Noninvasive monitoring of the cardiovascular regulation based on heart rate variability analysis: do non linear tools provide additional information?

Alberto Porta

Department of Biomedical Sciences for Health
Galeazzi Orthopedic Institute
University of Milan
Milan, Italy

Introduction

Cardiovascular variables are regulated according to multiple control mechanisms

Cardiovascular control mechanisms contain important non linearities, thus suggesting that accounting for non linear dynamics might provide additional information

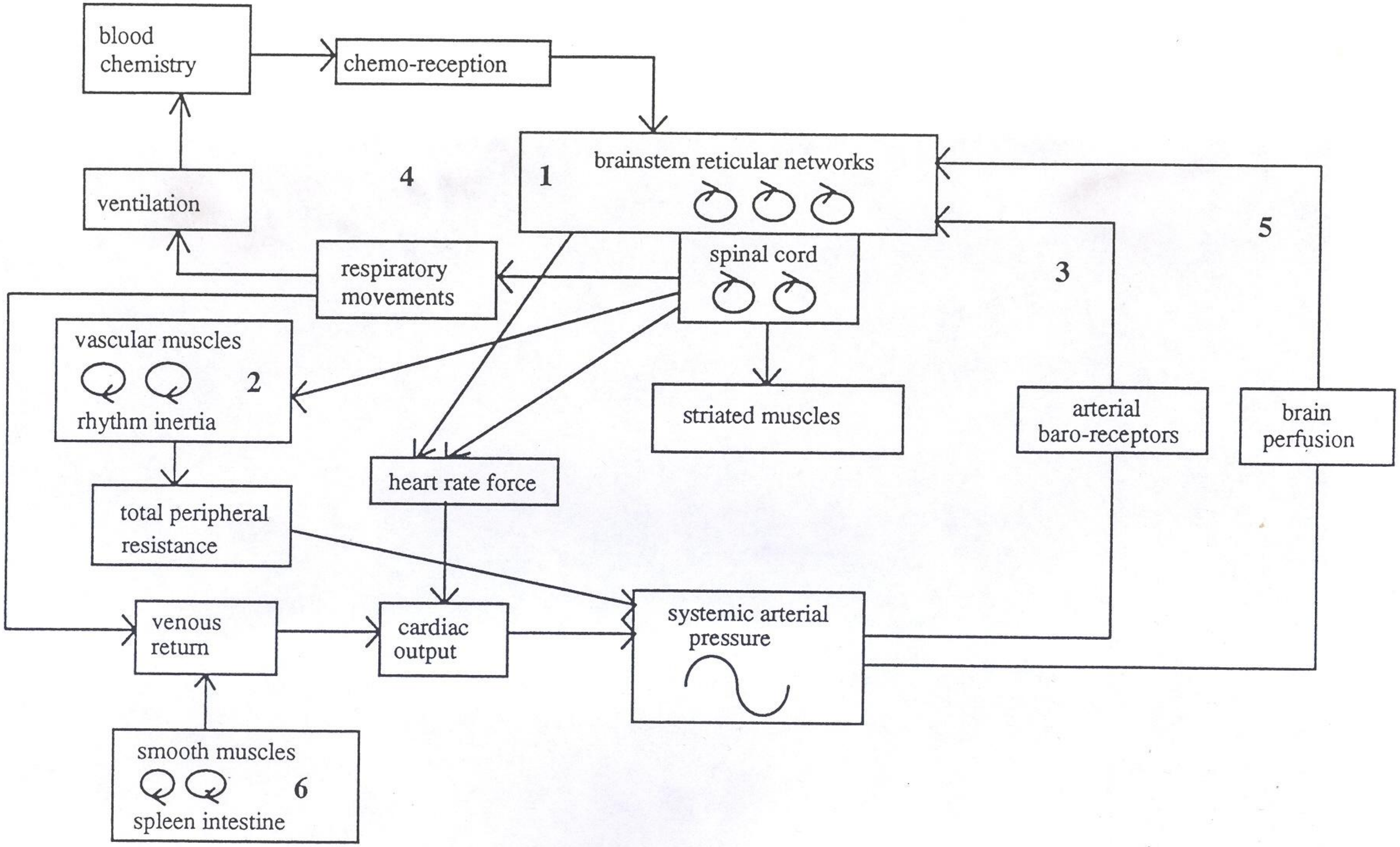
However, spectral analysis considering only linear features is found to be sufficient to detect changes of the state of the autonomic nervous system and distinguish pathological conditions

Aims

To demonstrate the value of non linear tools “per se” to detect changes of the state of the autonomic nervous system and typify pathological patients

To quantify the additional information of non linear analysis to the linear one

Short-term cardiovascular regulation



" the interference of at least three oscillatory systems can be made responsible:

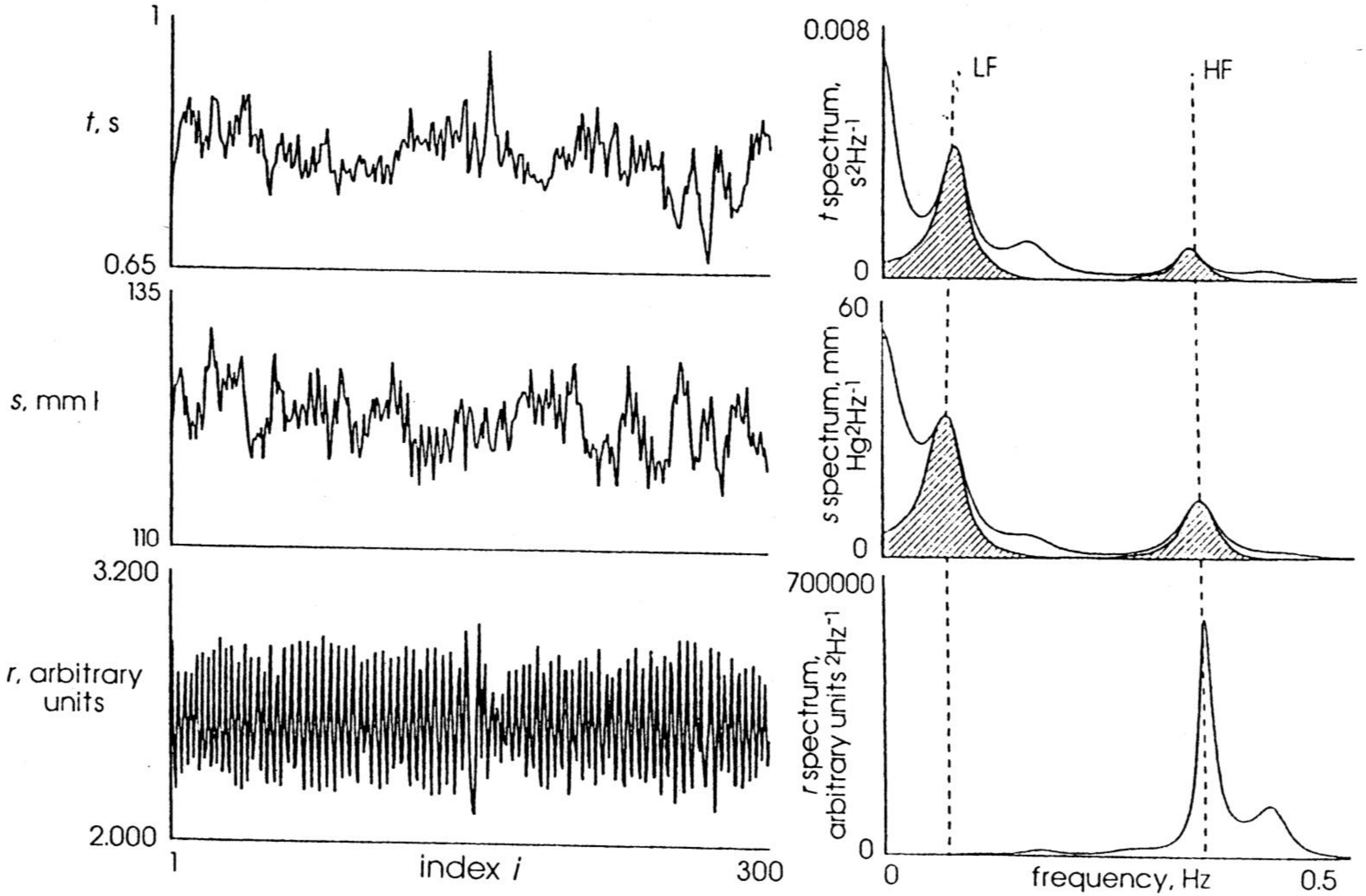
1) centrogenic rhythms ....

2) the baroreceptor feedback system

3) the autorhythmicity of vascular smooth muscle "

H.P. Koepchen, in “Mechanisms of blood pressure waves”, Springer-Verlag, 3-23, 1984

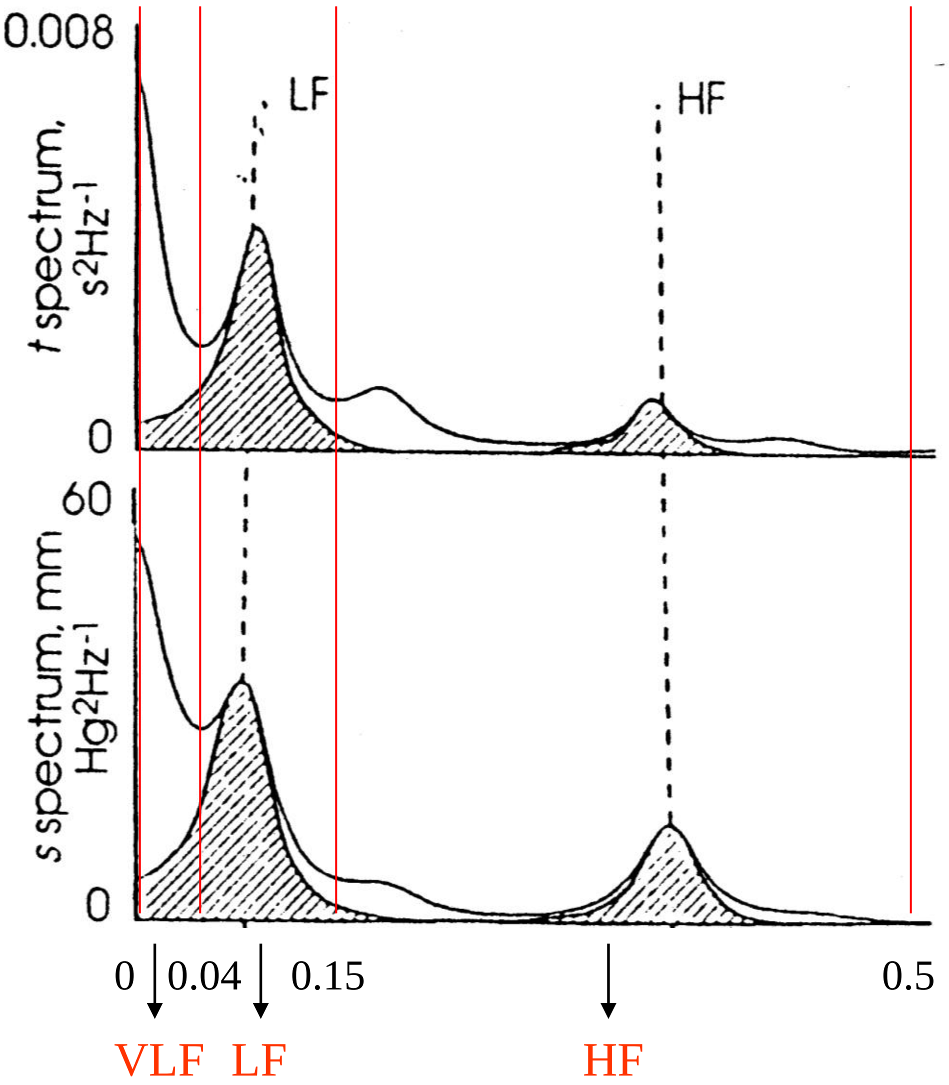
Cardiovascular variability



G. Baselli et al, Med Biol Eng Comput, 32:143-152, 1994

Spectral analysis of cardiovascular variability

VLF band: 0-0.04 Hz
LF band: 0.04-0.15 Hz
HF band: 0.15-0.5 Hz



Task Force of the European Society of Cardiology, Circulation, 93:1043-1065, 1996

Markers of cardiovascular regulation based on the spectral analysis of heart period variability

LF_{ass} = the power in the LF band (0.04-0.15 Hz)
HF_{ass} = the power in the HF band (0.15-0.5 Hz)

S. Akselrod et al, Science, 213:220-223, 1981

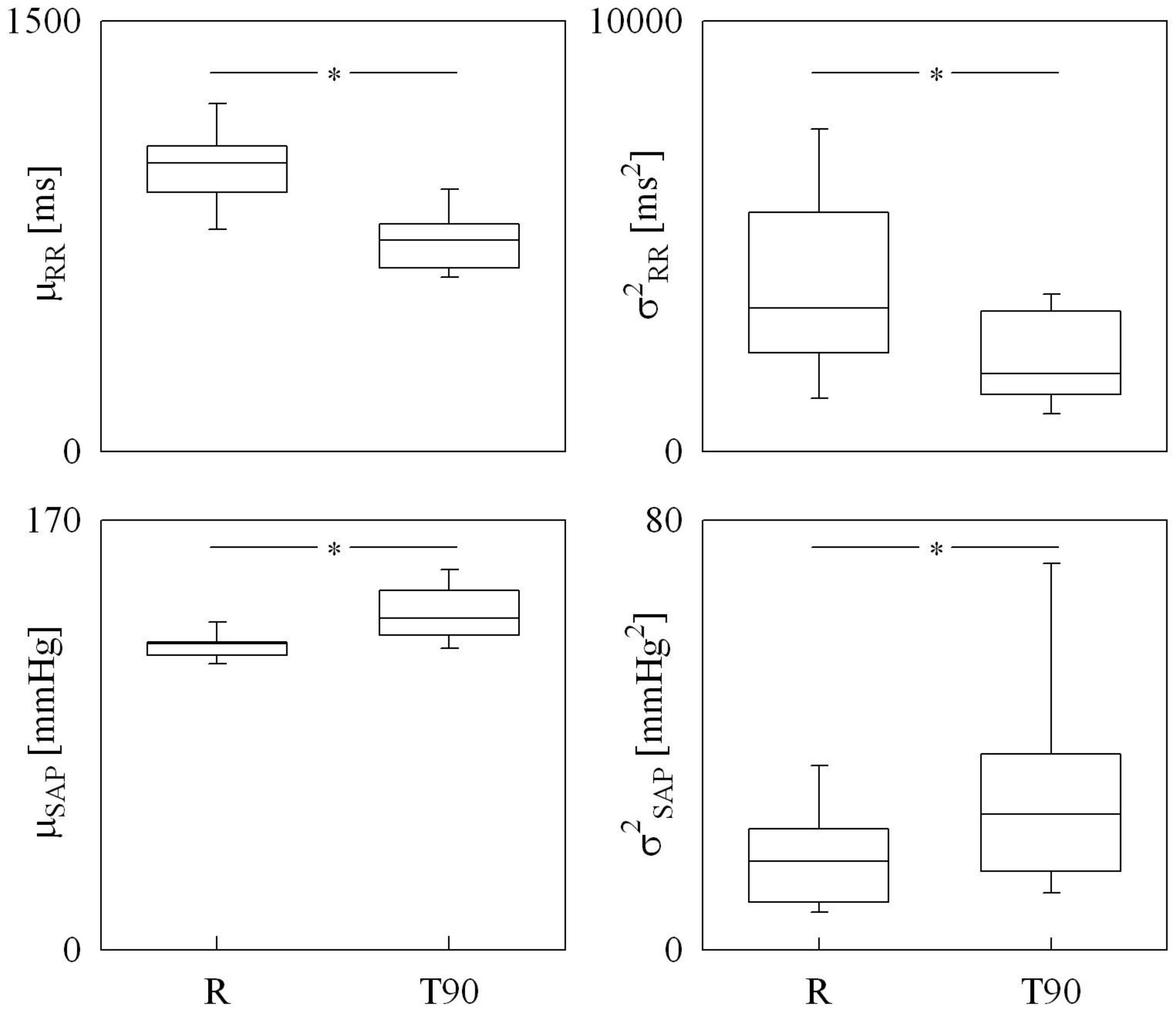
LF_{nu} = the power in the LF band (0.04-0.15 Hz)
HF_{nu} = the power in the HF band (0.15-0.5 Hz)

M.Pagani et al, Circ Res, 59:178-193, 1986

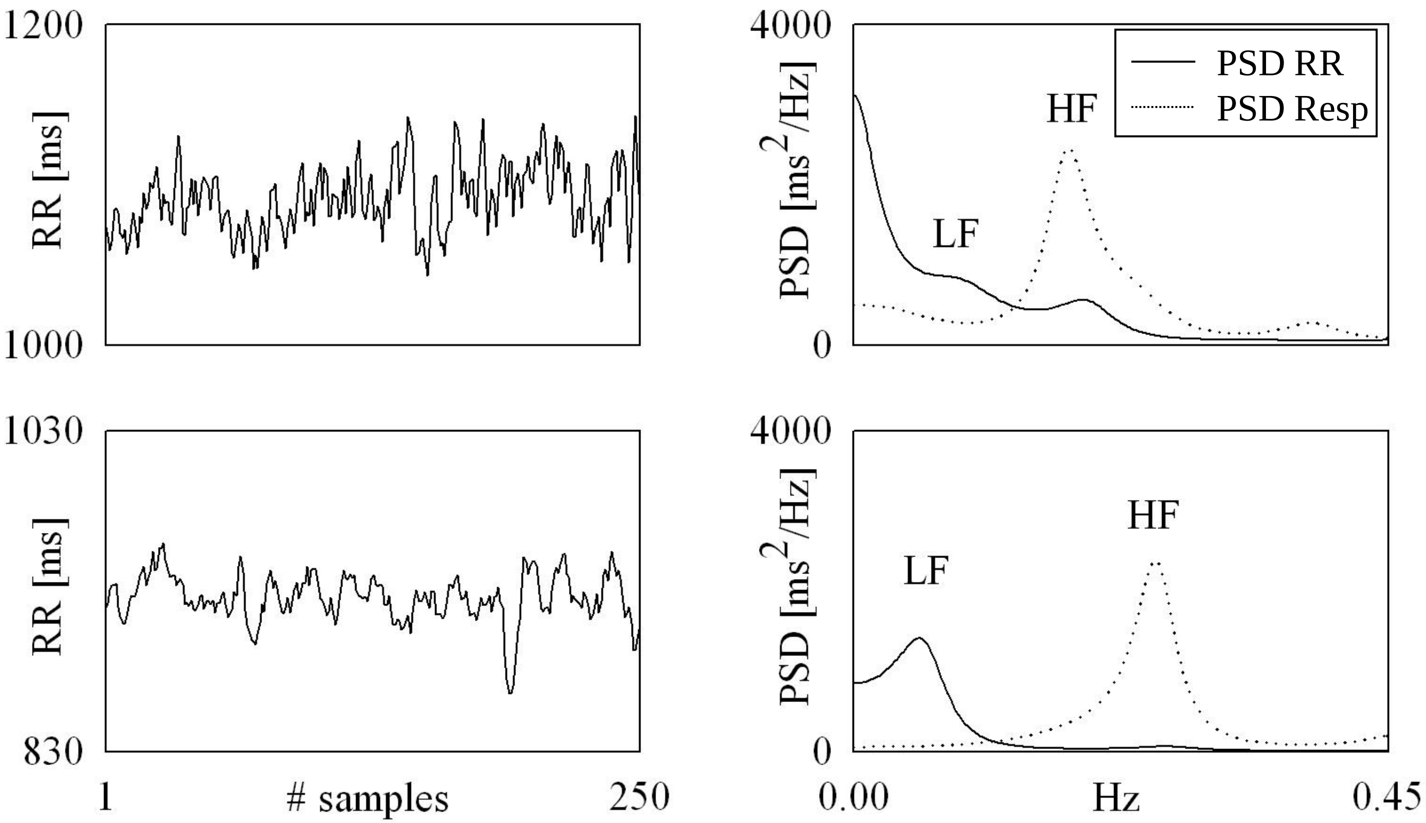
The physiological meaning of markers derived from the spectral analysis of heart period variability

Maneuver of passive orthostatism

Maneuver of passive orthostatism



The physiological meaning of markers derived from the analysis of heart period variability



Supine

90° head-up tilt

LF_{nu} ↑ **HF_{ass}** ↓

N. Montano et al, Circulation, 90:1826-1831, 1994

Experimental protocol

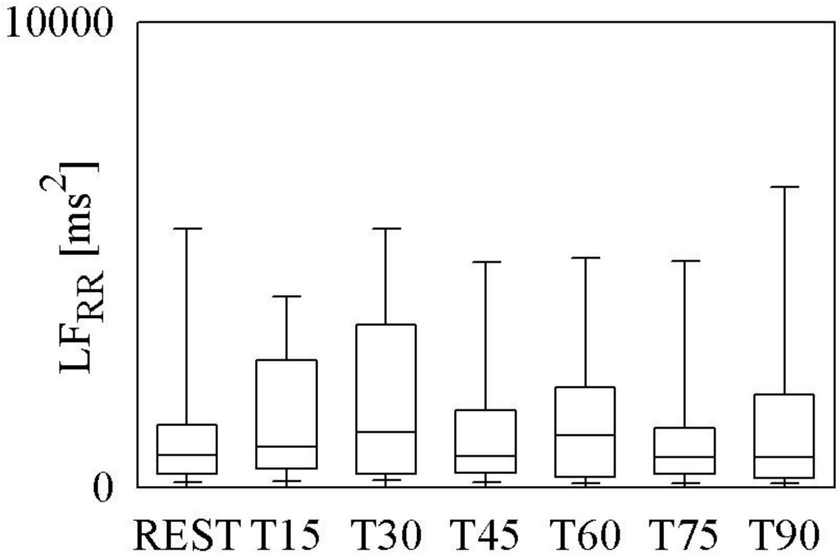
17 healthy young humans (age from 21 to 54, median=28)

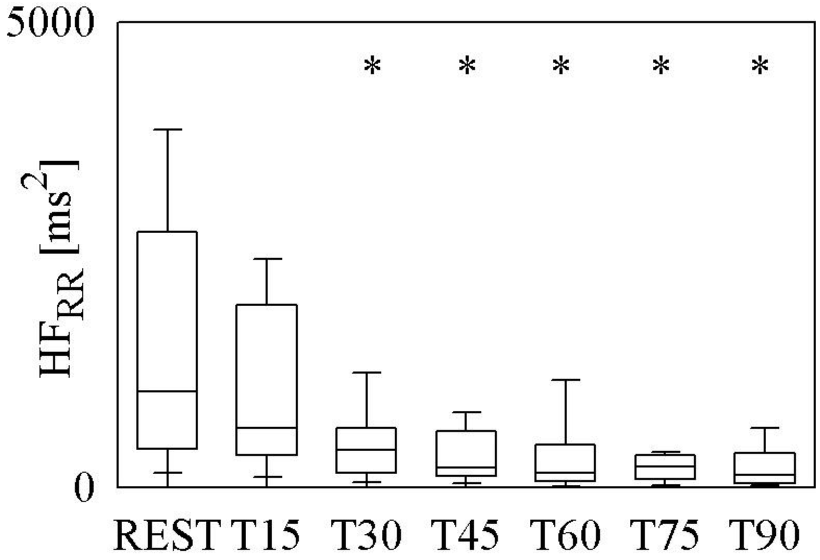
We recorded ECG (lead II) and respiration (thoracic belt) at 1 kHz during head-up tilt (T)

Table angles were randomly chosen within the set {15,30,45,60,75,90}

Each T session (10 min) was always preceded by a session (7 min) at rest (R) and followed by a recovery period (3 min)

The physiological meaning of markers derived from the spectral analysis of heart period variability



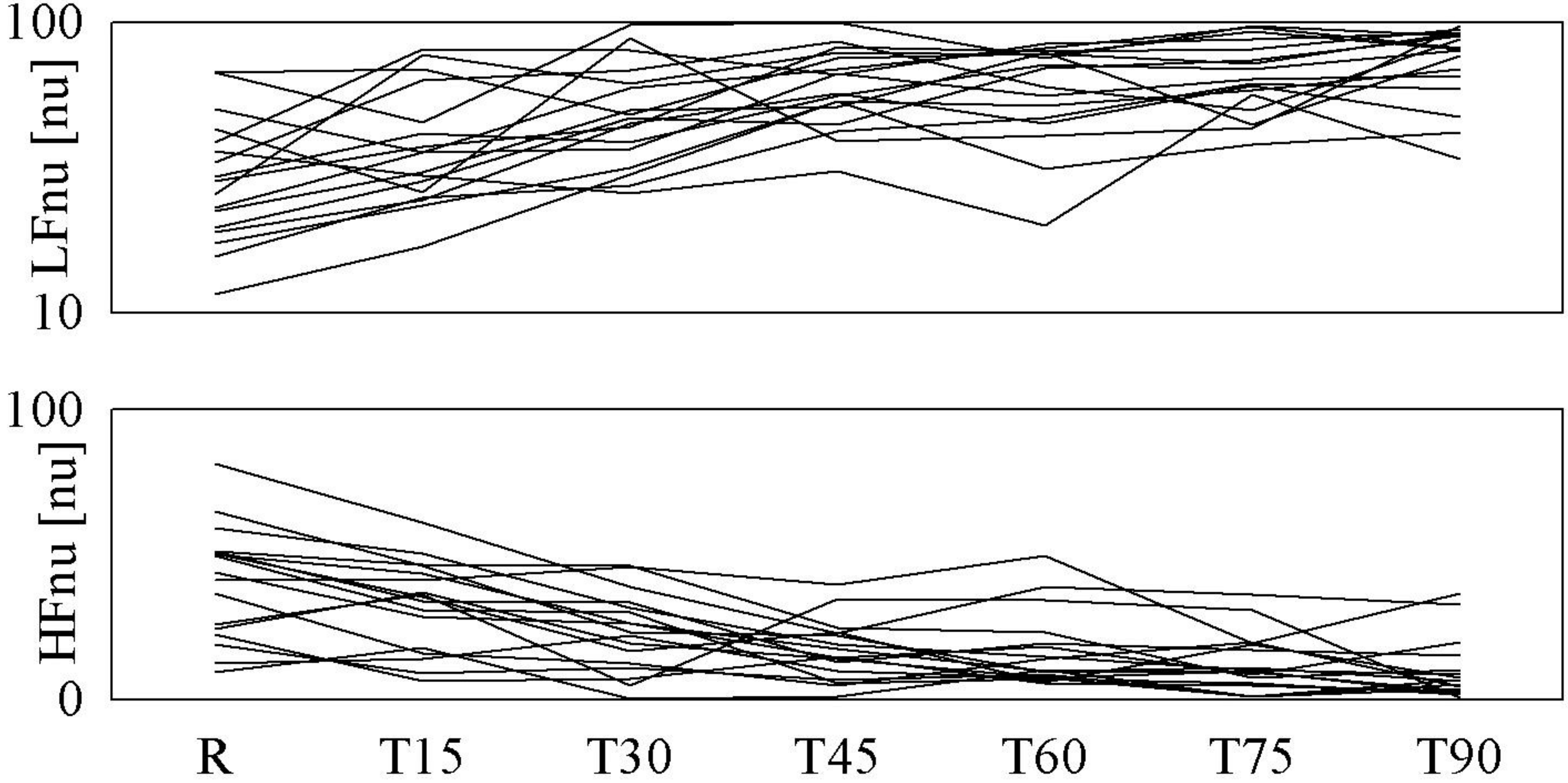


N. Montano et al, Circulation, 90:1826-1831, 1994

A. Porta et al, Am J Physiol, 293:H702-H708, 2007

A. Porta et al, J Electrophysiol, 44:662-668, 2011

The physiological meaning of markers derived from the spectral analysis of heart period variability



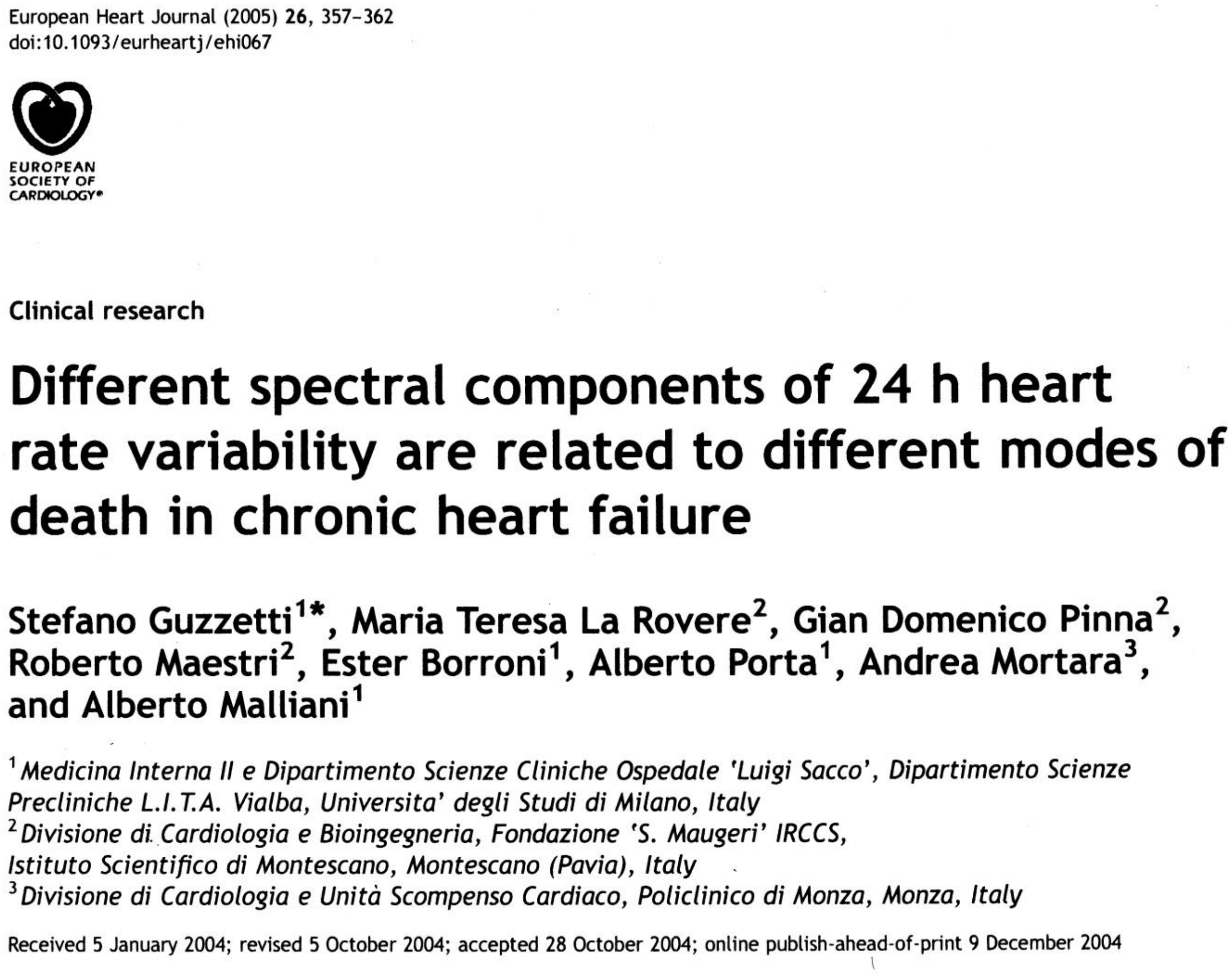
N. Montano et al, Circulation, 90:1826-1831, 1994

A. Porta et al, Am J Physiol, 293:H702-H708, 2007

The spectral analysis of heart period variability is helpful to describe physiological conditions but what about pathological situations?

Does spectral analysis provide non redundant information with respect to descriptors traditionally utilized in clinics?

Spectral analysis of heart period variability and heart failure



European Heart Journal (2005) **26**, 357–362
doi:10.1093/eurheartj/ehi067

EUROPEAN
SOCIETY OF
CARDIOLOGY®

Clinical research

Different spectral components of 24 h heart rate variability are related to different modes of death in chronic heart failure

Stefano Guzzetti[1*], Maria Teresa La Rovere[2], Gian Domenico Pinna[2], Roberto Maestri[2], Ester Borroni[1], Alberto Porta[1], Andrea Mortara[3], and Alberto Malliani[1]

[1] *Medicina Interna II e Dipartimento Scienze Cliniche Ospedale 'Luigi Sacco', Dipartimento Scienze Precliniche L.I.T.A. Vialba, Universita' degli Studi di Milano, Italy*
[2] *Divisione di Cardiologia e Bioingegneria, Fondazione 'S. Maugeri' IRCCS, Istituto Scientifico di Montescano, Montescano (Pavia), Italy*
[3] *Divisione di Cardiologia e Unità Scompenso Cardiaco, Policlinico di Monza, Monza, Italy*

Received 5 January 2004; revised 5 October 2004; accepted 28 October 2004; online publish-ahead-of-print 9 December 2004

Clinical parameters in a population of heart failure patients (n=330)

Clinical	**Age (years)**	54 (47 - 59)
	Male (%)	87
	BMI (Kg/m^2)	25.2 (23.1-27.9)
	SBP (mmHg)	110 (100-120)
	Diabetes (%)	16
	Smoking history: Current smoker (%)	25
	Previous smoker (%)	49
	Never smoker (%)	26
	NYHA Class: I (%)	11
	II (%)	53
	III (%)	36
	Etiology: Ischemic (%)	49
	Idiopathic (%)	45
	Valvular (%)	4
	Other (%)	2
Echocardiographic	**LVEF (%)**	24 (19- 28)
	LVESD (mm)	61 (54 – 68)
	LVEDD (mm)	71 (66 – 78)
	DT (ms)	125 (95 – 160)
	Mitral Regurgitation grade 3-4 (%)	41
Hemodynamic	**PWP (mmHg)**	18 (10 – 27)
	RAP (mmHg)	4 (2 – 7)
	CI (l/min/m^2)	2.2 (1.9 – 2.6)
Holter	**VPCs/h (N)**	18 (4 – 59)
Cardiopulmonary Exercise	**VO2 peak (ml/kg/min)**	14.3 (11.9 – 17.4)
Blood chemistry	**Cholesterol total (mg/dL)**	211 (176-239)
	Triglycerides (mg/dL)	137 (99-197)
	BUN (mg/dl)	47 (39 – 59)
	Creatinine (mg/dl)	1.19 (1.03 -1.34)
	Na (mEq/l)	139 (137 – 141)
	K (mEq/l)	4.36 (4.1 – 4.6)
	Bilirubin (mEq/l)	0.99 (0.68 – 1.32)

S. Guzzetti et al, Eur Heart J, 26:357-362, 2005

Spectral analysis in a population of heart failure patients (n=330)

HRV	**RR 24-hour (ms)**	813 (730 – 902)
	RR night (ms)	907 (786 – 1017)
	SDNN 24-hour (ms)	89 (68 – 121)
	SDNN night (ms)	71 (54 – 94)
	VLF 24-hour (ms^2)	894 (422 – 1734)
	VLF night (ms^2)	1147 (509 – 2530)
	LF 24-hour (ms^2)	63 (25 – 189)
	LF night (ms^2)	70 (20 – 235)
	HF 24-hour (ms^2)	127 (58 – 269)
	HF night (ms^2)	140 (60 – 360)
	LF 24-hour (nu)	21 (12-32) %
	LF night (nu)	23 (12-33) %
	HF 24-hour (nu)	58 (48-66) %
	HF night (nu)	65 (53-74) %
	LF/HF 24-hour	0.82 (0.37 – 1.57)

24 Holter recordings, frame length: 300 beats; overlap: 50%

S. Guzzetti et al, Eur Heart J, 26:357-362, 2005

Endpoints of the survival analysis

1) Progressive pump failure death or urgent transplantation

2) Sudden cardiac death

During a 3 year follow-up

- 79 patients out of 330 died because pump failure (n=62) or underwent urgent transplantation (n=17)
- 29 patients out of 330 died because sudden cardiac death

Predictors of pump failure death (univariate analysis)

	Variable (cutoff value)	χ^2	p	RR (95% CI)
Clinical	**NYHA class (= 3)**	15.8	< 0.0001	2.5 (1.6 – 3.8)
	SBP (≤ 110 mmHg)	9.1	0.0026	2.2 (1.3 – 3.6)
Echocardiographic	**LVEF (≤ 24%)**	15.3	< 0.0001	2.7 (1.6 – 4.4)
	LVESD (≥ 68 mm)	9.4	0.0022	2.1 (1.3 – 3.2)
	LVEDD (≥ 78 mm)	6.8	0.009	1.8 (1.2 – 2.9)
	Mitral Regurgitation (≥ 3)	5.2	0.02	1.7 (1.1 – 2.7)
Hemodynamic	**PWP (≥ 18 mmHg)**	13.9	0.0002	2.8 (1.6 – 4.7)
	RAP (≥ 7 mmHg)	11.6	0.0007	2.4 (1.5 – 4.1)
	CI (≤ 1.9 l/min/m^2)	10.6	0.0012	2.3 (1.4 – 3.8)
HRV	**RR 24-hour (≤ 730 ms)**	7.3	0.0068	1.9 (1.2 – 3.0)
	RR night (≤ 786 ms)	12.7	0.0004	2.3 (1.5 – 3.7)
	SDNN 24-hour (≤ 68 ms)	13.6	0.0002	2.4 (1.5 – 3.7)
	SDNN night (≤ 71 ms)	11.8	0.0006	2.3 (1.4 – 3.6)
	VLF 24-hour (≤ 894 ms^2)	17.0	< 0.0001	2.7 (1.7 – 4.4)
	VLF night (≤ 509 ms^2)	22.6	< 0.0001	3.0 (1.9 – 4.7)
	LF 24-hour (≤ 63 ms^2)	13.8	0.0002	2.4 (1.5 – 3.9)
	LF night (≤ 70 ms^2)	11.5	0.0007	2.3 (1.4 – 3.7)
	HF 24-hour (≤ 58 ms^2)	6.0	0.0146	1.8 (1.1 – 2.8
	HF night (≤ 60 ms^2)	8.0	0.0047	1.9 (1.2 – 3.1)
	LF/HF 24-hour (≤ 0.37)	6.5	0.011	1.8 (1.1 – 2.9)
	1/f slope (≤ -1.33)	15.2	< 0.0001	2.4 (1.6 – 3.8)
Cardiopulmonary Exercise	**VO2 (≤ 11.9 ml/kg/min)**	4.9	0.026	1.7 (1.1 – 2.8)
Blood chemistry	**Cholesterol total (≤ 176)**	10.2	0.0014	2.1 (1.3 - 3.4)
	Sodium (≤ 137 mEq/l)	5.3	0.021	1.7 (1.1 – 2.7)
	Bilirubin (≥ 0.99 mEq/l)	7.8	0.0053	1.9 (1.2 – 3.1)
Baseline therapy	**Beta-blockers**	4.6	0.03	0.11 (0.02-0.82)

S. Guzzetti et al, Eur Heart J, 26:357-362, 2005

Predictors of pump failure death (multivariate analysis)

Variable (cutoff value)	χ^2	p	RR (95% CI)
VLF night (≤ 509 ms^2)	9.7	0.0018	2.3 (1.4 – 3.8)
PWP (≥ 18 mmHg)	6.0	0.0145	2.0 (1.1 – 3.5)
LVEF (≤ 24%)	5.0	0.0252	1.9 (1.1 – 3.3)

S. Guzzetti et al, Eur Heart J, 26:357-362, 2005

Predictors of sudden cardiac death (univariate analysis)

Variable (cutoff value)	χ^2	p	RR (95% CI)
LF night (≤ 20 ms^2)	7.0	0.0079	2.7 (1.3 – 5.6)
HF night (≤ 60 ms^2)	4.3	0.0385	2.2 (1.0 – 4.6)
LVESD (≥ 61 mm)	5.1	0.0239	2.6 (1.1 – 5.9)

S. Guzzetti et al, Eur Heart J, 26:357-362, 2005

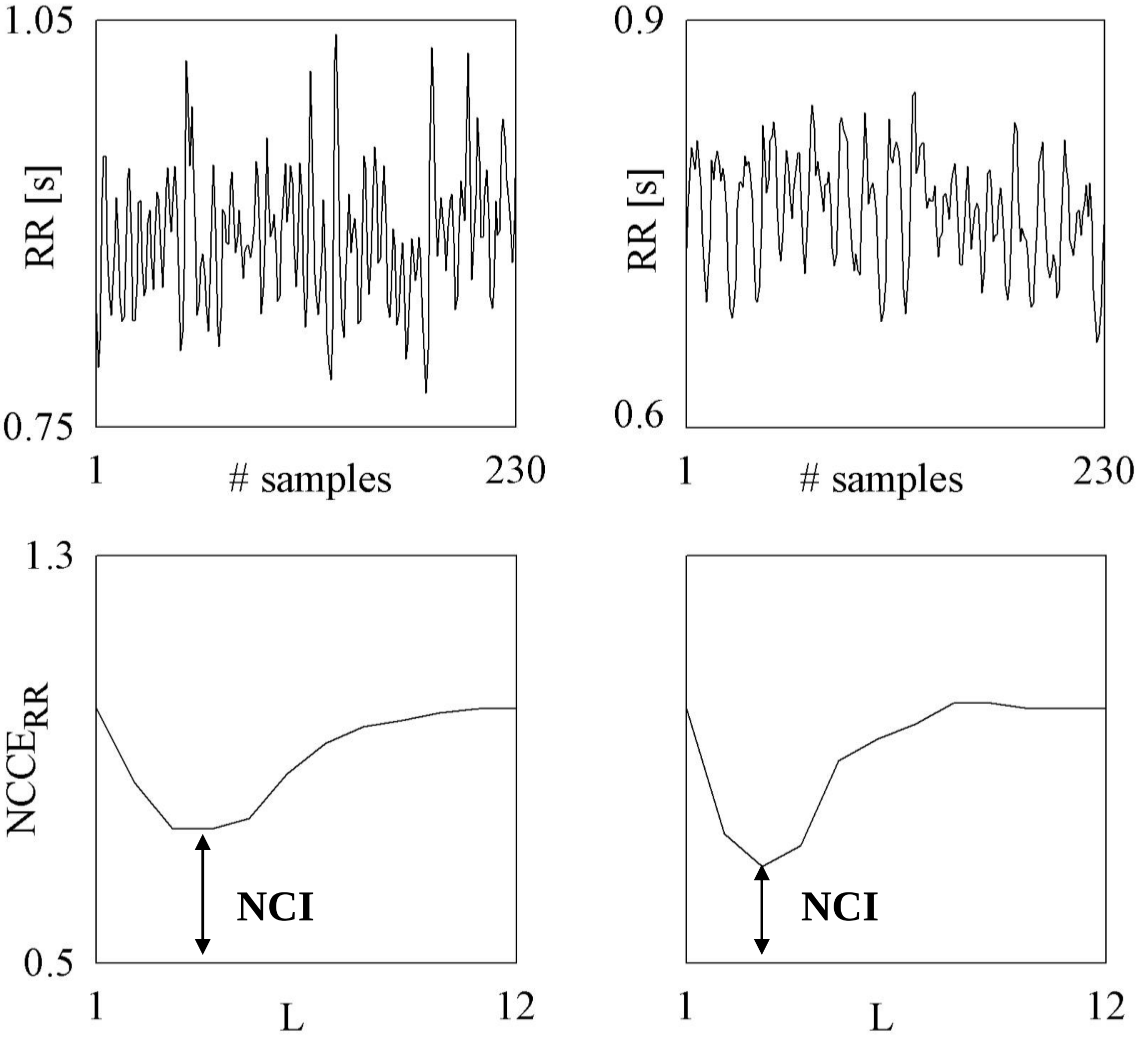
Predictors of sudden cardiac death (multivariate analysis)

Variable (cutoff value)	χ^2	p	RR (95% CI)
LF night (≤ 20 ms^2)	7.0	0.0079	2.7 (1.3 – 5.6)
HF night (≤ 60 ms^2)	4.3	0.0385	2.2 (1.0 – 4.6)
LVESD (≥ 61 mm)	5.1	0.0239	2.6 (1.1 – 5.9)

S. Guzzetti et al, Eur Heart J, 26:357-362, 2005

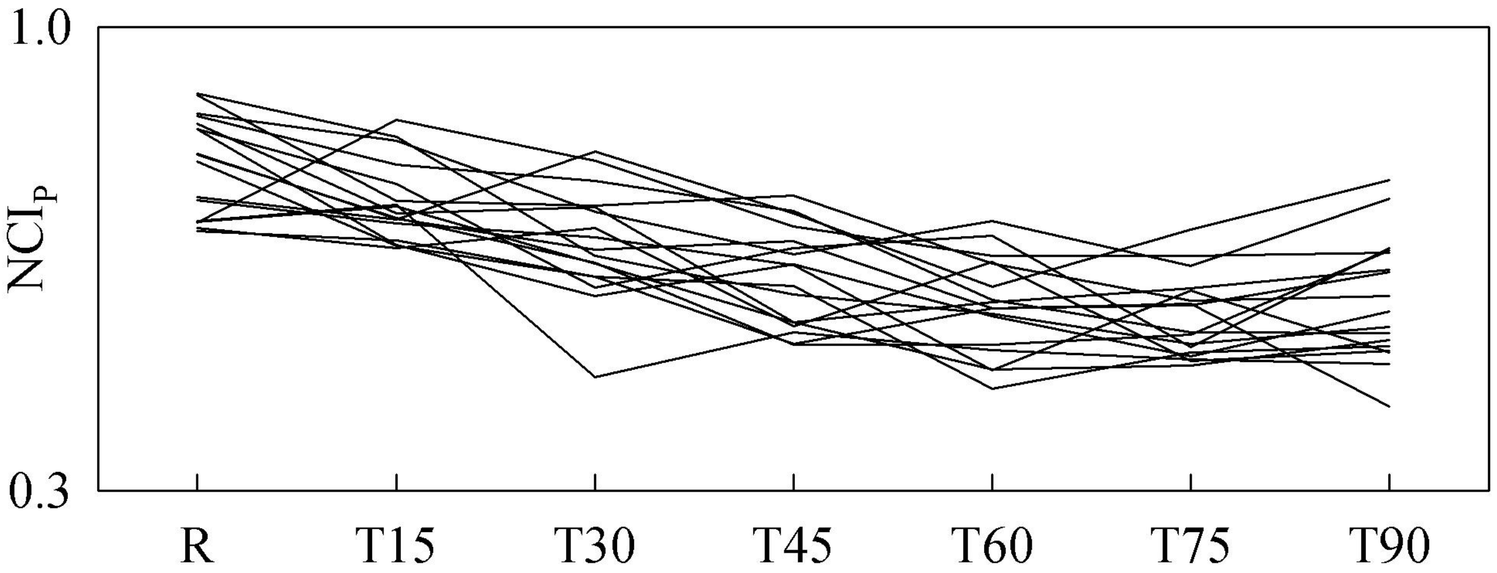
Linear analysis of heart period variability is helpful to describe physiological conditions and provides indexes useful in clinics but what about non linear indexes?

Complexity analysis provides non linear indexes



A. Porta, PhD Thesis in Biomedical Engineering, 1998

Complexity indexes can follow the gradual changes of the sympatho-vagal balance



A. Porta et al, J Appl Physiol, 103:1143-1149, 2007

Non linear indexes can detect “per se” changes of the state of the autonomic nervous system

Non linear indexes can detect “per se” modifications of the sympatho-vagal balance

A. Porta et al, J Appl Physiol, 103:1143-1149, 2007

Limitation of linear and non linear indexes

Linear and non linear indexes can not track separately sympathetic and vagal modulation

Limitation of linear indexes in the frequency domain

$LF_{nu} + HF_{nu} = 100$

M. Pagani et al, Circ Res, 59:178-193, 1986

HF_{ass} = index of vagal modulation
but LF_{ass} power is of mixed origin

S. Akselrod et al, Science, 213:220-223, 1981

LF_{nu}/HF_{nu} (or LF_{ass}/HF_{ass}) is an index of sympatho-vagal balance

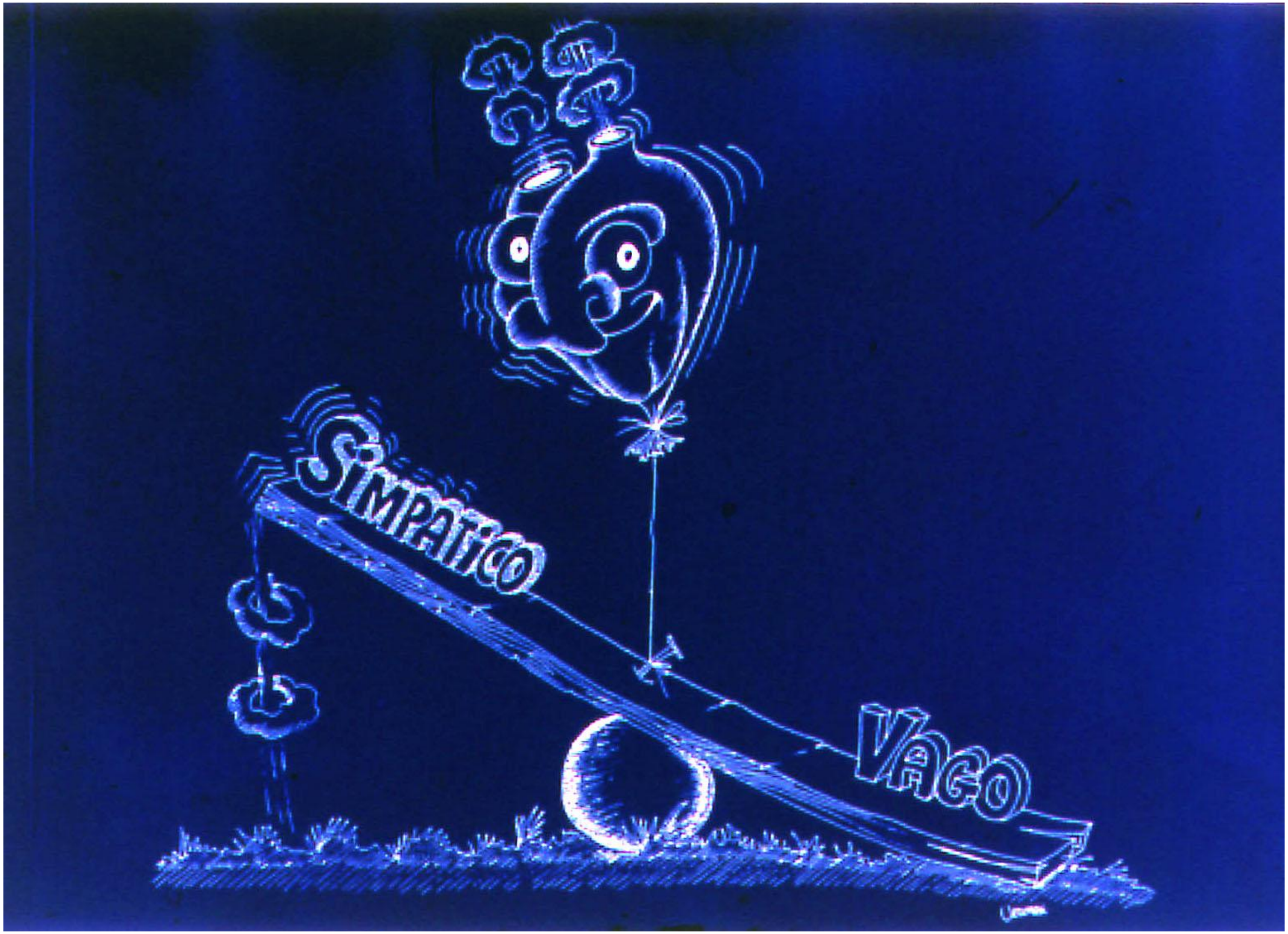
A. Malliani et al, Circulation, 84:482-492, 1991

Limitation of the non linear indexes in the information domain

CI and NCI are indexes of sympatho-vagal balance

A. Porta et al, J Appl Physiol, 103:1143-1149, 2007

Cartoon of the sympatho-vagal balance



M. Pagani et al, Circ Res, 59, 178-193, 1986

Can limitations of linear and non linear indexes in providing independent measures of vagal and sympathetic modulations be overcome?

Symbolic analysis

Symbolic analysis approach is based on:

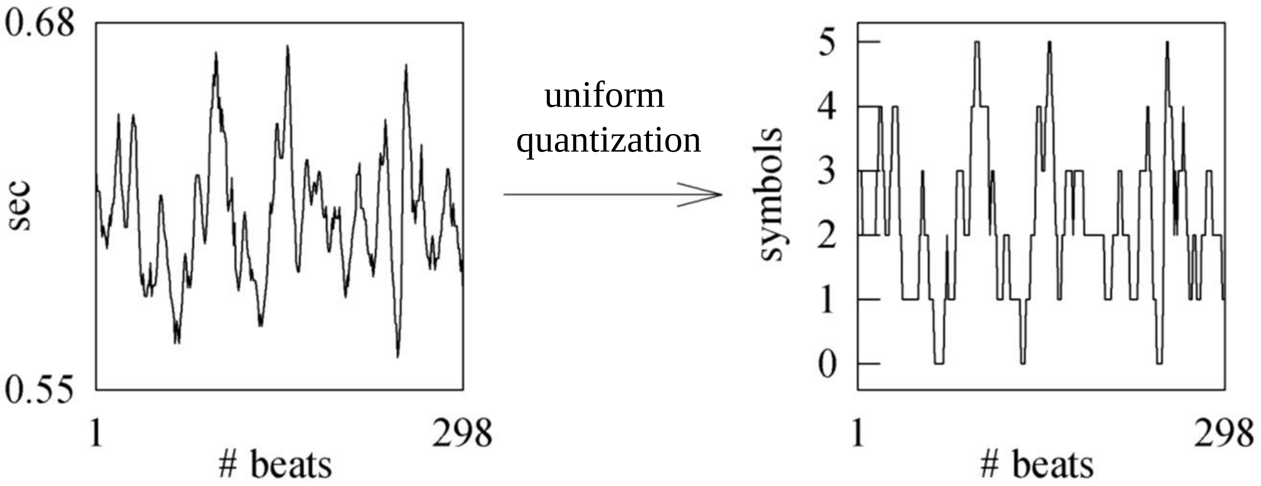
i) the transformation of short heart period variability series into a sequence of integers (i.e. the symbols)

ii) the construction of patterns (i.e. the “words”)

iii) the reduction of the number of patterns by grouping them into a small number of families

iv) the evaluation of the rates of occurrence of these families

Symbolic analysis of heart period variability



$$\{x_q(i)\}=\{3,3,3,3,2,2,2,\ldots\}$$

$$(3,3,3)$$

$$(3,3,3)$$

$$(3,3,2)$$

$$(3,2,2)$$

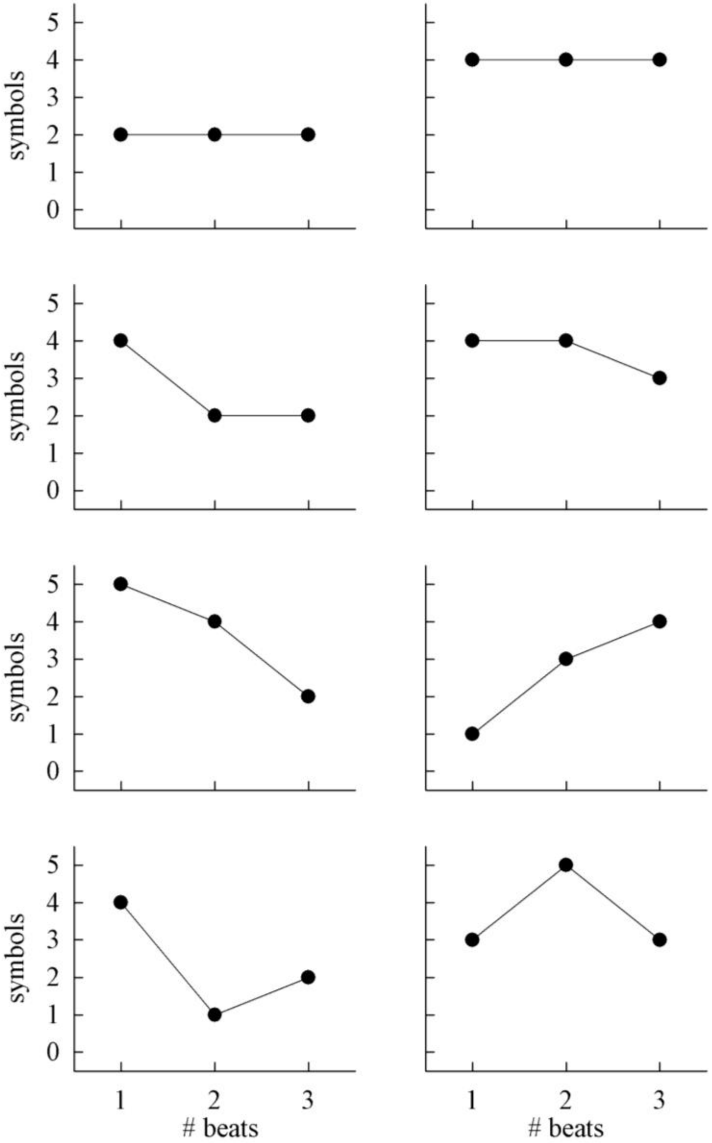
$$(2,2,2)$$

$$\ldots$$

$$\{x_{q,L}(i)\}=\{(3,3,3),(3,3,3),(3,3,2),(3,2,2),(2,2,2),\ldots\}$$

A. Porta et al, IEEE Trans Biomed Eng, 48:1282-1291, 2001

Symbolic analysis of heart period variability



0V

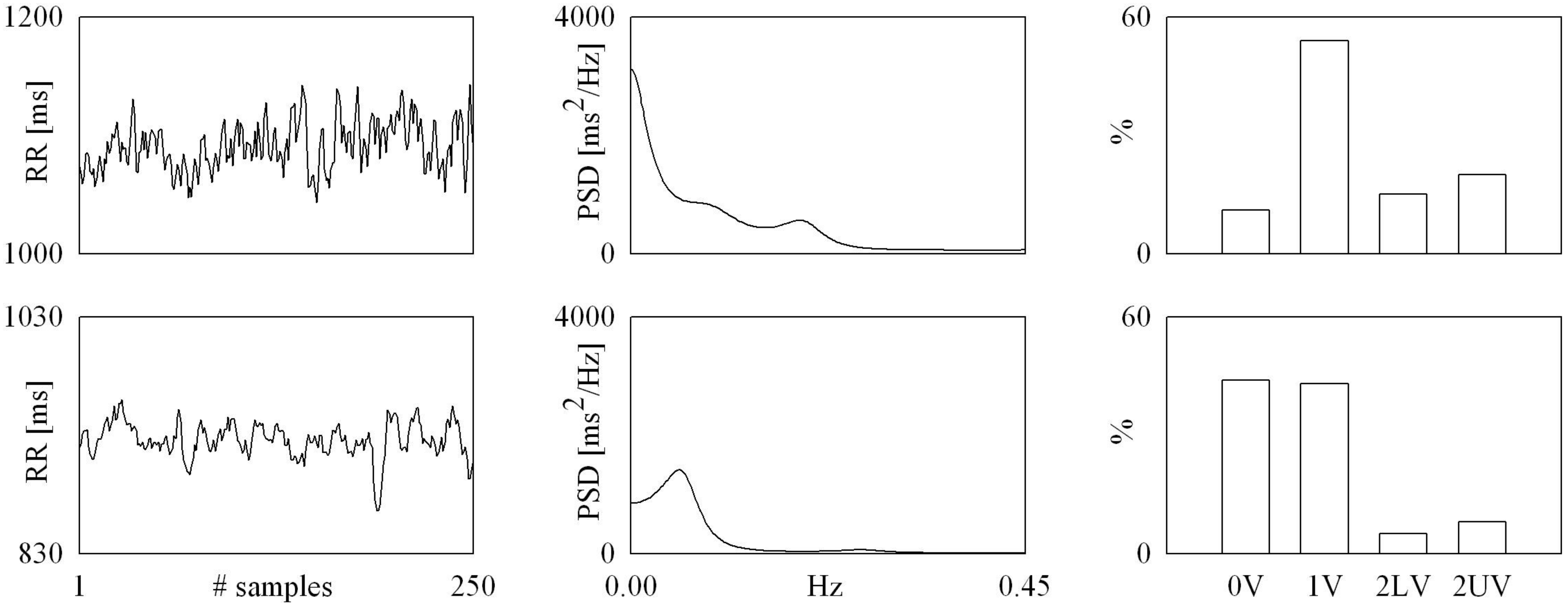
1V

2LV

2UV

A. Porta et al, IEEE Trans Biomed Eng, 48:1282-1291, 2001

Symbolic analysis of heart period variability



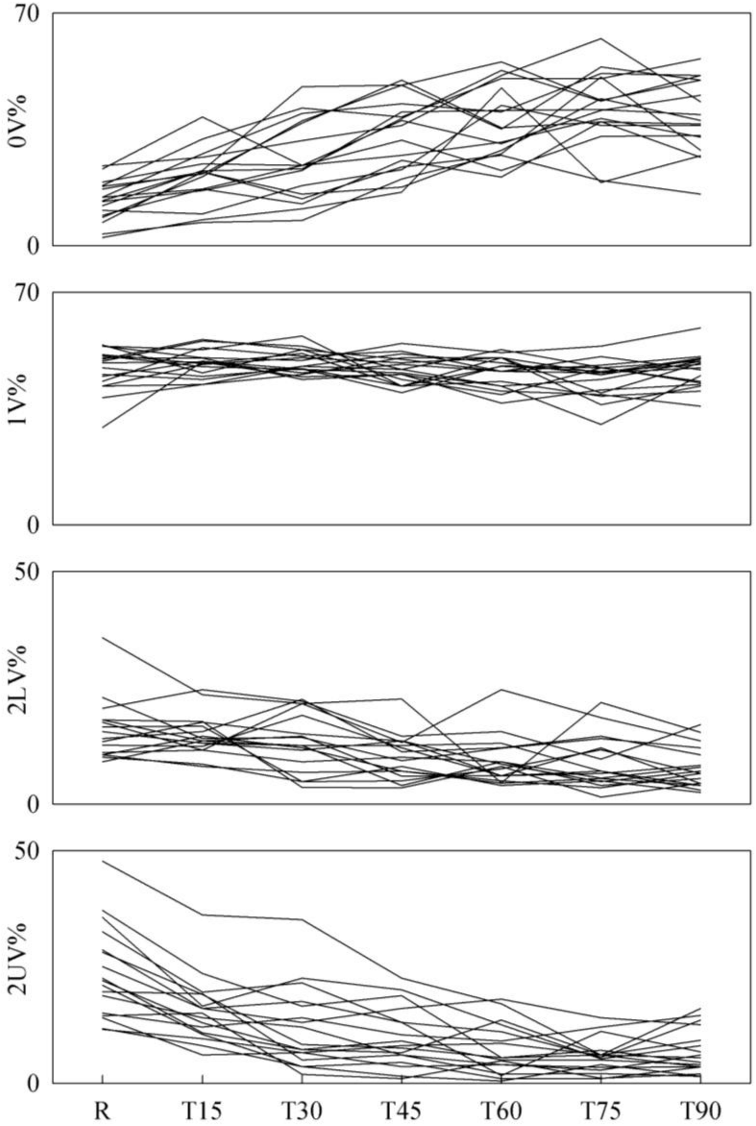
0V% ⇨ Index of sympathetic modulation

2UV% ⇨ Index of vagal modulation

S. Guzzetti et al, Circulation, 112:465-470, 2005

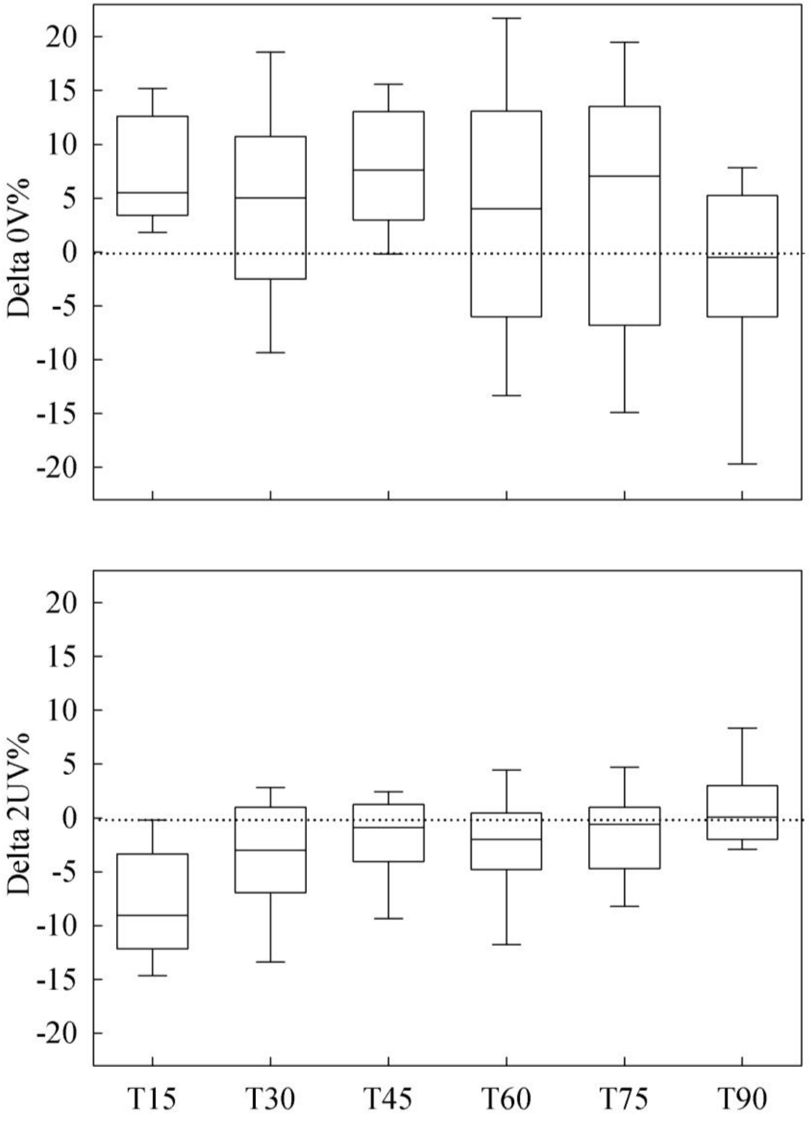
A. Porta et al, Am J Physiol, 293:H702-H708, 2007

Symbolic analysis of heart period variability



A. Porta et al, Am J Physiol, 293:H702-H708, 2007

Symbolic analysis of heart period variability

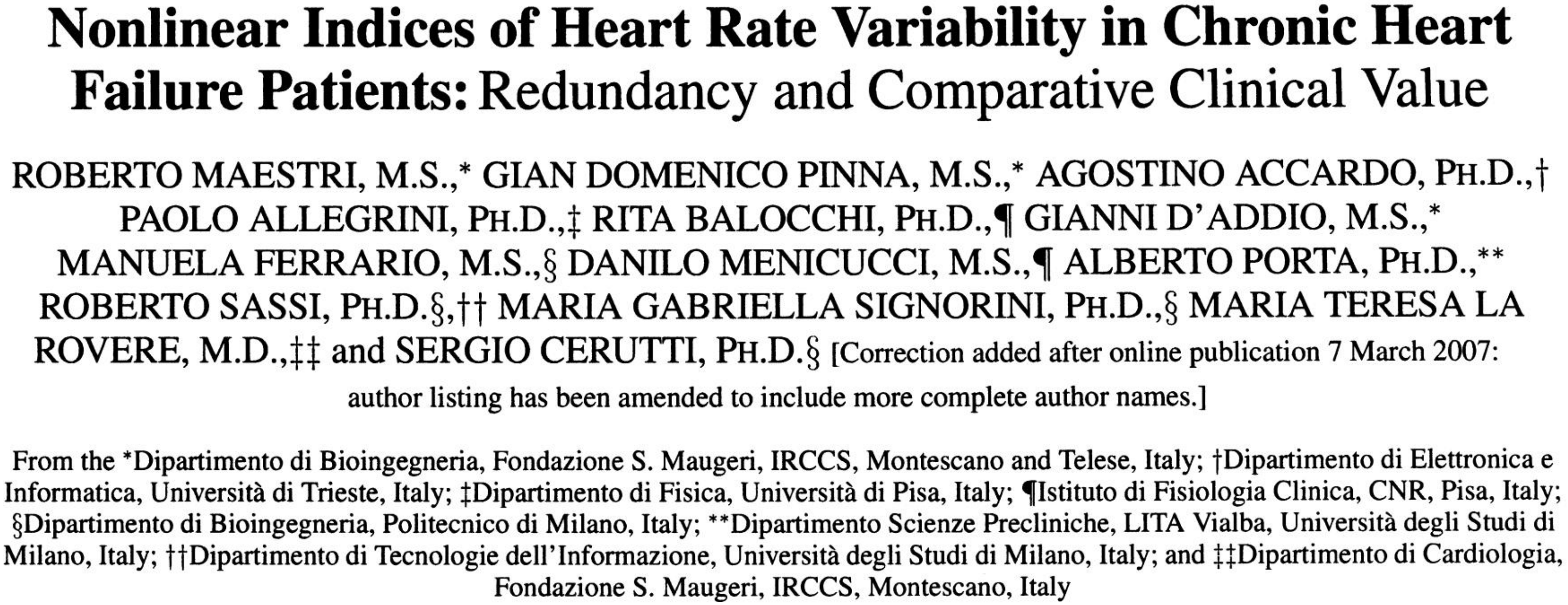


A. Porta et al, Am J Physiol, 293:H702-H708, 2007

Non linear indexes is helpful to describe physiological conditions and to overcome limitations of linear ones but what about pathological situations?

Does non linear analysis provide non redundant information with respect to descriptors traditionally utilized in clinics?

Nonlinear indexes of heart period variability and heart failure



Nonlinear Indices of Heart Rate Variability in Chronic Heart Failure Patients: Redundancy and Comparative Clinical Value

ROBERTO MAESTRI, M.S.,[*] GIAN DOMENICO PINNA, M.S.,[*] AGOSTINO ACCARDO, Ph.D.,[†] PAOLO ALLEGRINI, Ph.D.,[‡] RITA BALOCCHI, Ph.D.,[¶] GIANNI D'ADDIO, M.S.,[*] MANUELA FERRARIO, M.S.,[§] DANILO MENICUCCI, M.S.,[¶] ALBERTO PORTA, Ph.D.,[**] ROBERTO SASSI, Ph.D.[§,††] MARIA GABRIELLA SIGNORINI, Ph.D.,[§] MARIA TERESA LA ROVERE, M.D.,[‡‡] and SERGIO CERUTTI, Ph.D.[§]

[Correction added after online publication 7 March 2007: author listing has been amended to include more complete author names.]

From the [*]Dipartimento di Bioingegneria, Fondazione S. Maugeri, IRCCS, Montescano and Telese, Italy; [†]Dipartimento di Elettronica e Informatica, Università di Trieste, Italy; [‡]Dipartimento di Fisica, Università di Pisa, Italy; [¶]Istituto di Fisiologia Clinica, CNR, Pisa, Italy; [§]Dipartimento di Bioingegneria, Politecnico di Milano, Italy; [**]Dipartimento Scienze Precliniche, LITA Vialba, Università degli Studi di Milano, Italy; [††]Dipartimento di Tecnologie dell'Informazione, Università degli Studi di Milano, Italy; and [‡‡]Dipartimento di Cardiologia, Fondazione S. Maugeri, IRCCS, Montescano, Italy

Clinical parameters in a population of heart failure patients (n=200)

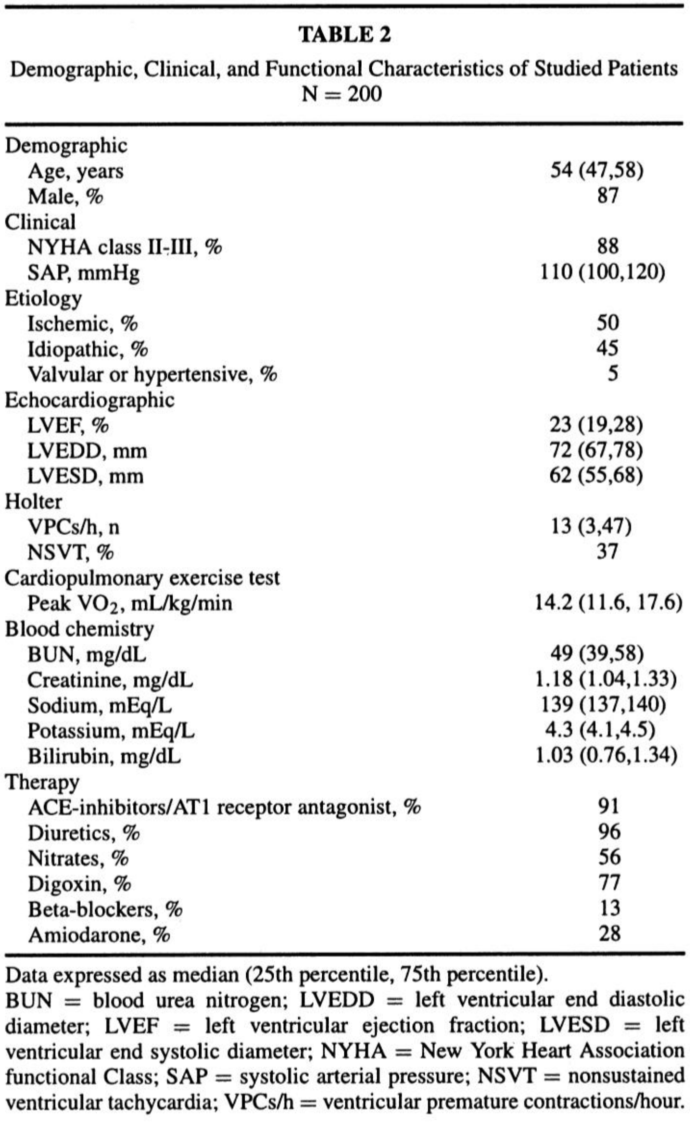


TABLE 2

Demographic, Clinical, and Functional Characteristics of Studied Patients
N = 200

Demographic	
Age, years	54 (47,58)
Male, %	87
Clinical	
NYHA class II-III, %	88
SAP, mmHg	110 (100,120)
Etiology	
Ischemic, %	50
Idiopathic, %	45
Valvular or hypertensive, %	5
Echocardiographic	
LVEF, %	23 (19,28)
LVEDD, mm	72 (67,78)
LVESD, mm	62 (55,68)
Holter	
VPCs/h, n	13 (3,47)
NSVT, %	37
Cardiopulmonary exercise test	
Peak VO_2, mL/kg/min	14.2 (11.6, 17.6)
Blood chemistry	
BUN, mg/dL	49 (39,58)
Creatinine, mg/dL	1.18 (1.04,1.33)
Sodium, mEq/L	139 (137,140)
Potassium, mEq/L	4.3 (4.1,4.5)
Bilirubin, mg/dL	1.03 (0.76,1.34)
Therapy	
ACE-inhibitors/AT1 receptor antagonist, %	91
Diuretics, %	96
Nitrates, %	56
Digoxin, %	77
Beta-blockers, %	13
Amiodarone, %	28

Data expressed as median (25th percentile, 75th percentile).
BUN = blood urea nitrogen; LVEDD = left ventricular end diastolic diameter; LVEF = left ventricular ejection fraction; LVESD = left ventricular end systolic diameter; NYHA = New York Heart Association functional Class; SAP = systolic arterial pressure; NSVT = nonsustained ventricular tachycardia; VPCs/h = ventricular premature contractions/hour.

R. Maestri et al, J Cardiovasc Electrophysiol 18: 425-433, 2007

Linear and non linear indexes derived from heart rate variability

- Linear indexes in the time and frequency domains

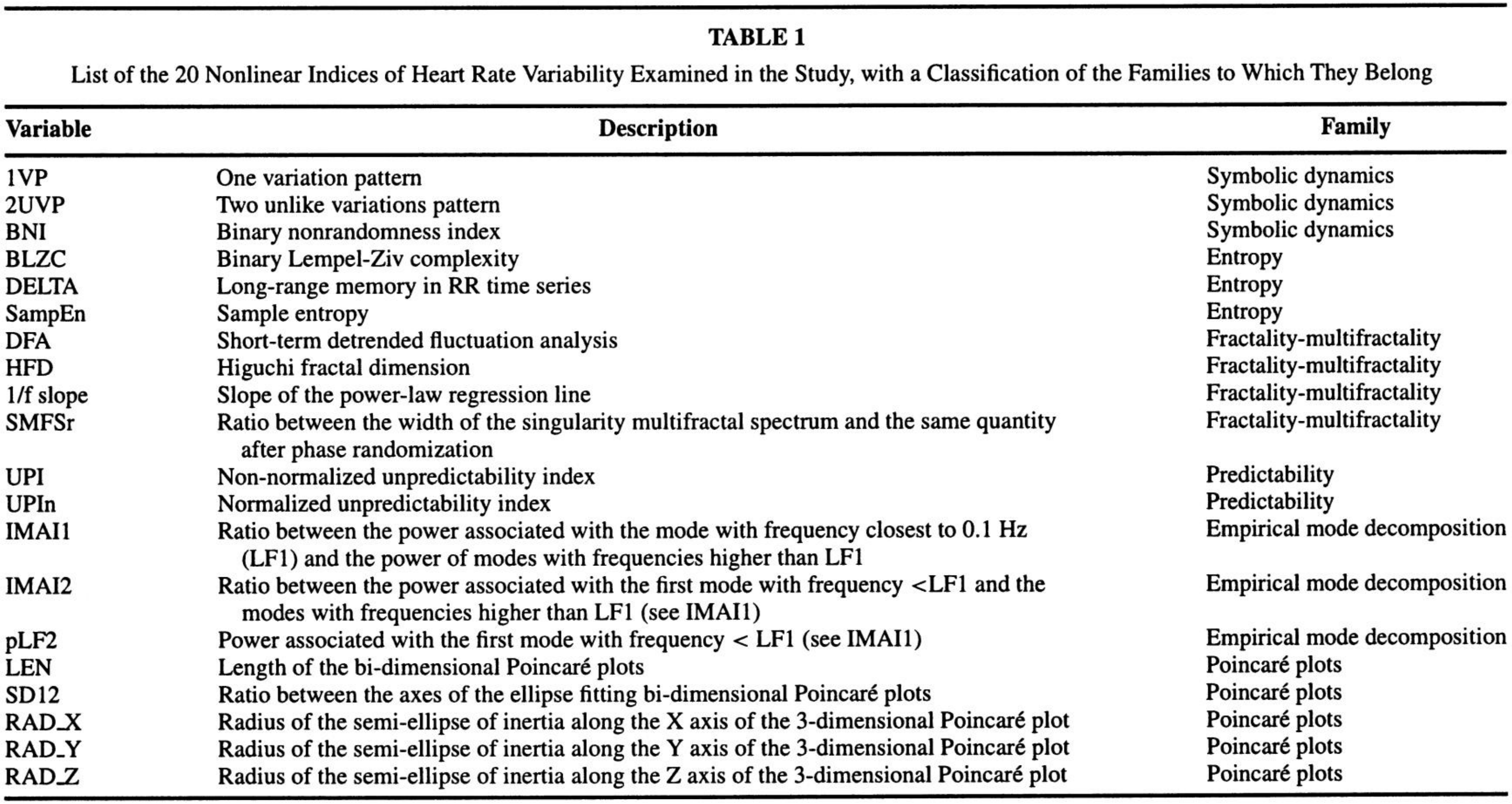


TABLE 1

List of the 20 Nonlinear Indices of Heart Rate Variability Examined in the Study, with a Classification of the Families to Which They Belong

Variable	Description	Family
1VP	One variation pattern	Symbolic dynamics
2UVP	Two unlike variations pattern	Symbolic dynamics
BNI	Binary nonrandomness index	Symbolic dynamics
BLZC	Binary Lempel-Ziv complexity	Entropy
DELTA	Long-range memory in RR time series	Entropy
SampEn	Sample entropy	Entropy
DFA	Short-term detrended fluctuation analysis	Fractality-multifractality
HFD	Higuchi fractal dimension	Fractality-multifractality
1/f slope	Slope of the power-law regression line	Fractality-multifractality
SMFSr	Ratio between the width of the singularity multifractal spectrum and the same quantity after phase randomization	Fractality-multifractality
UPI	Non-normalized unpredictability index	Predictability
UPIn	Normalized unpredictability index	Predictability
IMAI1	Ratio between the power associated with the mode with frequency closest to 0.1 Hz (LF1) and the power of modes with frequencies higher than LF1	Empirical mode decomposition
IMAI2	Ratio between the power associated with the first mode with frequency <LF1 and the modes with frequencies higher than LF1 (see IMAI1)	Empirical mode decomposition
pLF2	Power associated with the first mode with frequency < LF1 (see IMAI1)	Empirical mode decomposition
LEN	Length of the bi-dimensional Poincaré plots	Poincaré plots
SD12	Ratio between the axes of the ellipse fitting bi-dimensional Poincaré plots	Poincaré plots
RAD_X	Radius of the semi-ellipse of inertia along the X axis of the 3-dimensional Poincaré plot	Poincaré plots
RAD_Y	Radius of the semi-ellipse of inertia along the Y axis of the 3-dimensional Poincaré plot	Poincaré plots
RAD_Z	Radius of the semi-ellipse of inertia along the Z axis of the 3-dimensional Poincaré plot	Poincaré plots

R. Maestri et al, J Cardiovasc Electrophysiol 18: 425-433, 2007

Endpoint of the survival analysis

Total cardiac death (both for pump failure and sudden death) or urgent transplantation

During a 3 year follow-up

- 75 patients out of 200 died because cardiac death (n=60) or underwent urgent transplantation (n=15)

Best multivariate clinical model for the prediction of the total cardiac death

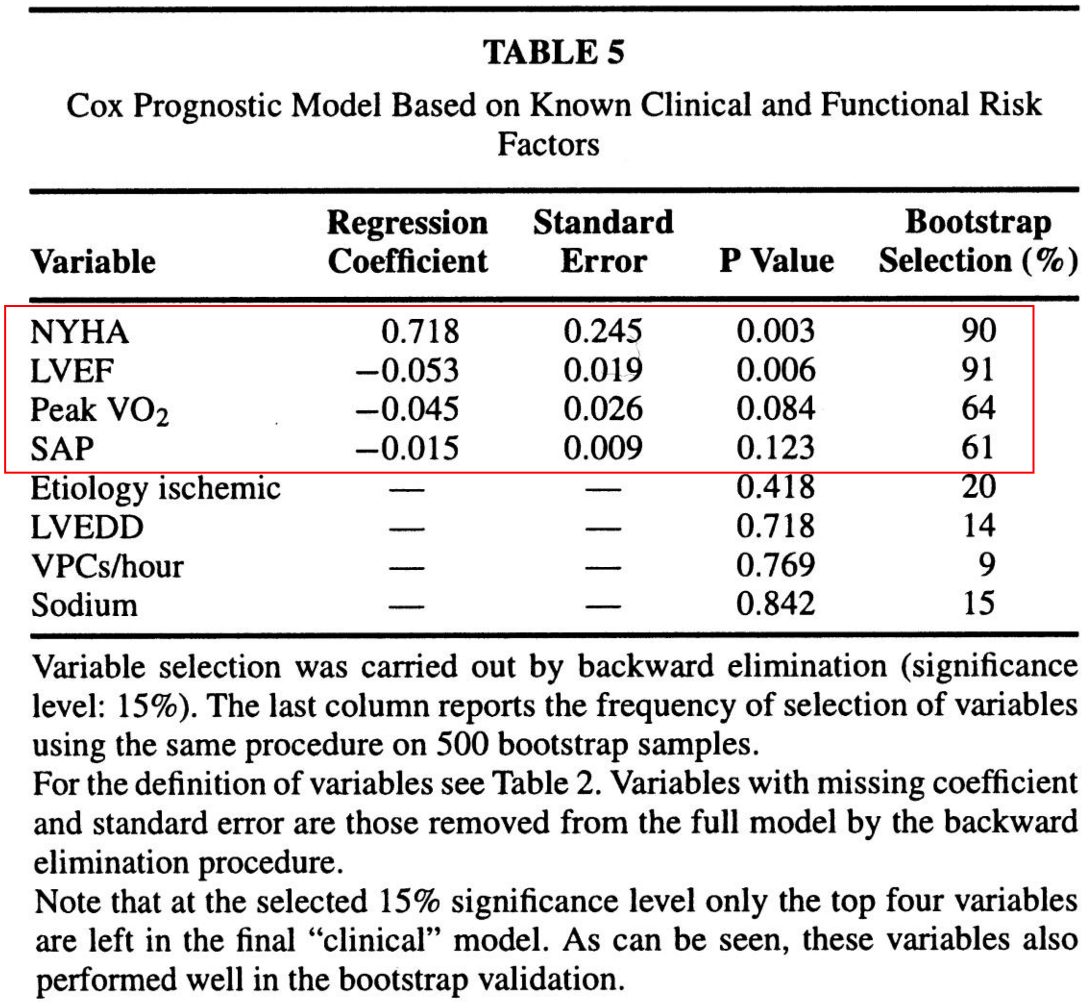


TABLE 5

Cox Prognostic Model Based on Known Clinical and Functional Risk Factors

Variable	Regression Coefficient	Standard Error	P Value	Bootstrap Selection (%)
NYHA	0.718	0.245	0.003	90
LVEF	−0.053	0.019	0.006	91
Peak VO_2	−0.045	0.026	0.084	64
SAP	−0.015	0.009	0.123	61
Etiology ischemic	—	—	0.418	20
LVEDD	—	—	0.718	14
VPCs/hour	—	—	0.769	9
Sodium	—	—	0.842	15

Variable selection was carried out by backward elimination (significance level: 15%). The last column reports the frequency of selection of variables using the same procedure on 500 bootstrap samples.

For the definition of variables see Table 2. Variables with missing coefficient and standard error are those removed from the full model by the backward elimination procedure.

Note that at the selected 15% significance level only the top four variables are left in the final "clinical" model. As can be seen, these variables also performed well in the bootstrap validation.

R. Maestri et al, J Cardiovasc Electrophysiol 18: 425-433, 2007

Additive predictive value to the best multivariate clinical model

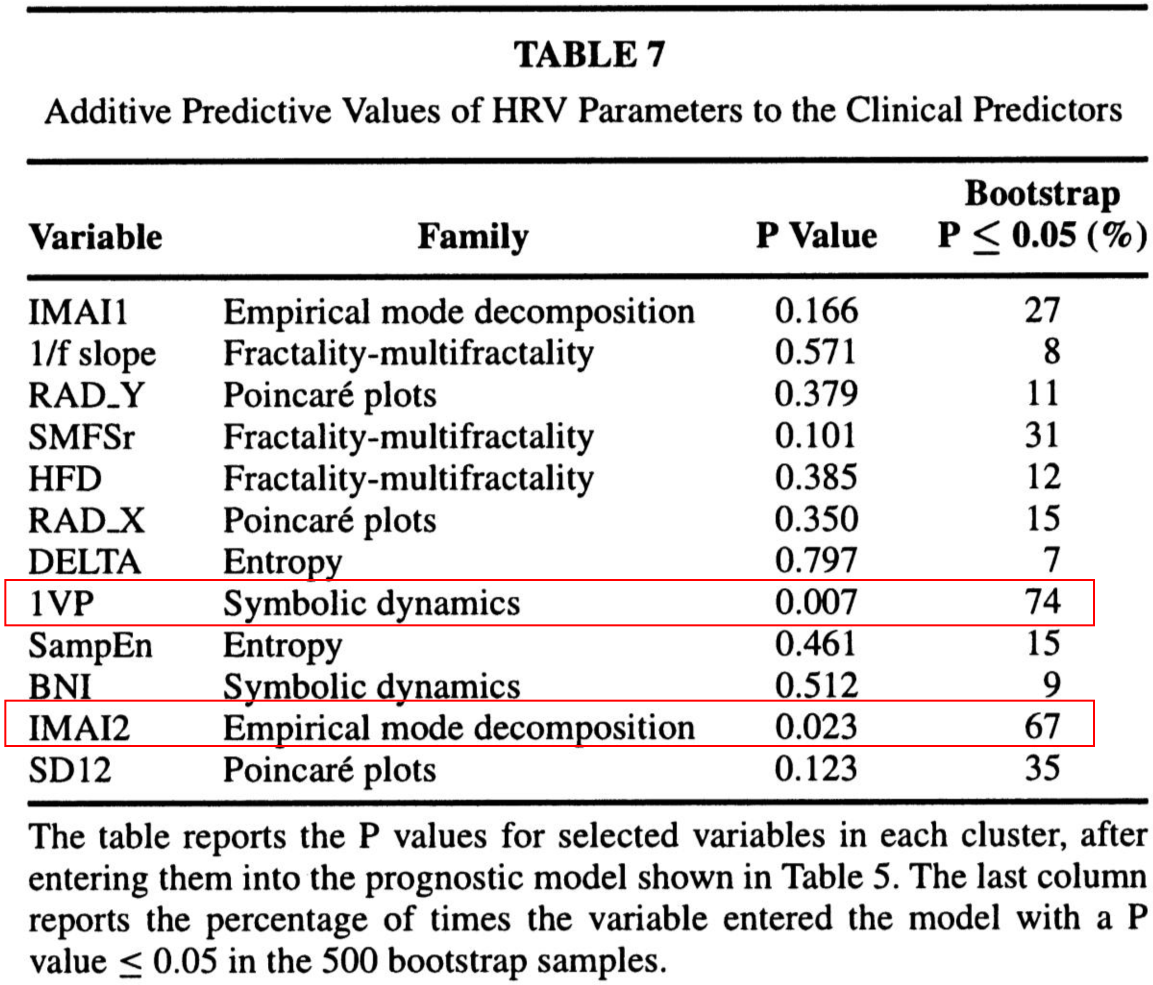


TABLE 7

Additive Predictive Values of HRV Parameters to the Clinical Predictors

Variable	Family	P Value	Bootstrap $P \leq 0.05$ (%)
IMAI1	Empirical mode decomposition	0.166	27
1/f slope	Fractality-multifractality	0.571	8
RAD_Y	Poincaré plots	0.379	11
SMFSr	Fractality-multifractality	0.101	31
HFD	Fractality-multifractality	0.385	12
RAD_X	Poincaré plots	0.350	15
DELTA	Entropy	0.797	7
1VP	Symbolic dynamics	0.007	74
SampEn	Entropy	0.461	15
BNI	Symbolic dynamics	0.512	9
IMAI2	Empirical mode decomposition	0.023	67
SD12	Poincaré plots	0.123	35

The table reports the P values for selected variables in each cluster, after entering them into the prognostic model shown in Table 5. The last column reports the percentage of times the variable entered the model with a P value ≤ 0.05 in the 500 bootstrap samples.

No linear indexes provided additive predicted value

R. Maestri et al, J Cardiovasc Electrophysiol 18: 425-433, 2007

Conclusions

Non linear indexes can track “per se” changes of the state of the autonomic nervous system

Non linear analysis provides additional information to to the linear one

The additional information is clinically relevant