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Effects of some class IC antarrhythmic drugs on the human heart rate variability (HRV): a new original methodology to evaluate effectiveness and contraindications of a biochemical compound on the human health. Preliminary results

Abstract

The effects of three Class IC antiarrhytmic drugs - Encainide, Flecainide, Moricizine – on the human health have been measured and quantified through the measurement of the patient HRV before and after the treatment. The proposition of this HRV-based methodology for validation and follow-ups of pharmaceutical therapies is the true novelty of the research referred in the paper. Some 1000 patients Heart Rate are monitored in the research: in the present paper a preliminary set of results is given for a first group of 120 peoples. The Research is aimed to develop, validate and promote the adoption in the clinical practice of new modern algorithms-borrowed from SMCDS and AI – to supply new extra-ordinary mass-scale diagnostic, preventive and cognitive tools both in the clinical practice and for policy making in the health sector towards an actual PPPM, as well as to suggest a new non-invasive cost effective methodology to monitor the effects of new/old pharmaceutical therapies on a patient and/or to adapt dosages and/or to identify important contraindications. The start point is the simple recording of a patient Heart Rate to analyze its time Variability before and during the therapies, by means of some tenths of HRV markers evaluated by the algorithms above, with the aim to identify therapy's positive and negative effects (or trends towards them) on the pathological status fought by the adopted therapy. The results, even if at a preliminary level, confirm the eligibility of the HRV-based analyses as a powerful new tool to follow up a therapy and its effects on a patient with high specific accuracy and sensibility! Even some well known clinical conclusions are reproduced: for examples the Encainide pro-arrhythmic effect – which is the reason why it is no longer used - is clearly highlighted. In general terms, they show that HRV is a powerful biomarker of the overall body health, not yet adequately exploited, but very promising to become in a near future a powerful PPPM diagnostic tool as well as a significant methodology to monitor the effects of new therapies on a single patient or on entire populations (especially if monitored through cheap wearable devices).

Keywords: electrophysyology, mathematical physics, cardiac and circulatory physiology, mathematical modelling of complex systems, precision medicine, heart rate variability, pharmacology, dosage evaluation, contraindications, health technology assessment

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Abbreviations: AI, artificial intelligence; ANN, artificial neural network; CAST, cardiac arrhythmia suppression trial; CRDB, common reference data base; CFM, cardio–frequency–meters; DEC, data elaboration centre; DL, deep learning; ECG, electrocardiogram; HR, heart rate; HRV, heart rate variability; MI, myocardial infarction; ML, machine learning; PPPM, predictive preventive personalized medicine; PVCs, Premature Ventricular Complexes; SMCDS, statistical mechanics of complex disordered systems

Introduction

State of the art and advancement of knowledge

Since the first paper of Akselrod et al.[1] HRV studies have shown a considerable potential to assess the role of autonomic nervous system fluctuations in healthy individuals as well as in patients with various disorders. In an ECG record, each QRS complex is detected, and the RR intervals are determined. Their variability in the short/long term period (from 10-15min to 24h, as in the Holter tests) or in a continuous monitoring, produces RR-Data Files of some 100000 numbers (in 24h) apparently chaotic, which can be well characterized by several markers (some 40-50 today) evaluable through advanced algorithms coming from SMCDS and, when the Data Base is huge, BIG DATA, ANN, ML and, in general, AI Techniques.

Despite the huge information present in these RR data, HRV is not yet a diffused tool in the clinical practice. Main factors limiting the development of HRV-based diagnostics are:

i. The non-existence of an open access and reliable CRDB of RR-Data files, huge enough and well managed, to allow to the scientific community the accomplishment of reliable HRV data analyses thorugh the algorithms above. After the work of an International Task Force on 1996[2]- which refers only to a few HRV markers and is 20 years old - and a recent comprehensive work of Voss et al.[3] - relating only to short term HRV - no other systematic approach has been developed and no procedures have been standardized.

ii. Because of the non-existence of CRDB above, there is a complete lack of knowledge of the ranges of "normal values" for most of the aforesaid HRV markers and, consequently, a total ignorance on the limits of these ranges besides or beyond the ones the presence of light or severe pathologies must be considered.

iii. Linear markers are still more diffused than the more appropriate non-linear approaches.

iv. HRV is still used to analyze heart diseases only, rather than a more complex body's equilibrium

v. Statistical analyses of HRV variables are normally carried out comparing Holter Tests, recorded once-in-a-life on different patients but no analysis of the HRV time evolution for a given set of patients is still available.

vi. No comparative analysis ("crossed analyses") between HRV and other simultaneous biochemical, acoustic, electromagnetic or "imaging" diagnostic tools has yet been carried out to validate the HRV results.

vii. No ANN has not yet designed/implemented to identify pathologies from an RR-Data File.

Several Researches are today on-going to overcome the above limits, including those named MATCH and

PYTHAGORAS, led by the University of Calabria (UNICAL) and International Polytechnics of Vibo Valentia (POLISA), Italy, and involving several European Universities and Hospitals[4,5] and the potentiality of the HRV to be elected as a powerful biomarker of the status of health of the whole body, is already clearly envisaged; among others the following topics are particularly relevant:

a) The heart rate is, instant by instant, the equilibrium point between the actions of two autonomic nervous system (sympathetic and parasympathetic) one aimed to accelerate the heart rate, the other one to reduce it, obeying each one to a myriad of bio-sensors located all over the human body: therefore the resulting HRV must be a complex expression of the status of the whole body!

b) A clear separation between HRV values of healthy and ill individuals has already been demonstrated for some modern HRV variables (such as the Barra-Moretti Potential) by Barra et al.[6,7]

c) A clear dependency of the most modern HRV variables from gender and age has already been demonstrated as well[4,5]

d) Very different patterns of values of the most part of HRV variables have already been registered for individuals affected by some different pathology.

The researches on going at UNICAL and POLISA premises is aimed to allow the health monitoring of entire populations by means of new simple cheap not-invasive and wearable devices, useful "for the individuals" to diagnose and to prevent important pathologies or to check the success of a personalized therapy, and "for the sanitary operators/authorities" to follow up epidemiological studies, to manage actions of "personalized medicine", to monitor sanitary campaigns or the effects of new drugs in different human, social and environmental conditions. Furthermore HRV is now considered a powerful biomarker of the overall body health and, once this novel perspective in mathematical modeling of information processing occurring in heart rate kinetics will be fully set-up, it will be capable to reveal the status of health of the whole human body and its reactions to any external stimulus, including the assumption of pharmaceutical drugs! The main 9 research targets are:

a. to ascertain the ranges of normal values for the most significant HRV markers, both in the long and in the short term HRV analyses and to determine the values of the alarm thresholds for the clinical practice for each one of the analyzed variables, eventually discriminating between "moderate alarm" and "severe alarm", and their dependence on age, gender, ethnicity, social and environmental patient living conditions;

b. to introduce new "non-linear variables analyses", which might generate new predictive-diagnostic algorithms?

c. to introduce HRV "time-evolution analyses" on the same patients which could confirm or reject several of the conclusions reached with once-in-a-lifetime analyses, and could also help assessing the effects of pharmaceutical drugs, and "crossed analyses" among two or more different independent methodologies, for example biochemical labs analyses, 3D imaging recordings, Thermographic screens and so on;

d. to develop and diffuse cheap, wearable and advanced technologies to allow each patient to collect by himself his own HRV data pattern, capable to dialogue with a DEC managed by the Project proposers/consultants, as well as , in a near future, by health institutional or private operators network, generated as a MATCH "spin-off";

e. to promote the creation of a large size CRDB, with certified formats and procedures, having data organized by gender, age, ethnicities, patient pathologies and followed therapies, environmental and social living conditions;

f. to introduce a "systematic approach" – and both long term (24h) and short term (15 minutes) standard procedures – to link HRV analysis with a general clinical characterization of patients, aimed to use the values of the HRV variables as a diagnostic tool to identify specific pathologies, to generate alarms suggesting the tendency of the patient to develop a specific serious pathology in a near future and/or to submit data to ANN hereinafter;

g. to introduce the most advanced approaches used for Big Data systems , such as ML, DL, AI and ANN, once CRDB has reached a size large enough to allow these approaches, and to develop patterns of HRV markers values as a reference label of each individual (at a certain stage of his/her life) to implement an actual PPPM

h. to use - once the methodology will be diffused at a mass-scale level - the variations of the HRV patterns of each individual as a bio-indicator for epidemiological studies as well as to follow up the results of specific campaigns in the health sector (new drugs,

prevention campaigns, etc.): a small "revolution" in living our health!

i. To use the HRV-based methodology to monitor, to understand and to validate the effects and the contraindications of a drug and/or of a therapy on a specific patient, or group of patients, for a specific pathology. In this scenario, the point 9 above is the target or the specific research whose preliminary results are reported in this paper.

Experimental

Materials and methods

The methodology is based on the collection and analyses of the RR files (15 minutes, 24 hours or continuous monitoring) of thousands of peoples with the final aim to identify the typical patterns of RR-values sequences of each important pathology, in order to transform the HRV analysis in a new powerful cheap extraordinary predictive preventive and personalized diagnostic tool! In this scenario the work is organized in 2 successive Phases, each one subdivided into 3 sections.

The 1st phase is aimed to the generation, collection and storage of the "raw" RR data files (as they come from the measurement equipment), and it is structured in:

a. Sec.1A: Monitoring of the peoples, by means of Holter recorders or new wearable CFM devices;

b. Sec.1B: Transmission, via internet, of the raw RR-files to a DEC;

c. Sec.1C: Classification of the raw RR-files and their insertion in a CRDB organized by ages, genders, ethnicities, pathologies and therapies, social and environmental living conditions.

The 2nd Phase is aimed to the Handling and Analysis of the raw data files and to the production of clinical results, by means of Proprietary Software, and it is articulated in:

a. Sec.2A: Conversion of the Raw-Data Files into Computer-Intelligible Open-Data Numerical Files;

b. Sec.2B: Evaluation of the information present in the data files by means of the evaluation of some 50 advanced algorithms coming from the most advanced SMCDS, producing a set of values for some 50 markers, fully characterizing each RR data file: when the CRDB will reach the size of Petabytes, Exabytes or more, the SNCDS methods will be progressively assisted by a ML Program, typical of the ANN (data come from tenths/hundreds of thousands of people and must be kept in mind that each person can have about 100.000 heartbeats/day, to join with an even wider information coming from personal data, clinical stories and pharmacological prescriptions of the peoples);

c. Sec.2C: Analysis of the Makers Values for each data file belonging to each pathology and identification of the typical patterns of the markers values for each main pathology and state of human being.

The MARKERS evaluated in the Project for each RR-data file are of 3 main typologies:[8–39]

i. Linear markers in the time domain, including: Mean RR Value (Mean RR); RR Standard deviation (SDNN); Mean Heart Rate value (Mean HR); HR Standard Deviation (STD-HR); Square Root of the mean squared differences between successive intervals (RMS-SD); Number of successive interval pairs which differ >50 ms (NN50); Percentage of NN50 respect to the total number of RR intervals (pNN50); HRV Triangular Index (HRV-TIN); Baseline of the TIN (Baseline-TIN); Average value of the 5-minutes SD-values (Mean-RR5); SD of RR5 intervals with respect to Mean-RR5 (SDANN).

ii. Linear markers in the frequency domain (evaluated both by Fast Fourier Transform and by Autoregressive Methods): including for each Very Low Frequency (VLF), Low Frequency (LF) and High Frequency (HF) domain the markers: Frequency Range; Absolute Power; Relative Power; Total Power; Ratio between LF and HF Powers (LF/HF).

iii. Non-linear markers, including; Poincarè Plots (both SD1 and SD2); Recurrence Plots [Mean Line Length, RPL_{mean} and Maximum Line Length (RPL_{max}); Recurrence Rate (REC); Determinism (DET)]; Shannon Entropy (ShE); Approximate entropy (ApEn); Sample entropy (SapEn); Detrended Fluctuation Analyses, both short term (DFAα1) and long term (DFAα2); Correlation Dimension (D2); Barra-Moretti Potential[4,5] both simplified (BMP) and extended life potential (EBMP).

The total number of markers is around 50, and other useful new markers could be identified, defined and employed during the duration of the research. Table 1 gives a list of the analyzed markers and their basic definitions.

Once the typical patterns of HRV Marker values was identified and validated for each pathology, the pathologies identification clinical procedure was set-up in accordance with a 3-steps "decisional tree" such as:

a) A first Patient screen was carried out, to distinguish an healthy from a non-healthy people, mainly by means of the BMP marker values.[6,7]

b) In case of non healthy people, the pattern of the markers was compared to those of the main pathologies and a moderate or a severe alarm was generated when one of these pathologies, on-going or a trend to it, was highlighted.

c) Furthermore a parallel procedure was carried-out to evaluate the effect of a therapy on a patient , measuring the HRV before ("baseline") and after the assumption of the relevant drugs ("on-therapy") and evaluating through the HRV markers variations, the human being and the therapy effectiveness.

Pathologies considered in the research (2nd step above) were chosen in order to cover the widest spectrum of typologies and included: cardiac (such as Atrial Fibrillation and Congestive Heart Failure and Brugada's Syndrome), autoimmune (as diabetes), neurodegenerative (as Alzheimer's desease), chronic inflammatory (as Chron's disease), genetic (as Down's syndrome), and oncological pathologies. A wide Control Group of young and healthy peoples (full absence of pathologies) has been already established since the beginning, and their markers values were commonly assumed as the "normal values" which all the other values were referred to. Therapies since the beginning considered in the Research (3rd step above) were those related to the use of some important antiarrhythmic drugs, such as Encainide, Flecainide, Moricizine, which will be followed by many others during the duration of the research.

Table 1 List of HRV Markers evaluated from RR "Raw" Data files

Type		Marker (Variable)	Units	Definition
Linear Variables	Time Domain	RR or NN interval	[ms]	Time Interval between two consecutive QRS complexes
		Mean RR	[ms]	The Mean of RR Intervals over a 24 hours period
		SDNN	[ms]	Standard Deviation of RR Intervals (24h)
		Mean HR	[b/m]	The Mean Heart Rate (24h)
		STD-HR	[b/m]	Standard Deviation of Instantaneous Heart Rate Values (24h)
		RMS-SD	[ms]	Square Root of Mean Square Differences between Successive RR Intervals (24h)
		NN50	[n]	Number of Successive RR Interval Pairs that Differ > 50 ms (24h)
		pNN50	[%]	NN50 divided by the Total Number of RR Intervals (24h)
		HRV TIN	-	Integral of the 24h RR Interval Histogram divided by its Height
		Baseline TIN	[ms]	Baseline Width of the RR Interval Histogram (24h)
		Mean RR5	[ms]	The Mean of the Average NN Intervals over 5 min periods
		SDANN	[ms]	Standard Deviation of the Average NN Intervals over 5 min periods
	Frequency Domain*	Peak Frequency	[Hz]	VLF, LF and HF Band Peak Frequencies, evaluated both by FFT and AR Methods
		Absolute Power	[ms^2]	Absolute Powers of VLF, LF and HF Bands (both FFT and AR)
		Relative Power	[%]	Relative Powers of VLF, LF and HF Bands (both FFT and AR)
		Normalized Power	[%]	Powers of LF and HF Bands in Normalized Units [i.e. excluding VLF Band]
		Total Power	[ms^2]	Total Power
		LF/HF	-	Ratio Between LF and HF Band Powers
Non Linear Variables	Poincarè	SD1	[ms]	Standard Deviation of Poincarè Plot [Rn+1 vs Rn] Orthogonal to the Identity Line
		SD2	[ms]	Standard Deviation of Poincarè Plot [Rn+1 vs Rn] Along the Identity Line
	Recurrence plot analysis	RPL min	[b]	Mean Line Length
		RPL max	[b]	Maximum Line Length
		REC	[%]	Recurrence Rate
		DET	[%]	Determinism
		SHA	_	Shannon Entropy
	Others	ApEn	_	Approximate Entropy
		SampEn	_	Sample Entropy
		DFA $\alpha 1$	_	Detrended Fluctuations Analysis: Short Term Fluctuation Slope
		DFA $\alpha 2$	_	DFA: Long Term Fluctuation Slope
		D2	_	Correlation Dimension
		BMP	[%]	"LIFE Potential" or "BARRA-MORETTI Potential"[4]

Abbreviations: FFT, fast fourier transform; AR, autoregressive methods; VLF, very low frequencies; LF, low frequencies; HF, High Frequencies

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Retrieval of raw RR data files

Raw RR-data files are partially collected by Hospitals cooperating to the research, and partially come from international DATABASES.[40,41] The latter come from a study named CAST designed to test the hypothesis that the suppression of asymptomatic or mildly symptomatic ventricular premature complexes (PVCs) in survivors of myocardial infarction (MI) would decrease the number of deaths from ventricular arrhythmias and improve survival. Enrollment required an acute MI within the preceding 2 years and 6 or more PVCs per hour during a pre-treatment (qualifying) long-term ECG (Holter) recording. Those subjects enrolled within 90 days from the MI were required to have left ventricular ejection fractions less than or equal to 55%, while those enrolled after this 90 day window were required to have an ejection fraction less than or equal to 40%. CAST enrolled 3,549 patients in all, and after initial qualification, patients were randomly assigned to receive encainide, flecainide, moricizine or a placebo. Patients who had significant suppression of PVCs with a particular agent were then continued on that agent or on placebo. In April of 1989, the US Data and Safety Monitoring Board recommended that the encainide and flecainide arms of the study be discontinued because of excessive mortality in the drug arms of the trial primarily due to arrhythmia, acute MI with shock, or chronic congestive heart failure. CAST was then followed by CAST-II, which involved continuation of the moricizine arm of the CAST and placebo. CAST-II was divided into two blinded, randomized phases: an early, 14-day exposure phase that evaluated the risk of starting treatment with moricizine after MI and a long-term phase that evaluated the effect of moricizine on survival after MI in patients whose PVCs were either adequately suppressed by moricizine or only partially suppressed. CAST-II was stopped early because long-term treatment with moricizine after an MI was associated with a trend to excess mortality as compared with no treatment or placebo and the CAST-II study authors concluded that as with the other antiarrhythmic agents used in CAST (flecainide and encainide), the use of moricizine to suppress asymptomatic or mildly symptomatic ventricular premature complexes after MI was not only ineffective but also harmful.

In order to investigate further the relationship between survival and changes in heart rate variability in response to anti-arrhythmic treatment, a subset of the CAST/CAST-II patients, was selected, consisting of those who had usable pre-treatment and on-therapy recordings, based on data collected during the original CAST and CAST II studies. Those peoples received a randomly-assigned antiarrhythmic treatment that successfully reduced their PVC rates by at least 80% on the first attempt and continued on that treatment.

These criteria were satisfied by 734 patients, of whom 69 died during the study period. The CAST RR Interval Sub-Study Database consists of RR interval time series from the pre-treatment and on-therapy recordings from these patients. To these CAST patients some more 250 patients are added during the research, for a total of some 1000 patients, with a total number of 2000 raw RR-data files (including baseline and on-therapy files) to be analyzed during the whole research. The present article provides the preliminary results obtained on a first set of 240 files (12%) distributed in equal parts among the 3 considered antiarrhythmic drugs.

The DEC and the CRDB employed in the research have been implemented and managed in this research and in a previous one[40,41] by the Politecnico Internazionale of Vibo Valentia (POLISA), a public-private research organization working since 2013 in cooperation with UNICAL-DIATIC under a specific agreement signed in 2013, which is also the developer and the owner of the physical mathematical know-how and of the relevant software.

Results and discussion

The whole set of preliminary results, obtained on this sample of 12% of patients, is shown in Tables 2 & Table 3. Tables 2 summarizes the results regarding the linear markers whereas the non linear marker values are reported in Table 3. In both Tables 2,3 vertical columns blocks are presented - respectively for encainide, flecainide and morizicine - each one containing for each marker: the marker average value - AV - shown by the patients before the therapy (baseline values) and the relative standard deviation (RSD) of the distribution of the marker values around their average value (expressed as a% of the average value); the marker average value shown by the patients during the therapy (on-therapy values) and the RSD of the distribution of the marker values around their average value (expressed as a% of the average value); the average variation of the marker average values ante- and post- therapy [expressed as a percentage (post-ante)values/ ante value i.e. (on-therapy-baseline)values/baseline value] and the RSD of the distribution of these marker variation values around their average value (expressed as a% of the AV variation value).

The analysis of the results of Table 2 & Table 3 seems to suggest the following considerations:

1. The HRV-based analysis seems to be a new tool fully appropriate and very promising to follow-up a therapy and the effects of a therapy on a patient.
2. The most part of the HRV markers appear to be very sensible to the adoption of the considered therapies.
3. In particular, for the results regarding the linear markers in the time domain, they exhibit in most cases a strong reduction of their values because of the therapy action , as it is expected for an antyarrhythmic therapy; the only exception is represented by SDANN , which is significantly growing-up for flecainide and morizicine based therapies , but even decreasing for encainide therapy (and a SDANN reduction is a well know indicator of high risk of sudden death or other similar severe adverse events)!
4. For results regarding the linear markers in the frequency domain, it is evident the effect of therapy because of a much more equilibrated distribution between LF and HF powers obtained through the administration of drugs to the patient, as well as of an improvement of the LF/HF value , when it is initially too low (<1).
5. For results regarding the non linear markers it is evident:

a. A positive effect of the therapies on the Poincarè SD1, whereas SD2 seems to be indifferent to the drug intake;

b. About the recurrence plot analysis, RPLmax seems to be the only indicator affected by the drug intake whereas the Shannon Entropy remains quite indifferent: in agreement with the deep meaning of the Shannon Entropy, this fact seems to suggest that the therapy

effects regard only the "noise" present on the HRV , thus the temporary effect of an arrhythmia, and not the circadian Heart Rate variability responsible of the existence of the arrhythmia itself;

c. About the others non linear markers, they all seem responding to the therapies, with a particular sensibility of the Sample Entropy (SampEn) and of the variation of the Life Potential ,BMP, with respect to an healthy people of the same age, which has a particular improvement!

Table 2 HRV Markers Values, Before (Baseline) and During the Antiarrhytmic Therapy (on-Therapy): Linear Markers

				Encainide						Flecainide						Morizicine					
				Baseline		ON-Therapy		Δ (%)		Baseline		ON-Therapy		Δ (%)		Baseline		ON-Therapy		Δ (%)	
Type Of Analysis	Parameter		Units	Average value AV	Rel.St.Dev.RSD (%)	Average value AV	Rel.St.Dev.RSD (%)	AV Variation [(post-ante)/ante]	RSD Variation [(post-ante)/ante]	Average value AV	Rel.St.Dev.RSD (%)	Average value AV	Rel.St.Dev.RSD (%)	AV Variation [(post-ante)/ante]	RSD Variation [(post-ante)/ante]	Average value AV	Rel.St.Dev.RSD (%)	Average value AV	Rel.St.Dev.RSD (%)	AV Variation [(post-ante)/ante]	RSD Variation [(post-ante)/ante]
Time Domain	**Mean RR**		[ms]	788.6	18.3%	812.8	17.4%	3.1%	-4.7%	887.6	17.6%	933.3	18.5%	5.2%	5.0%	868.0	23.1%	908.7	19.5%	4.7%	-15.7%
	SDNN		[ms]	100.3	36.4%	86.5	35.4%	-13.8%	-2.7%	137.8	41.9%	124.6	34.6%	-9.6%	-17.4%	112.1	41.0%	113.3	32.0%	1.0%	-21.9%
	Mean HR		[b/m]	80.1	18.3%	76.9	17.0%	-3.9%	-7.2%	71.5	18.7%	67.6	19.2%	-5.4%	2.6%	74.3	24.5%	69.5	19.8%	-6.4%	-19.4%
	STD-HR		[b/m]	10.9	38.9%	8.5	34.5%	-22.4%	-11.1%	11.5	25.6%	9.0	29.1%	-21.4%	13.7%	11.5	61.9%	8.8	35.0%	-23.3%	-43.5%
	RMS-SD		[ms]	78.4	52.8%	36.9	52.1%	-52.9%	-1.3%	137.1	82.0%	71.5	103.0%	-47.8%	25.6%	83.2	47.7%	53.3	66.2%	-35.9%	38.6%
	NN50		[n.10^3]	12.38	83.2%	5.06	0.6%	-59.1%	-99.3%	19.64	93.5%	12.10	128.0%	-38.4%	36.9%	9.29	89.4%	11.95	107.8%	28.7%	20.5%
	pNN50		[%]	12.0	74.5%	5.4	132.6%	-55.0%	78.0%	25.7	111.6%	17.8	147.3%	-30.7%	32.0%	11.9	115.3%	13.4	96.8%	12.4%	-16.1%
	HRV TIN		[n.p.]	14.4	45.5%	13.6	45.1%	-5.8%	-1.0%	19.2	43.2%	18.1	43.3%	-5.7%	0.3%	17.1	58.4%	18.6	57.6%	8.4%	-1.5%
	Baseline TIN		[ms]	557	13.9%	489	23.2%	-12.3%	67.6%	549	13.0%	460	21.7%	-16.3%	67.3%	522	23.9%	450	31.5%	-13.8%	31.5%
	Mean RR5		[ms]	57.0	42.7%	37.9	43.5%	-33.4	2.0%	93.6	67.4%	59.1	63.0%	-36.8%	-6.5%	69.8	55.7%	55.9	41.8%	-20.0%	-25.0%
	SDANN		[ms]	76.3	42.2%	74.3	37.1%	-2.6%	-12.0%	84.2	36.4%	101.6	37.5%	20.7%	3.0%	81.8	28.8%	93.6	34.9%	14.4%	21.2%
Frequency Domain	FFT Method	**LF Norm. Power**	[%]	33.4%	48.3%	48.4%	32.6%	44.8%	-32.6%	35.9%	50.3%	45.3%	33.3%	26.4%	-33.9%	43.2%	55.9%	47.3%	38.2%	9.4%	-31.6%
		HF Norm. Power	[%]	66.6%	24.3%	51.6%	30.5%	-22.5%	25.9%	64.1%	28.2%	54.7%	27.6%	-14.8%	-1.9%	56.8%	42.5%	52.7%	34.3%	-7.2%	-19.3%
		Total Power	[ms^2]	7528.9931	66.4%	5972.9799	73.2%	-20.7%	10.2%	13502.02	72.6%	11647.023	56.9%	-13.7%	-21.6%	9136	91.1%	9995.8843	55.3%	9.4%	-39.4%
		LF/HF	-	0.61	79.4%	1.1204633	57.6%	83.6%	-27.4%	0.80	126.4%	0.99	67.2%	24.3%	-46.9%	1.16	93.6%	1.15	77.1%	-0.8%	-17.6%
	AR Methods	**LF Norm. Power**	[%]	33.0%	42.6%	46.1%	28.5%	39.9%	-33.2%	34.8%	48.2%	42.5%	33.8%	22.1%	-30.0%	42.4%	48.5%	45.0%	37.7%	6.0%	-22.2%
		HF Norm. Power	[%]	67.0%	20.9%	53.9%	24.3%	-19.6%	16.2%	65.2%	25.8%	57.5%	25.0%	-11.8%	-3.1%	57.6%	35.7%	55.0%	30.8%	-4.5%	-13.7%
		Total Power	[ms^2]	8463.3058	66.1%	6814.5521	70.2%	-19.5%	6.3%	15217	70.4%	15339	58.0%	0.8%	-17.7%	10077	88.5%	11651	52.9%	15.6%	-40.2%
		LF/HF	-	0.57	67.7%	0.97078	51.7%	71.4%	-23.7%	0.71	111.8%	0.86	64.7%	22.1%	-42.2%	0.99	80.9%	1.01	73.1%	2.3%	-9.6%

Table 3 HRV Markers values, before (baseline) and during the antiarrhytmic therapy (on-therapy): non linear markers

				Encainide						Flecainide						Morizicine					
				Baseline		ON-Therapy		Δ (%)		BASELINE		ON-Therapy		Δ (%)		Baseline		ON-Therapy		Δ (%)	
Type Of Analysis		Parameter	Units	Average value AV	Rel.St.Dev.RSD (%)	Average value AV	Rel.St.Dev.RSD (%)	AV Variation [(post-ante)/ante]	RSD Variation [(post-ante)/ante]	Average value AV	Rel.St.Dev.RSD (%)	Average value AV	Rel.St.Dev.RSD (%)	AV Variation [(post-ante)/ante]	RSD Variation [(post-ante)/ante]	Average value AV	Rel.St.Dev.RSD (%)	Average value AV	Rel.St.Dev.RSD (%)	AV Variation [(post-ante)/ante]	RSD Variation [(post-ante)/ante]
Non Linear	Poincaré	**SD1**	[ms]	55.4	52.8%	26.1	52.1%	-52.9%	-1.3%	96.9	82.0%	50.6	103.0%	-47.8%	25.6%	58.8	47.7%	37.7	66.2%	-35.9%	38.6%
		SD2	[ms]	128.5	38.0%	118.8	36.2%	-7.6%	-4.6%	161.6	34.4%	163.5	33.3%	1.2%	-3.4%	145.9	42.7%	153.7	33.8%	5.3%	-20.8%
	Recurrence Plot Analysis	**RPL min**	[b]	25.8	30.6%	29.2	21.2%	13.2%	-30.8%	23.3	41.7%	26.5	39.1%	13.3%	-6.3%	24.9	23.9%	26.5	29.2%	6.7%	22.1%
		RPL max	[b]	361	34.9%	537	27.0%	48.6%	-22.8%	330	50.4%	509	35.7%	54.3%	-29.2%	391	54.0%	527	39.7%	34.8%	-26.4%
		REC	[%]	49.9	17.1%	47.2	11.5%	-5.4%	-32.9%	45.6	30.1%	43.8	26.2%	-4.1%	-12.9%	52.3	12.4%	46.8	15.0%	-10.5%	21.3%
		DET	[%]	99.2	0.5%	98.9	0.7%	-0.3%	42.2%	98.8	1.1%	98.6	1.0%	-0.2%	-5.3%	99.5	0.2%	98.9	0.8%	-0.6%	310.2%
		SHA	_	3.86	7.1%	3.88	6.7%	0.5%	-5.7%	3.71	9.5%	3.76	10.2%	1.5%	7.4%	3.89	6.7%	3.83	9.4%	-1.5%	40.7%
	Others	**ApEn**	_	1.04	16.2%	1.18	9.3%	13.4%	-42.7%	1.08	14.7%	1.22	7.0%	13.2%	-51.9%	0.97	17.4%	1.14	12.3%	16.7%	-29.1%
		SampEn	_	1.02	22.8%	1.25	13.0%	21.7%	-43.2%	1.06	22.8%	1.34	11.7%	26.5%	-48.8%	0.92	25.5%	1.15	17.5%	24.4%	-31.2%
		DFA α1	_	0.64	35.3%	0.88	26.1%	38.3%	-26.0%	0.70	38.1%	0.88	29.7%	27.1%	-22.0%	0.74	43.3%	0.91	30.8%	23.2%	-29.0%
		DFA α2	_	0.92	16.6%	1.04	12.3%	12.9%	-25.6%	0.85	18.8%	0.97	18.3%	13.9%	-2.7%	0.89	27.1%	1.00	20.7%	11.9%	-23.6%
		D2	_	1.23	63.9%	0.92	76.4%	-25.8%	19.7%	1.78	58.1%	1.62	68.0%	-9.1%	17.0%	1.31	79.7%	1.53	73.9%	17.1%	-7.3%
		BMP rel	[%]	0.54	27.5%	0.59	16.9%	9.9%	-38.6%	0.62	27.7%	0.69	20.1%	12.0%	-27.6%	0.54	41.0%	0.65	30.6%	21.8%	-25.5%
		Δ(BMP) vs healthy peer	[%]	-0.16	90.9%	-0.10	95.1%	37.5%	4.6%	-0.07	25.5%	0.01	42.7%	114.3%	67.4%	-0.14	73.5%	-0.02	92.7%	85.7%	26.2%

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Conclusion

The preliminary results shown in the section above concern 12% of the patients foreseen in the research and therefore, even if they appear very promising and full of useful knowledge, they must be confirmed and validated once the research will be fully accomplished, especially in terms of the standard deviations values which are expected to become narrow and narrow when the number of analyzed patients will grow-up. As a policy tool, the HRV analyses, because of its capability to monitor whole populations, seems to be, therefore, really able to allow the follow up of large scale sanitary actions (epidemiological studies, impacts of new drugs, prevention campaigns, special communities therapeutic actions, follow-up of personal response of each individual to different clinical conditions or therapeutic treatments, or socio-environmental living conditions) with sharp increasing of its effectiveness and drastic reduction of its costs. A second article will be published in the next months including the final results and the considerations suggested by those results both from clinical and cognitive points of view.

Ethics

As far as "ethics" is concerned, the research is made of "observational studies" which don't imply new drugs or invasive methodologies. Data gathering and transmission will not have any influence on the people normal life. Data will be treated in a completely anonymous form and in the full respect of the so called "DECLARATION OF HELSINKI". All the Hospitals participating to the Project already have the written consensus of their relevant Ethical Committees.

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Conflict of interest

There is no conflict of interest.

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