè plots.

References

1 Floras JS. *Clinical aspects of sympathetic activation and parasympathetic withdrawal in heart failure*. J Am Coll Cardiol 1993;4:72A-84A.

2 Conti V, Corbi G, Simeon V, et al. *Aging-related changes in oxidative stress response of human endothelial cells*. Aging Clin Exp Res 2015;27:547-53.

3 Byrne EA, Fleg JL, Vaitkevicius PV, et al. *Role of aerobic capacity and body mass index in the age-associated decline in heart rate variability*. J Appl Physiol 1996;81:743-50.

4 Ferrara N, Longobardi G, Nicolino A, et al. *Effect of beta-adrenoceptor blockade on dipyridamole-induced myocardial asynergies in coronary artery disease*. Am J Cardiol 1992;70:724-7.

5 Corbi G, Conti V, Russomanno G, et al. *Adrenergic signaling and oxidative stress: a role for sirtuins?* Front Physiol 2013;4:324.

6 Maio S, Baldacci S, Simoni M, et al.; ARGA Study Group. *Impact of asthma and comorbid allergic rhinitis on quality of life and control in patients of Italian general practitioners.* J Asthma. 2012;49:854-61.

7 Bootsma M, Swenne C A, Van Bolhuis HH, et al. *Heart rate and heart rate variability as indexes of sympathovagal balance.* Am J Physiol 1994;266(4 Pt 2):H1565-71.

8 Ferrara N, Abete P, Corbi G, et al. *Insulin-induced changes in beta-adrenergic response: an experimental study in the isolated rat papillary muscle*. Am J Hypertens 2005;18:348-53.

9 Corbi G, Conti V, Davinelli S, et al. *Dietary Phytochemicals in Neuroimmunoaging: A New Therapeutic Possibility for Humans?* Front Pharmacol 2016;7:364.

10 Longobardi G, Ferrara N, Leosco D, et al. *Angiotensin II-receptor antagonist losartan does not prevent nitroglycerin tolerance in patients with coronary artery disease*. Cardiovasc Drugs Ther 2004;18:363-70.

11 Corbi G, Acanfora D, Iannuzzi GL, et al. *Hypermagnesemia predicts mortality in elderly with congestive heart disease: relationship with laxative and antacid use*. Rejuvenation Res 2008;11:129-38.

12 Malliani A. *Association of heart rate variability components with physiological regulatory mechanism.* In: Malik M, Camm AJ (Eds.). *Heart rate variability*. Armonk, NY: Futura publishing Company 1995, pp. 173-88.

13 Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. *Heart rate variability: standards of measurement, physiological interpretation and clinical use.* Circulation 1996;93:1043-65.

14 Porta A, D'Addio G, Corbi G, et al. *Circadian variations of short-term heart period irreversibility in healthy and chronic heart failure patients*. Proceedings of the 30th Annual International Conference of the IEEE Engineering in Medicine and Biology Society, EMBS'08 2008, pp. 2116-9.

15 Porta A, Faes L, Masé M, et al. *An integrated approach based on uniform quantization for the evaluation of complexity of short-term heart period variability: application to 24 h Holter recordings in healthy and heart failure humans.* Chaos 2007;17:015117.

16 Pinna GD, Maestri R, Di Cesare A. *Application of time series spectral analysis theory: analysis of cardiovascular variability signals*. Med Biol Eng Comput 1996;34:142-8.

17 Glass L, Hunter P, McCulloch A. *Theory of the heart. Biomechanics, biophysics and non linear dynamics of cardiac functions*. New York: Springer-Verlag 1989.

18 D'Addio G, Accardo A, Corbi G, et al. *Fractal behaviour of pathological heart rate variability dynamics*. WIT Transactions on Biomedicine and Health 2009;13:39-47.

19 D'Addio G, Corbi G, Accardo A, et al. *Fractal behaviour of heart rate variability reflects severity in stroke patients.* Stud Health Technol Informatics 2009;150:794-8.

20 Maestri R, Pinna GD, Accardo A, et al. *Nonlinear indices of heart rate variability in chronic heart failure patients: redundancy and comparative clinical value.* J Cardiovasc Electrophysiol 2007;18:425-33.

21 D'Addio G, Accardo A, Corbi G, et al. *Effects of stroke localization in nonlinear indexes of HRV.* Computers in Cardiology 2006:621-4.

22 Maestri R, Pinna GD, Allegrini P, et al. *Linear and non-linear indices of heart rate variability in chronic heart failure: mutual interrelationships and prognostic value*. Computers in Cardiology 2005:981-4.

23 Maestri R, Pinna GD, Balocchi R, et al. *Clinical correlates of non-linear indices of heart rate variability in chronic heart failure patients*. Biomed Tech (Berl) 2006;51:220-3.

24 D'Addio G, Romano M, Maestri R, et al. *Indices of symbolic dynamic distribution in cardiac patients.* Computers in Cardiology 2013:437-40.

25 Porta A, D'Addio G, Pinna GD, et al. *Symbolic analysis of 24h holter heart period variability series: Comparison between normal and heart failure patients*. Computers in Cardiology 2005:575-8.

26 D'Addio G, Caiani EG, Turiel M, et al. *Poincarè plots and symbolic dynamics patterns of left ventricular function parameters extracted from echocardiographic acoustic quantification.* Ann Rep Res Reactor Inst, Kyoto University 2001:563-6.

27 Porta A, D'Addio G, Guzzetti S, et al. *Testing the presence of non stationarities in short heart rate variability series.* Computers in Cardiology 2004:645-8

28 D'Addio G, Pinna GD, La Rovere MT, et al. *Prognostic value of Poincarè plot indexes in chronic heart failure patients.* Computers in Cardiology 2001:57-60.

29 Bigger T, Steinman R, Rolnitzky L, et al. *Power law behavior of RR-Interval Variability in healthy middle-aged persons, patients with recent acute myocardial infarction and patient with hearth transplants*. Circulation 1996;93:2142-51.

30 Cusenza M, Accardo A, D'Addio G, et al. *Relationship*

between fractal dimension and power-law exponent of heart rate variability in normal and heart failure subjects. Computing in Cardiology 2010:935-8.

31 Brouwer J, van Veldhuisen DJ, Man in 't Veld AJ, et al. *Prognostic value of heart rate variability during long-term follow-up in patients with mild to moderate heart failure*. J Am Coll Cardiol 1996;28:1183-9.

32 Marciano F, Migaux M, Acanfora D, et al. *Quantification of poincarè maps for the evaluation of hearth rate variability*. Computers in Cardiology 1994:557-80.

33 D'Addio G, Acanfora D, Pinna GD, et al. *Reproducibility of short- and long-term Poincarè plot parameters compared with frequency- domain HRV indexes in congestive hearth failure*. Computers in Cardiology 1998:381-4.

34 La Rovere MT, Bigger JT, Marcus FI, et al. *Baroreflex sensitivity and heart rat variability in prediction of total cardiac mortality after myocardial infarction*. Lancet 1998;351:478-84.

35 La Rovere MT, Pinna GD, Mortara A. *Assessment of baroreflex sensitivity*. In: Malik M (Ed.). *Clinical guide to cardiac autonomic tests*. Dordrecht, The Netherlands: Kluwer Academic Publishers 1998, pp. 257-81.

36 Romano M, Cesarelli M, Iuppariello L, et al. *Frequency domain and symbolic dynamics analysis for the study of cardiac pathologies.* E-Health and Bioengineering Conference, EHB 2013; art. no. 6707269.

37 Rengo F, Acanfora D, Trojano L, et al. *Congestive heart failure in the elderly*. Arch Gerontol Geriatr 1996;23:201-23.

38 Simpson DM, Wicks R. *Spectral analysis of heart rate indicates reduced baroreceptor-related heart rate variability in elderly persons*. J Gerontol 1988;43:M21-4.

39 Reardon M, Malik M. *Changes in heart rate variability with age*. Pace 1996;19:1863-6.

40 Umetani K, Singer DH, McCraty R, et al. *Twenty-four hour time domain heart rate variability and heart rate: relations to age and gender over nine decades*. J Am Coll Cardiol 1998;31:593-601.

41 D'Addio G, Pinna GD, Maestri R, et al. C*hanges induced by tilting on Poincare plots and symbolic dynamic patterns on HRV compared to spectral indexes in post-MI and normal subjects.* Computers in Cardiology 2000:449-52.

42 D'Addio G, Pinna GD, Maestri R, et al. *Quantitative Poincare plots analysis contains relevant information related to heart rate variability dynamics of normal and pathological subjects.* Computers in Cardiology 2004;31:457-60.

43 Kuo TB, Lin T, Yang CC, et al. *Effect of aging on gender differences in neural control of heart rate*. Am J Physiol 1999;277:2233-9.

44 Cesarelli M, Romano M, Maestri R, et al. *Correlation between symbolic dynamics analysis indexes and neurohormonal and functional parameters in heart failure patients*. Stud Health Technol Inform 2014;205:516-20.

45 D'Addio G, Cesarelli M, Maestri R, et al. *Neurohormonal and functional correlates of linear and poincarè plot indexes of heart rate variability in heart failure patients.* Computing in Cardiology 2012;39:937-40.

46 D'Addio GD, Cesarelli M, Romano M, et al. *Correlation between fractal behavior of HRV and neurohormonal and functional indexes in chronic heart failure* IFMBE Proceedings 2010;29:53-6.

47 Leimbach WJ, Walin BG, Victor RG, et al. *Direct evidence from intraneural recording for increased central sympathetic outflow in patients with heart failure*. Circulation 1986;73:913-9.

48 Hasking GJ, Esler MD, Jennings GL, et al. *Norepinephrine spillover to plasma patients congestive heart failure: evidence of increased overall and cardiorenal sympathetic nervous activity*. Circulation 1986;73:615-21.

49 Rengo G, Lymperopoulos A, Zincarelli C, et al. *Blockade of β-adrenoceptors restores the GRK2-mediated adrenal β2-adrenoceptor-catecholamine production axis in heart failure.* Br J Pharmacol 2012;166:2430-40.

50 Leosco D, Iaccarino G, Cipolletta E, et al. *Exercise restores beta-adrenergic vasorelaxation in aged rat carotid arteries.* Am J Physiol Heart Circ Physiol 2003;285:H369-74.

51 Eckberg DL, Drabinsky M, Braunwald E. *Defective parasympathetic control in patients with heart disease.* N Engl J Med 1971;285:877-83.

52 Mortara A, La Rovere MT, Pinna GD, et al. *Arterial Baroreflex modulation of heart rate in chronic heart failure. Clinical and hemodynamic correlates and prognostic implications*. Circulation 1997;96:3450-8.

53 Mastantuono T, Lapi D, Battiloro L, et al. *Microvascular blood flow regulation impairments in hypertensive obese people.* 8th Conference of the European Study Group on Cardiovascular Oscillations, ESGCO 2014, pp. 191-2.

54 Mastantuono T, Muscariello E, Novellino T, et al. *Changes in frequency components of blood flow oscillations in hyperglycemic obese people.* 8th Conference of the European Study Group on Cardiovascular Oscillations, ESGCO 2014, pp. 185-6.

55 Porta A, D'addio G, Bassani T, et al. *Assessment of cardiovascular regulation through irreversibility analysis of heart period variability: a 24 hours Holter study in healthy and chronic heart failure populations*. Philos Trans A Math Phys Eng Sci 2009;367:1359-75.

56 Cusenza M, Accardo A, D'Addio G. *Day-Time and night-Time HRV ultradian rhythms in normal and pathological Subjects.* IFMBE Proceedings 2011;37:450-3.

57 Saul JP, Arai Y, Berger RD, et al. *Assessment of autonomic regulation in chronic congestive heart failure by heart rate spectral analysis*. Am J Cardiol 1988;61:1292-9.

58 Casolo GC, Balli E, Fazi A, et al. *Twenty-four-hour spectral analysis of heart rate variability in congestive heart failure secondary to coronary artery disease*. Am J Cardiol 1991;67:1154-8.

59 Kienzle MG, Ferguson DW, Birkett CL, et al. *Clinical, hemodynamic and sympathetic neural correlates of heart rate variability in congestive heart failure*. Am J Cardiol 1992;69:761-7.

60 Mortara A, La Rovere MT, Signorini MG, et al. *Can power spectral analysis of heart rate variability identify a high risk subgroup of congestive heart failure patients with excessive sympathetic activation? A pilot study before and after heart transplantation*. Br Heart J 1994;71:422-30.

[61] Van de Borne P, Oren R, Abouassaly C, et al. *Effect of Cheyne-Stokes respiration on muscle sympathetic nerve activity in severe congestive heart failure secondary to ischemic or idiopathic cardiomyopathy*. Am J Cardiol 1998;81:432-6.

[62] Corbi G, Gambassi G, Pagano G, et al. *Impact of an innovative educational strategy on medication appropriate use and length of stay in elderly patients*. Medicine (Baltimore). 2015;94:e918.

[63] D'Addio G, Romano M, Maresca L, et al. *Fractal behavior of heart rate variability during ECG stress test in cardiac patients.* 8th Conference of the European Study Group on Cardiovascular Oscillations, ESGCO 2014, pp. 155-6.

[64] Fornasa E, Accardo A, Zotti R, et al. *Relationships between linear and nonlinear indexes of heart rate variability in obstructive sleep apnea syndrome.* 8th Conference of the European Study Group on Cardiovascular Oscillations, ESGCO 2014, pp. 103-4.

[65] Castiglioni P, Faini A, Lombardi C, et al. *Characterization of apnea events in sleep breathing disorder by local assessment of the fractal dimension of heart rate.* 8th Conference of the European Study Group on Cardiovascular Oscillations, ESGCO 2014, pp. 107-8.

[66] D'Addio G, Accardo A, Fornasa E, et al. *Fractal behaviour of heart rate variability reflects abnormal respiration patterns in OSAS patients.* Computers in Cardiology 2013;40:445-8.

[67] Accardo A, Cusenza M, De Felice A, et al. *Ultradian rhythms during day and night in normal and COPD subjects.* Stud Health Technol Inform 2012;180:1120-2.

[68] D'Addio G, De Felice A, Insalaco G, et al. *Effects of pathological respiratory pattern on heart rate turbulence in sleep apnea*. Stud Health Technol Inform 2014;205:506-10.

[69] D'Addio G, Cesarelli M, Romano M, et al. *OSAS severity is associated with decreased heart rate turbulence slope.* Computers in Cardiology 2013;40:1007-10.

[70] D'Addio G, De Felice A, Balzano G, et al. *Diagnostic decision support of heart rate turbulence in sleep apnea syndrome*. Stud Health Technol Inform 2013;186:150-4.

[71] D'Addio G, Accardo A, Corbi G, et al. *Functional correlates of fractal behavior of HRV in COPD patients.* IFMBE Proceedings 2009;25:261-4.

[72] Antonelli Incalzi R, Corsonello A, Trojano L, et al. *Heart rate variability and drawing impairment in hypoxemic COPD.* Brain Cogn 2009;70:163-70

[73] Mortara A, Sleight P, Pinna GD, et al. *Abnormal awake respiratory patterns are common in chronic heart failure and may prevent evaluation of autonomic tone by measures of heart rate variability.* Circulation 1997;96:246-52.

[74] Ponikowski P, Anker SD, Chua TP, et al. *Oscillatory breathing patterns during wakefulness in patients with chronic heart failure: clinical implications and role of augmented peripheral chemosensitivity.* Circulation 1999;100:2418-24.

[75] Pinna GD, Maestri R, Mortara A, et al. *Cardiorespiratory interactions during periodic breathing in awake chronic heart failure patients*. Am J Physiol Heart Circ Physiol 2000;278:H932-41.

[76] Woo MA, Stevenson WG, Moser DK, et al. *Patterns of beat to beat hearth rate variability in advanced hearth failure.* Am Heart J 1992;123:704-10.

[77] Woo MA, Stevenson WG, Moser DK, et al. *Complex heart rate variability and serum norepinephrine levels in patients with advanced hearth failure*. J Am Coll Cardiol 1994;23:565-9.

[78] D'Addio G, Pinna GD, Maestri R, et al. *Correlation between power-law behavior and Poincarè plots of heart rate variability in congestive heart failure patients*. Computers in Cardiology 1999:611-4.

[79] Tilley DG, Rockman HA. *Role of beta-adrenergic receptor signaling and desensitization in heart failure: new concepts and prospects for treatment.* Exp Rev Cardiovasc Ther 2006;4:417-32.

[80] Rengo G, Leosco D, Zincarelli C, et al. *Adrenal GRK2 lowering is an underlying mechanism for the beneficial sympathetic effects of exercise training in heart failure*. Am J Physiol Heart Circ Physiol 2010;298:H2032-8.