Pathophysiology and clinical use of heart rate variability (HRV)

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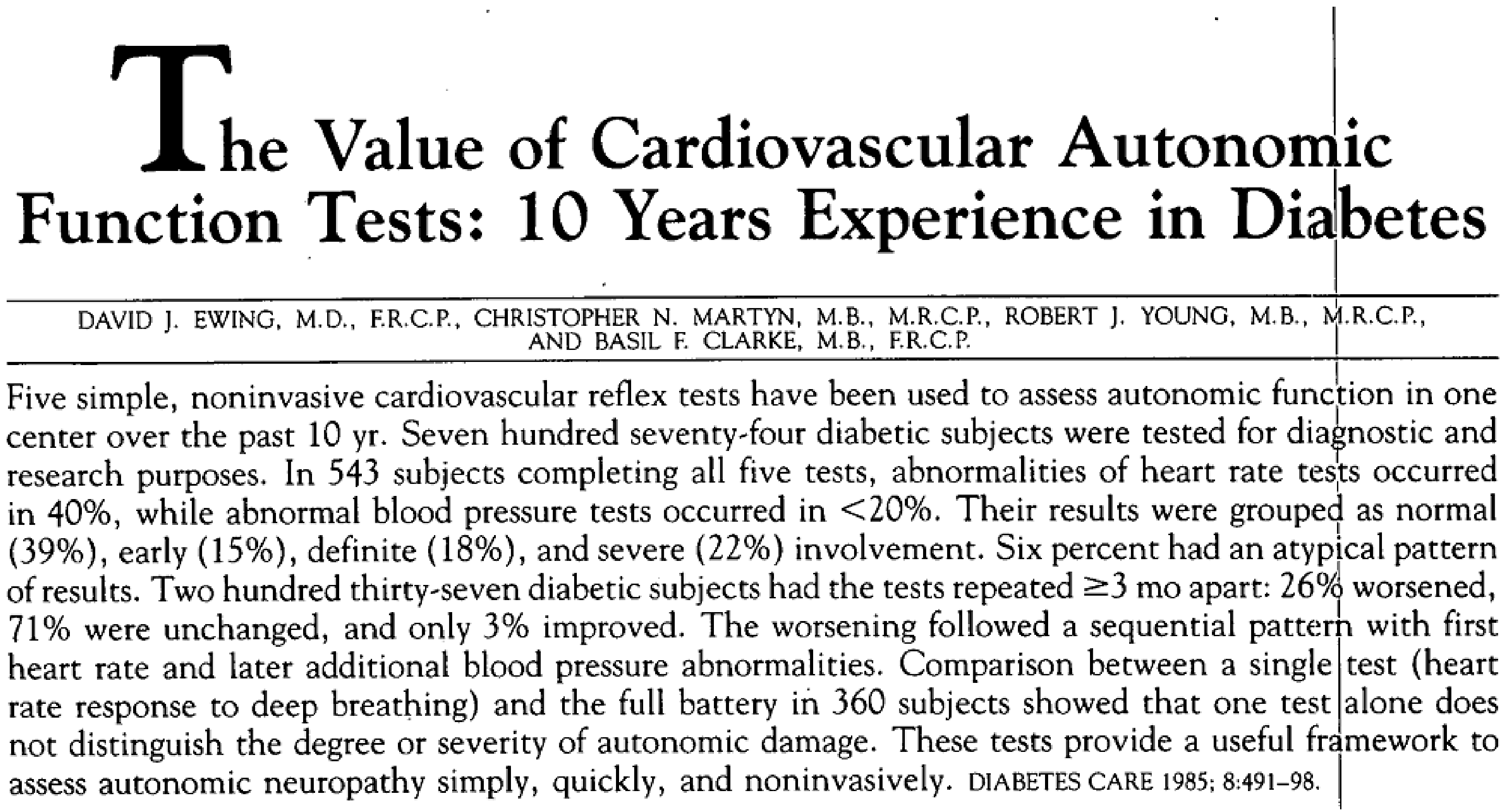
Agenda

- **Background**
- **Measurement of HRV**
- **Physiologic correlation**
- **Clinical utilization**

Background

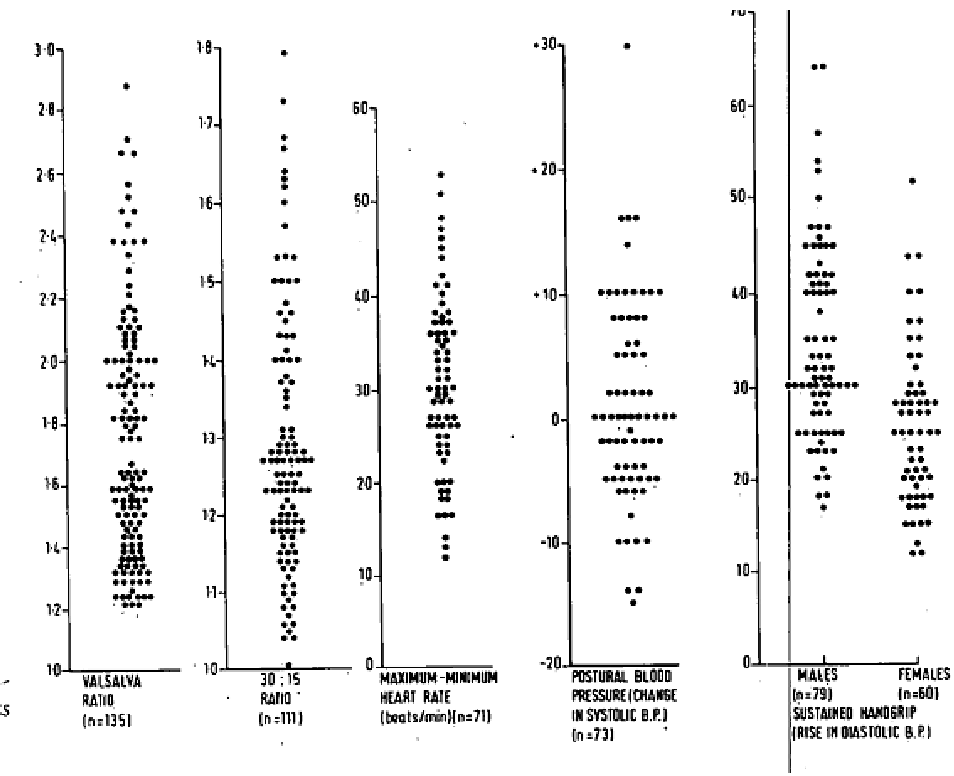
Early stage of HRV

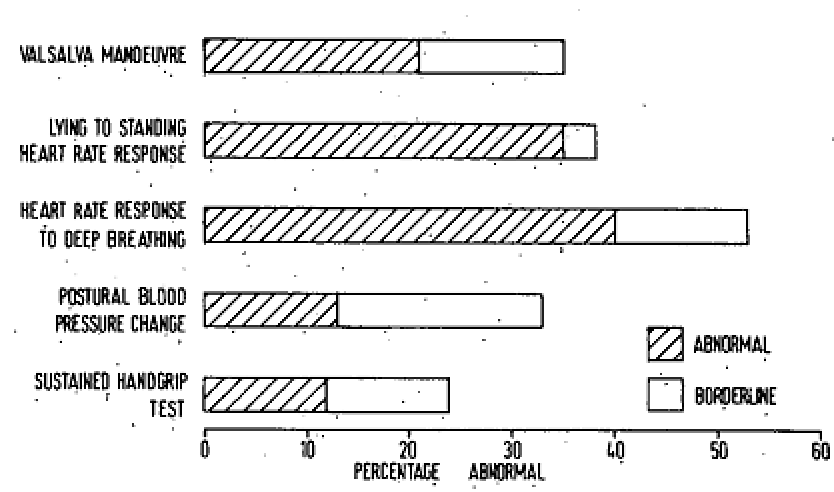

The Value of Cardiovascular Autonomic Function Tests: 10 Years Experience in Diabetes

DAVID J. EWING, M.D., F.R.C.P., CHRISTOPHER N. MARTYN, M.B., M.R.C.P., ROBERT J. YOUNG, M.B., M.R.C.P., AND BASIL F. CLARKE, M.B., F.R.C.P.

Five simple, noninvasive cardiovascular reflex tests have been used to assess autonomic function in one center over the past 10 yr. Seven hundred seventy-four diabetic subjects were tested for diagnostic and research purposes. In 543 subjects completing all five tests, abnormalities of heart rate tests occurred in 40%, while abnormal blood pressure tests occurred in <20%. Their results were grouped as normal (39%), early (15%), definite (18%), and severe (22%) involvement. Six percent had an atypical pattern of results. Two hundred thirty-seven diabetic subjects had the tests repeated ≥3 mo apart: 26% worsened, 71% were unchanged, and only 3% improved. The worsening followed a sequential pattern with first heart rate and later additional blood pressure abnormalities. Comparison between a single test (heart rate response to deep breathing) and the full battery in 360 subjects showed that one test alone does not distinguish the degree or severity of autonomic damage. These tests provide a useful framework to assess autonomic neuropathy simply, quickly, and noninvasively. DIABETES CARE 1985; 8:491–98.

Simple tests of short-term RR differences to detect autonomic neuropathy DM

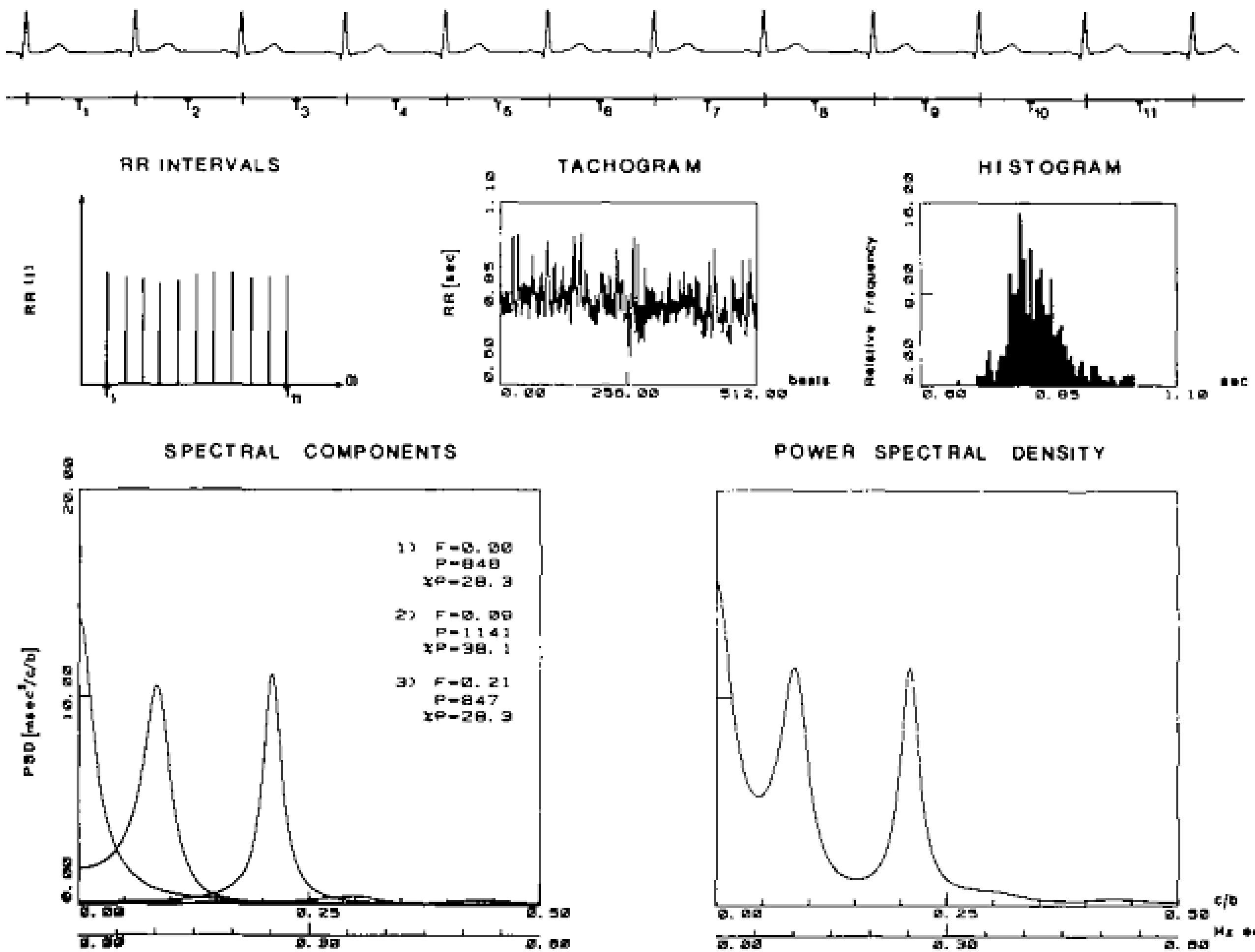




Power Spectral Analysis of Heart Rate and Arterial Pressure Variabilities as a Marker of Sympatho-Vagal Interaction in Man and Conscious Dog

MASSIMO PAGANI, FEDERICO LOMBARDI, STEFANO GUZZETTI, ORNELLA RIMOLDI, RAFFAELLO FURLAN, PAOLO PIZZINELLI, GIULIA SANDRONE, GABRIELLA MALFATTO, SIMONETTA DELL'ORTO, EMANUELA PICCALUGA, MAURIZIO TURIEL, GIUSEPPE BASELLI, SERGIO CERUTTI, AND ALBERTO MALLIANI

(*Circulation Research* 1986;59:178–193)


RR INTERVALS
RR (i)
TACHOGRAM
RR [sec]
beats
HISTOGRAM
Relative Frequency
sec
SPECTRAL COMPONENTS
PSD [msec²/c/b]
1) F=0.00
P=848
%P=28.3
2) F=0.09
P=1141
%P=38.1
3) F=0.21
P=847
%P=28.3
POWER SPECTRAL DENSITY
c/b
Hz eq

HRV as predictor of survival after AMI

Decreased Heart Rate Variability and Its Association with Increased Mortality After Acute Myocardial Infarction

ROBERT E. KLEIGER, MD, J. PHILIP MILLER, AB, J. THOMAS BIGGER, Jr., MD, ARTHUR J. MOSS, MD, and the MULTICENTER POST-INFARCTION RESEARCH GROUP*

(Am J Cardiol 1987;59:256–262)

Cumulative survival according to HRV

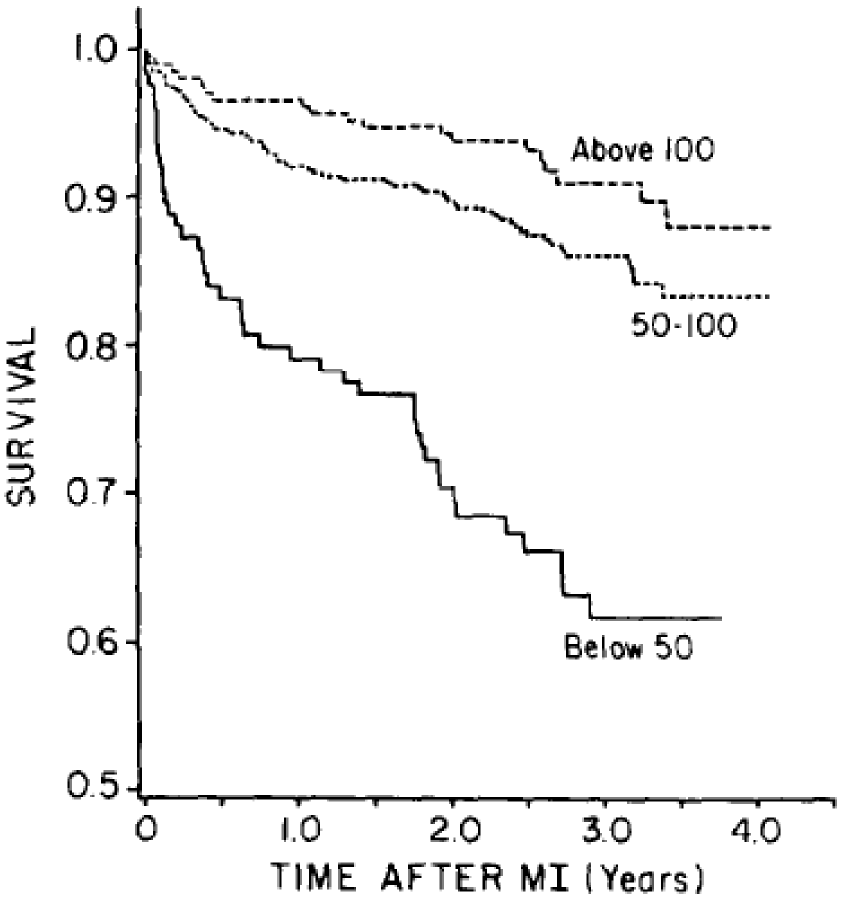
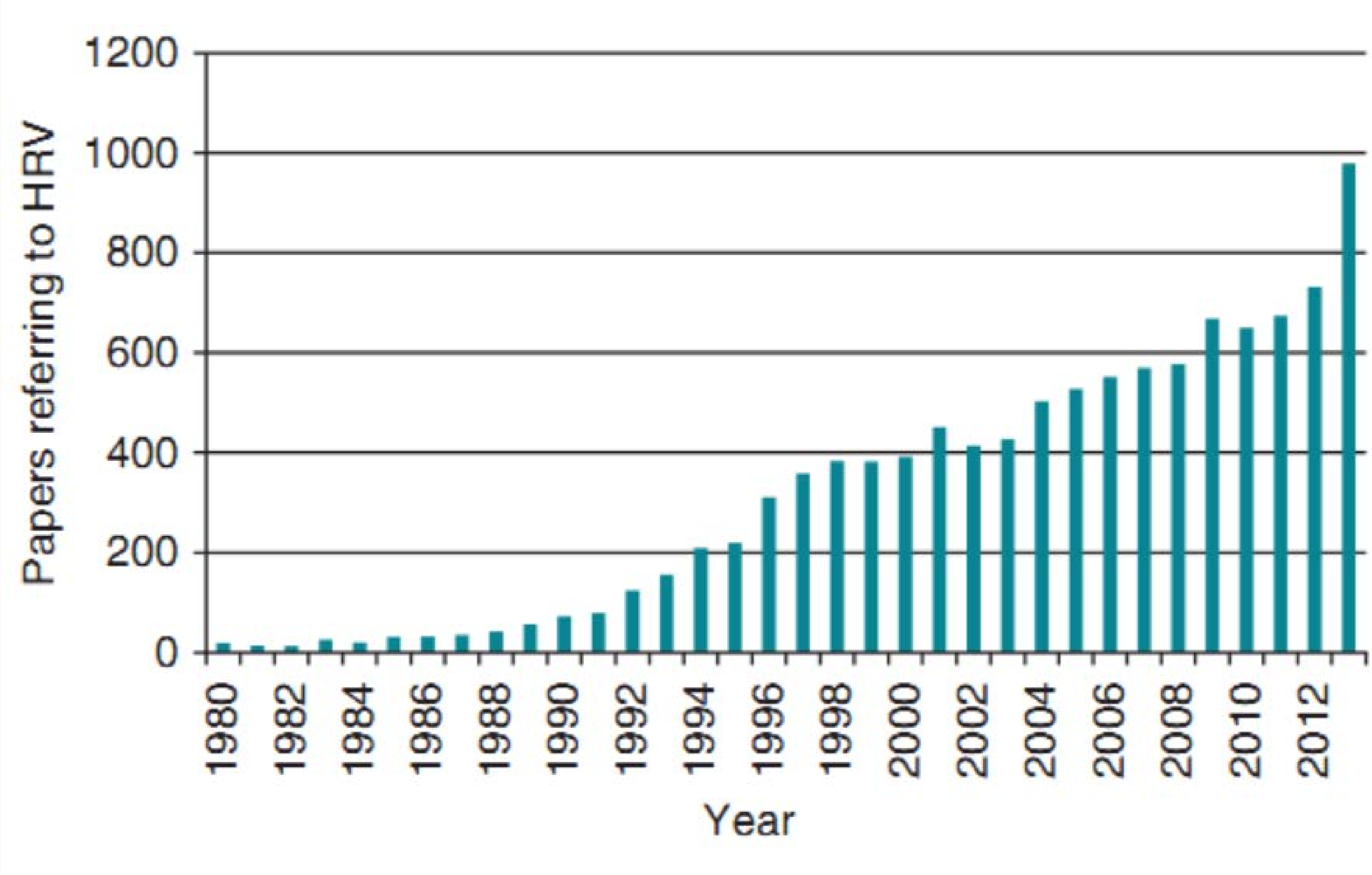


TABLE I Heart Rate Variability (Standard Deviation of RR intervals) After Myocardial Infarction and Mortality During 31 Months of Follow-Up

SD of RR of Normal Cycles (ms)	No. of Pts.	% of Total Group	No. of Deaths	Total Mortality Rate During Follow-Up	Odds Ratio
<50	125	15.5%	43	34.4%	5.3
50-100	472	58.4%	65	13.8%	1.6
>100	211	26.1%	19	9.0%	1.0

SD = standard deviation.

Increasing number of citation

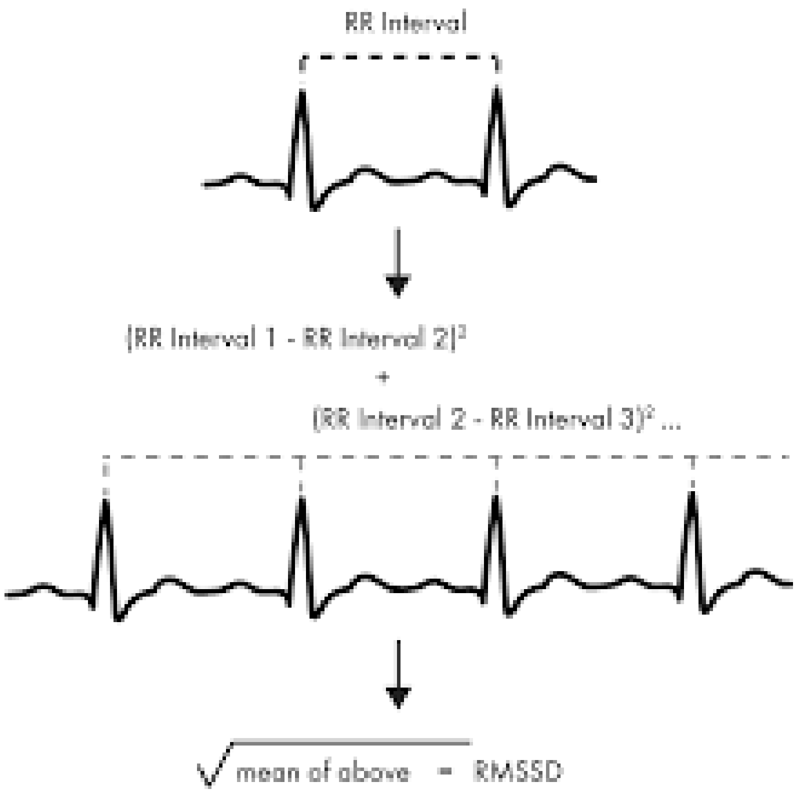


Measurement of HRV

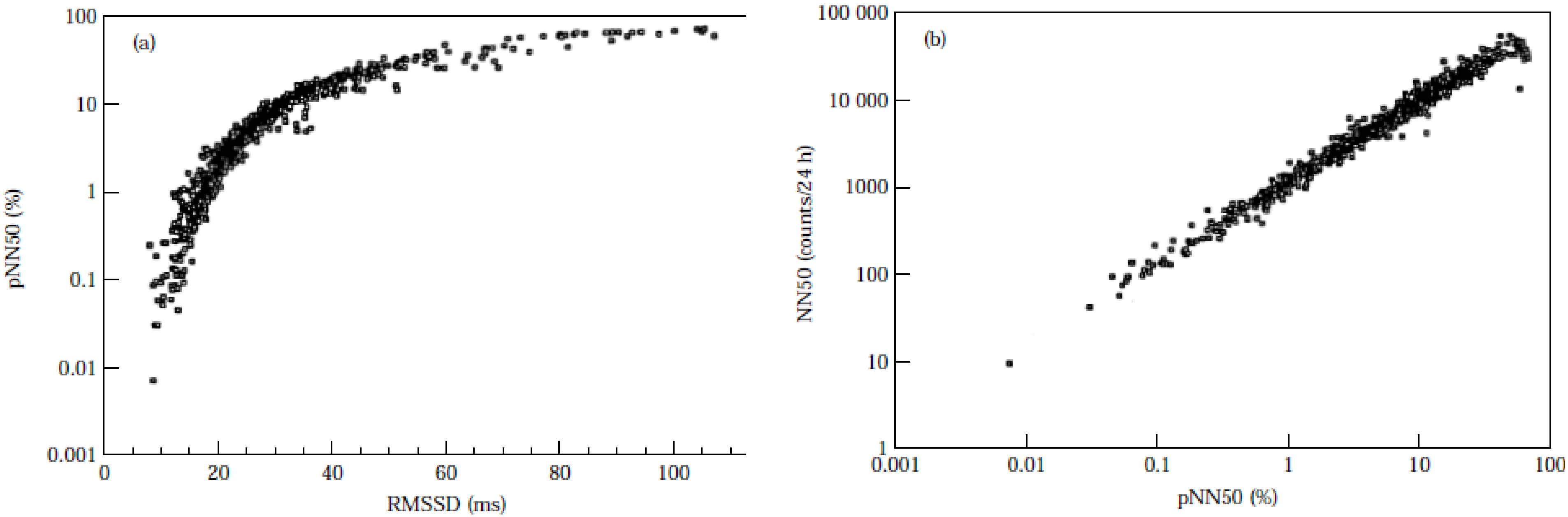
Time domain : statistical measures

- SDNN (ms) : Standard deviation of all NN intervals.
- SDANN (ms) :Standard deviation of the averages of NN intervals in all 5 min segments of the entire recording.
- RMSSD (ms) : The square root of the mean of the sum of the squares of differences between adjacent NN intervals.
- SDNN index (ms) : Mean of the standard deviations of all NN intervals for all 5 min segments of the entire recording.
- SDSD (ms) : Standard deviation of differences between adjacent NN intervals.
- NN50 count : Number of pairs of adjacent NN intervals differing by more than 50 ms in the entire recording.
- pNN50 (%) : NN50 count divided by the total number of all NN interval

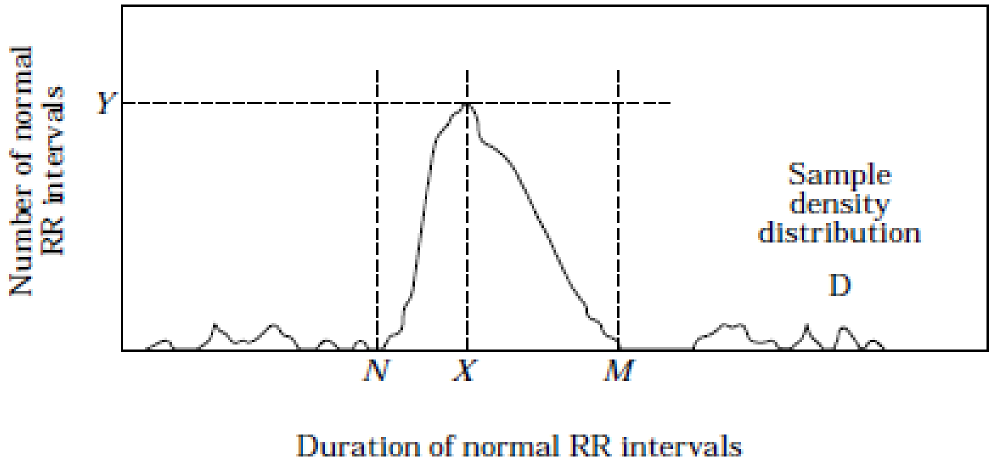
RMSSD


RR Interval
(RR Interval 1 - RR Interval 2)²
+
(RR Interval 2 - RR Interval 3)² ...
√ mean of above = RMSSD

Time domain : statistical measures



Time domain : Geometric domain measures



Geometrical measures on the NN interval histogram

: the sample density distribution D is constructed which assigns the number of equally long NN intervals to each value of their lengths. The most frequent NN interval length X is established, that is Y=D(X) is the maximum of the sample density distribution(D)

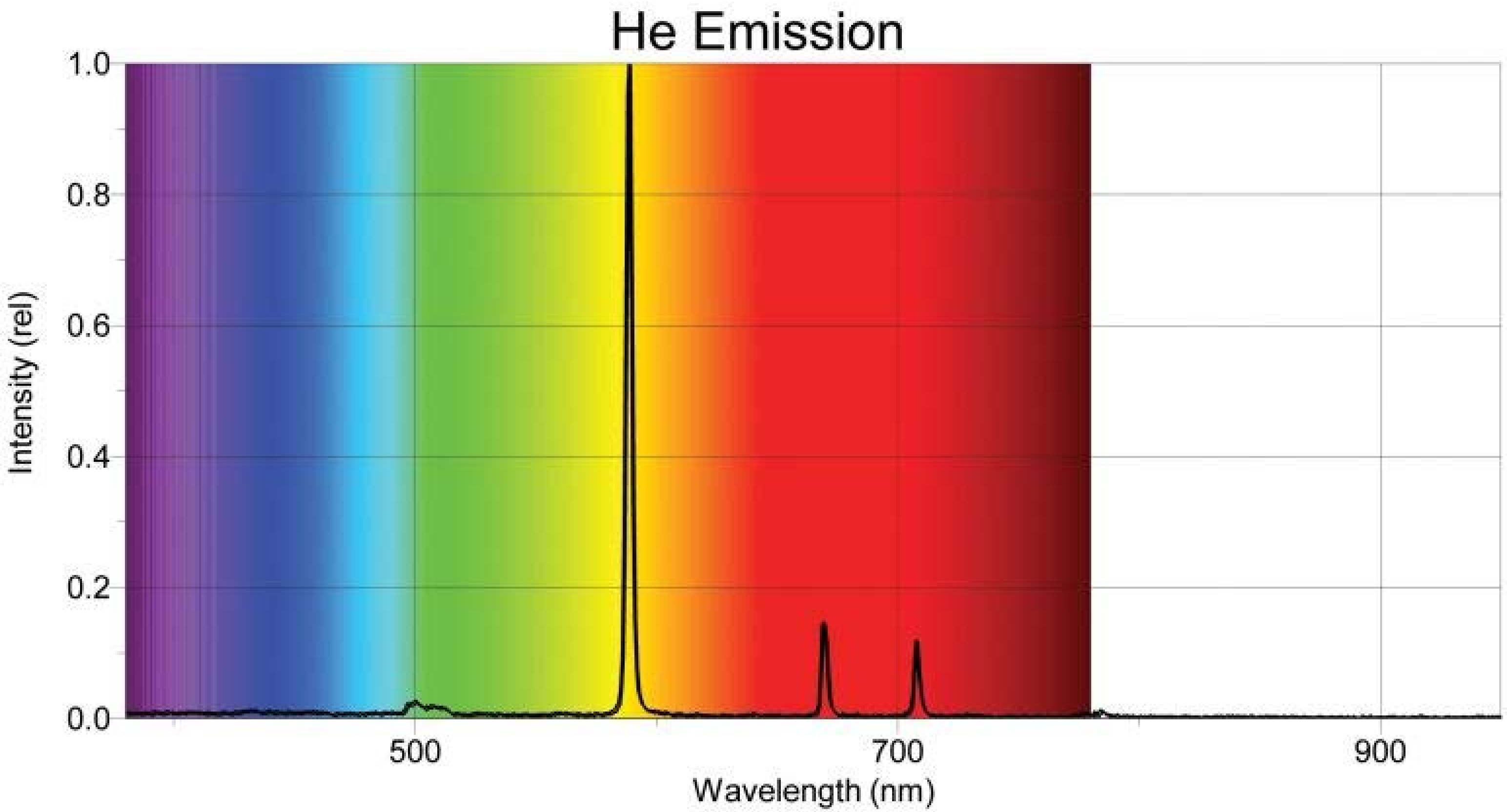
HRV index=(total number of all NN intervals)/Y.

The HRV triangular index : dividing the area integral of D by the maximum Y

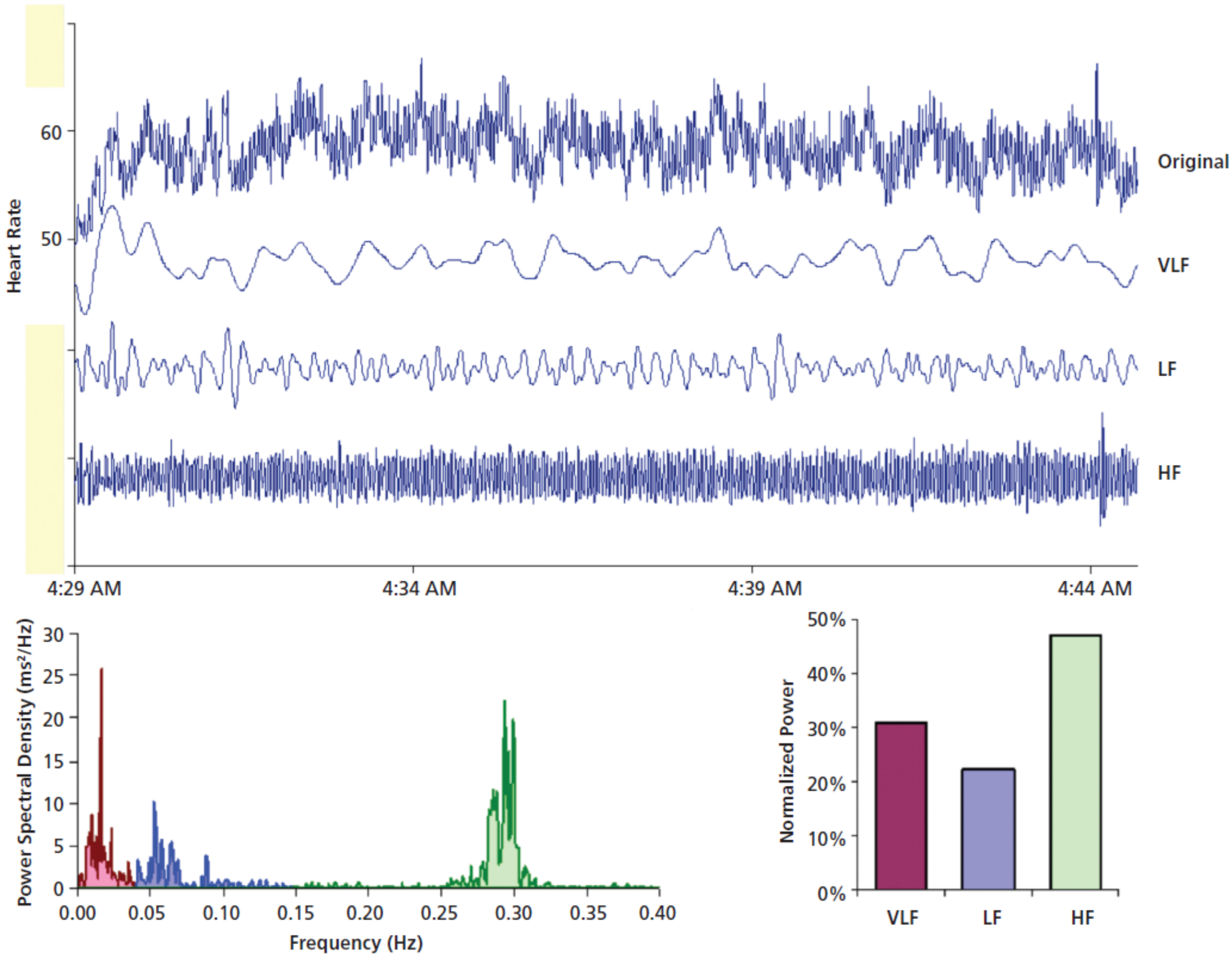
Time domain : Geometric domain measures

- HRV triangular index : Total number of all NN intervals divided by the height of the histogram of all NN intervals measured on a discrete scale with bins of 7·8125 ms (1/128 s)
- TINN (ms) : Baseline width of the minimum square difference triangular interpolation of the highest peak of the histogram of all NN intervals
- Differential index (ms) : Difference between the widths of the histogram of differences between adjacent NN intervals measured at selected heights (e.g. at the levels of 1000 and 10 000 samples)
- Logarithmic index : Coefficient ö of the negative exponential curve k · e"öt which is the best approximation of the histogram of absolute differences between adjacent NN intervals.

Frequency domain : spectral analysis



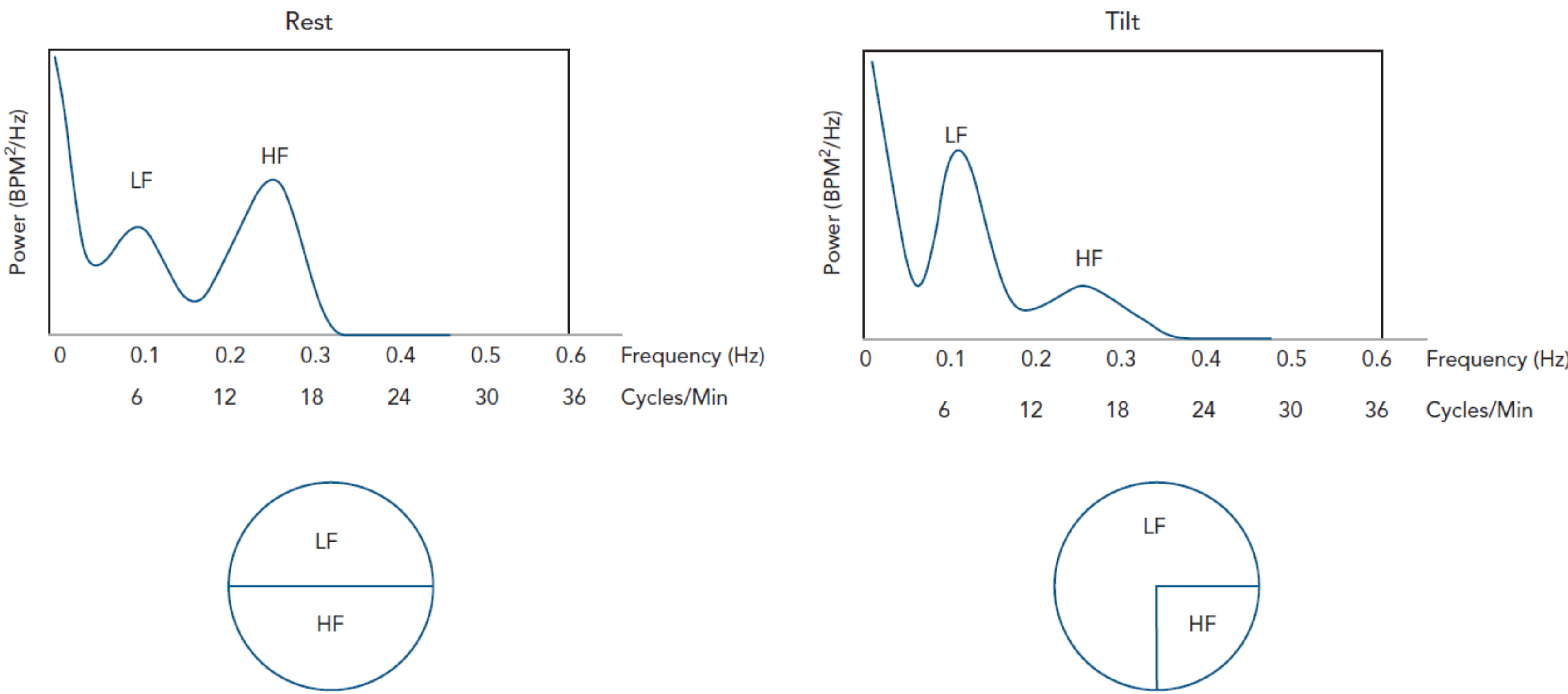
Frequency domain



Frequency domain

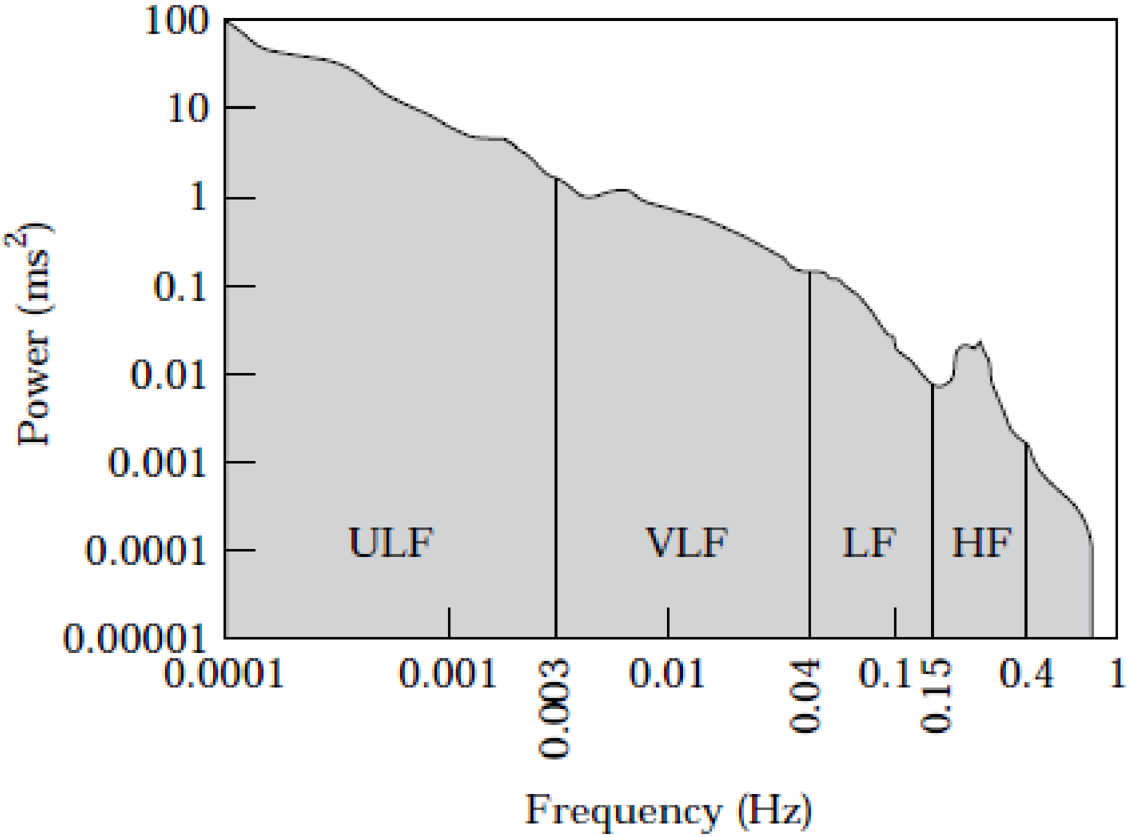
Variable	Units	Description	Frequency range
		Analysis of short-term recordings (5 min)	
5 min total power	ms^2	The variance of NN intervals over the temporal segment	approximately $\leq 0{\cdot}4$ Hz
VLF	ms^2	Power in very low frequency range	$\leq 0{\cdot}04$ Hz
LF	ms^2	Power in low frequency range	0·04–0·15 Hz
LF norm	n.u.	LF power in normalised units LF/(Total Power–VLF) × 100	
HF	ms^2	Power in high frequency range	0·15–0·4 Hz
HF norm	n.u.	HF power in normalised units HF/(Total Power–VLF) × 100	
LF/HF		Ratio LF [ms^2]/HF [ms^2]	
		Analysis of entire 24 h	
Total power	ms^2	Variance of all NN intervals	approximately $\leq 0{\cdot}4$ Hz
ULF	ms^2	Power in the ultra low frequency range	$\leq 0{\cdot}003$ Hz
VLF	ms^2	Power in the very low frequency range	0·003–0·04 Hz
LF	ms^2	Power in the low frequency range	0·04–0·15 Hz
HF	ms^2	Power in the high frequency range	0·15–0·4 Hz
α		Slope of the linear interpolation of the spectrum in a log-log scale	approximately $\leq 0{\cdot}04$ Hz

Frequency domain

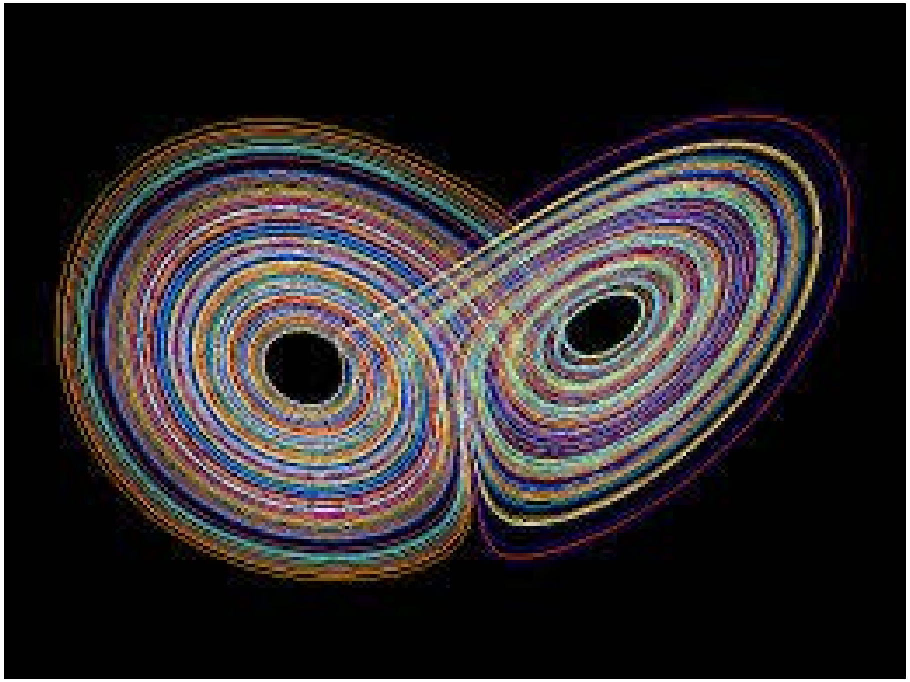


Arrhythmia & Electrophysiology Review 2018;7(3):193–8

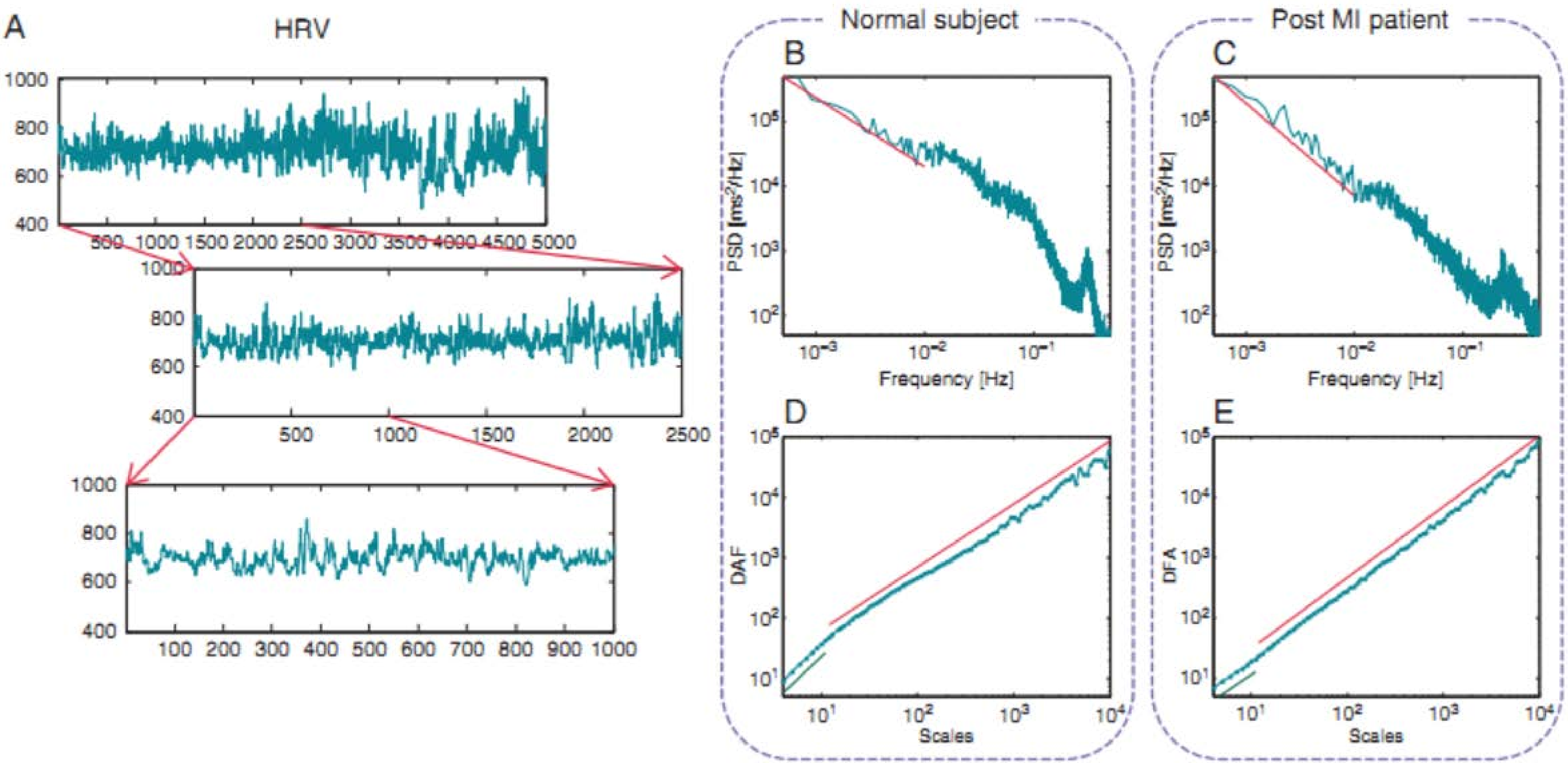
Frequency domain



Fractal analysis

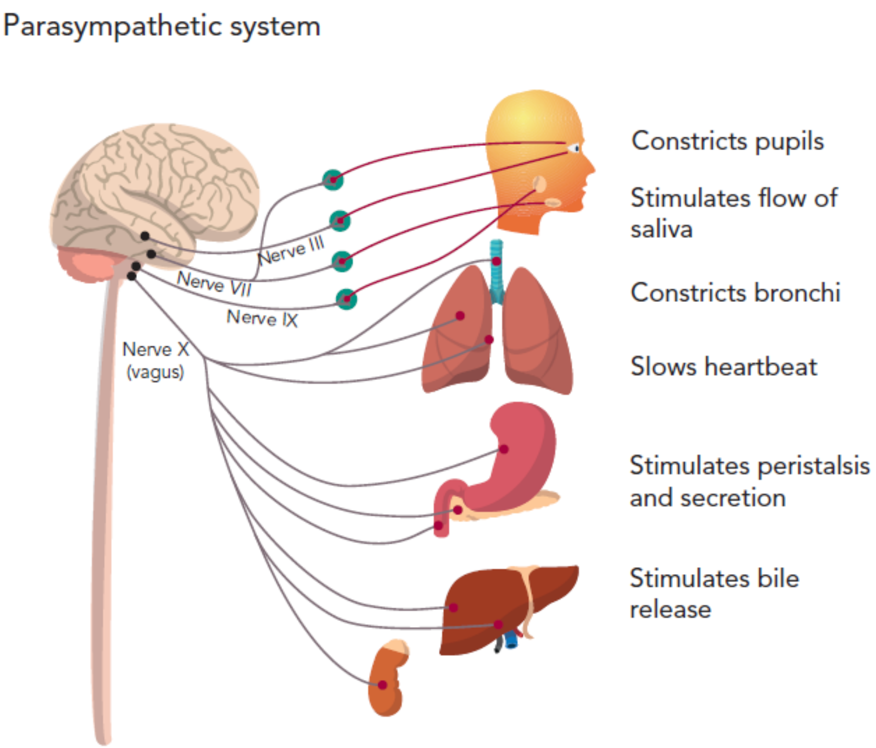


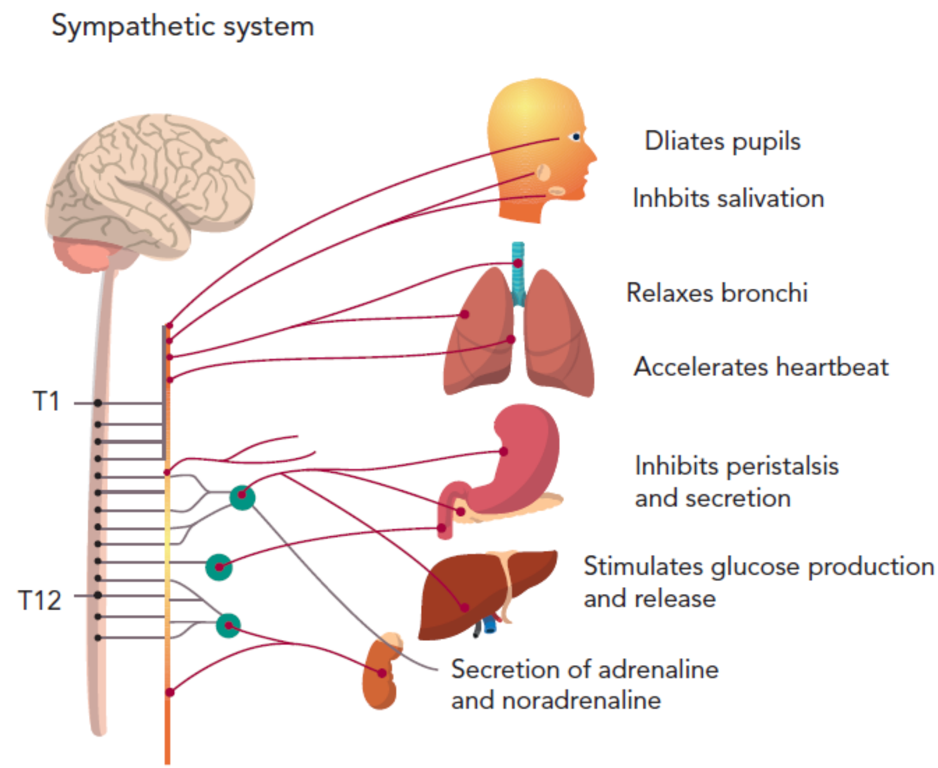
Fractal analysis : DFA alpha1



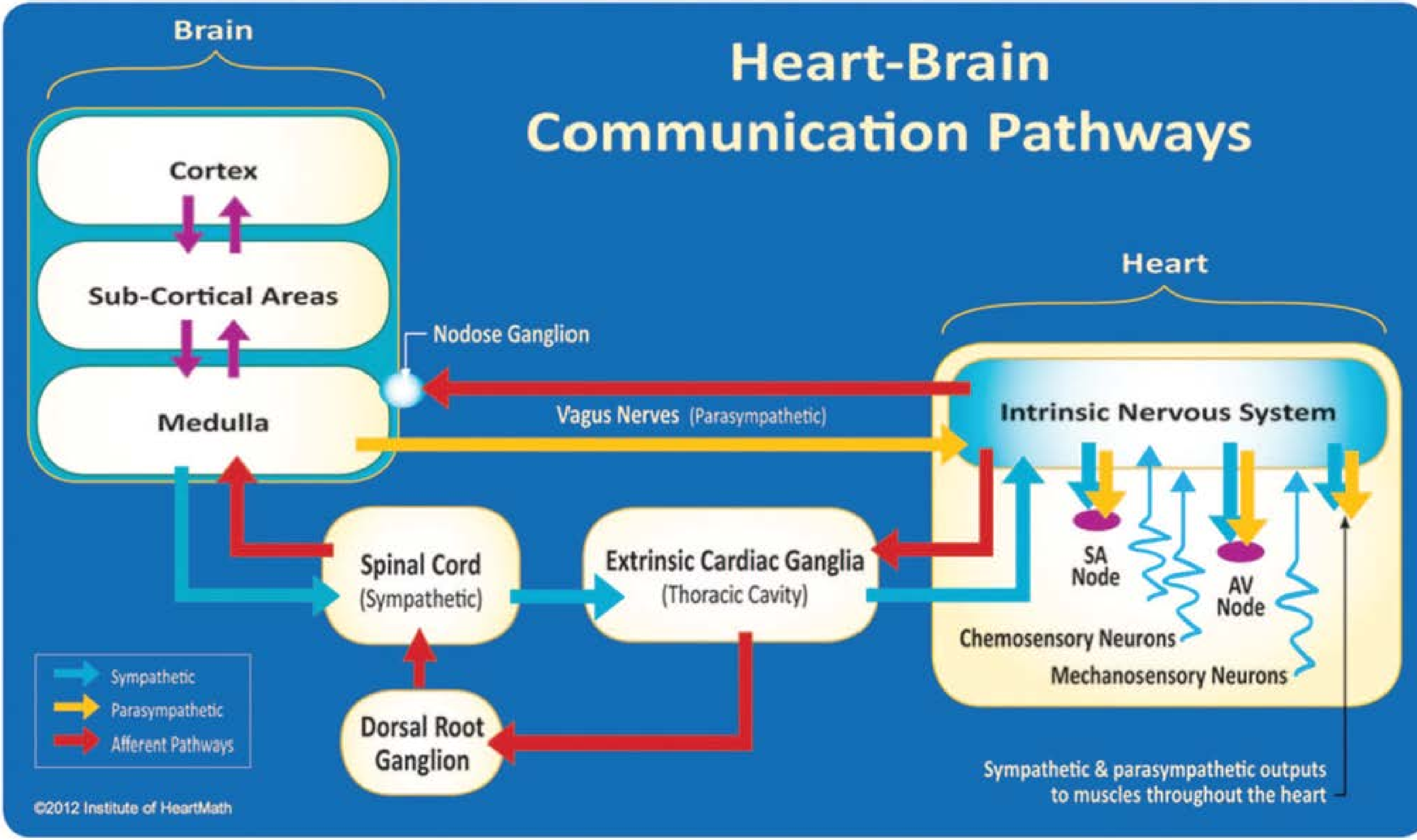
Physiologic correlation

ANS system

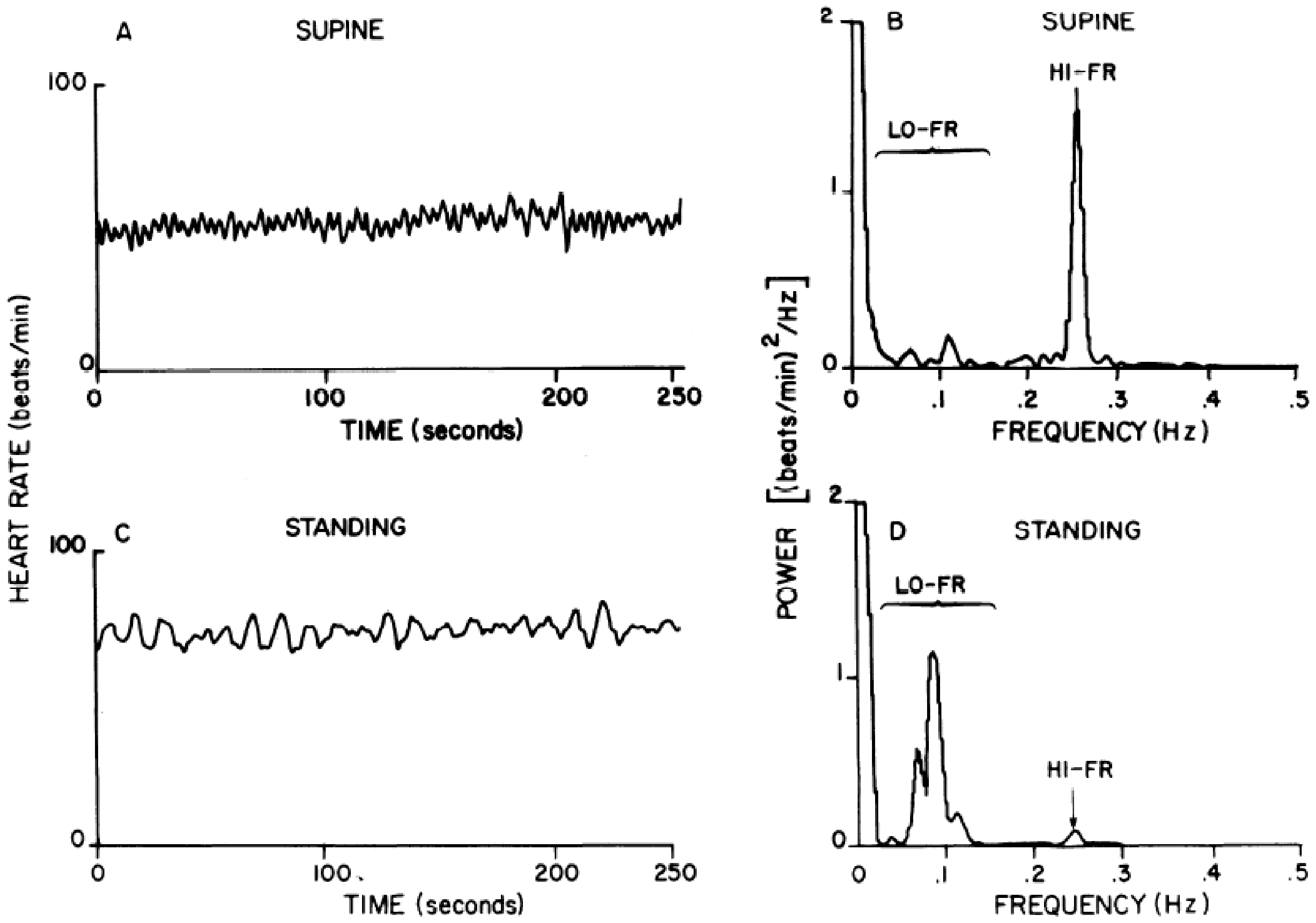

Parasympathetic system
Nerve III
Nerve VII
Nerve IX
Nerve X
(vagus)
Constricts pupils
Stimulates flow of
saliva
Constricts bronchi
Slows heartbeat
Stimulates peristalsis
and secretion
Stimulates bile
release


Sympathetic system
T1
T12
Dliates pupils
Inhbits salivation
Relaxes bronchi
Accelerates heartbeat
Inhibits peristalsis
and secretion
Stimulates glucose production
and release
Secretion of adrenaline
and noradrenaline

ANS system – cardiac communication



Autonomic function : HR spectral analysis



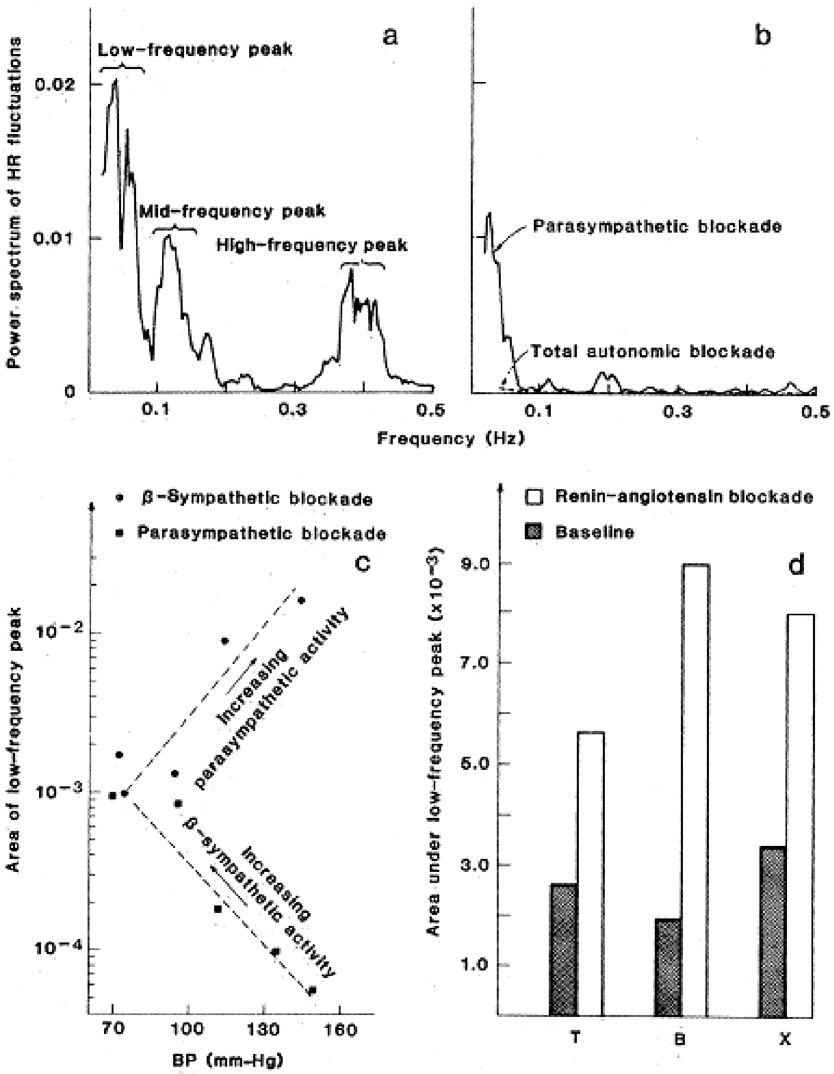
Science

AAAS

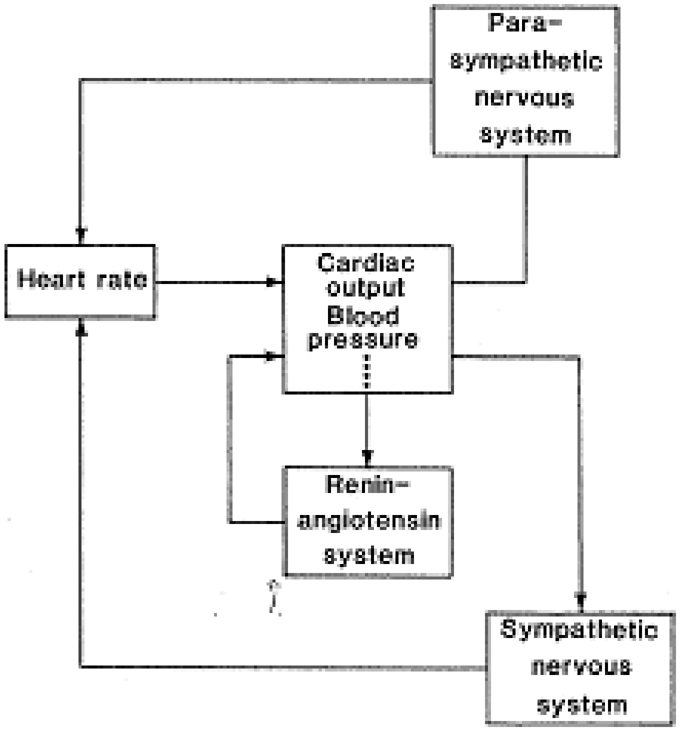
Power Spectrum Analysis of Heart Rate Fluctuation: A Quantitative Probe of Beat-To-Beat Cardiovascular Control

Author(s): Solange Akselrod, David Gordon, F. Andrew Ubel, Daniel C. Shannon, A. Clifford Barger and Richard J. Cohen

Source: *Science*, New Series, Vol. 213, No. 4504 (Jul. 10, 1981), pp. 220-222
Published by: American Association for the Advancement of Science



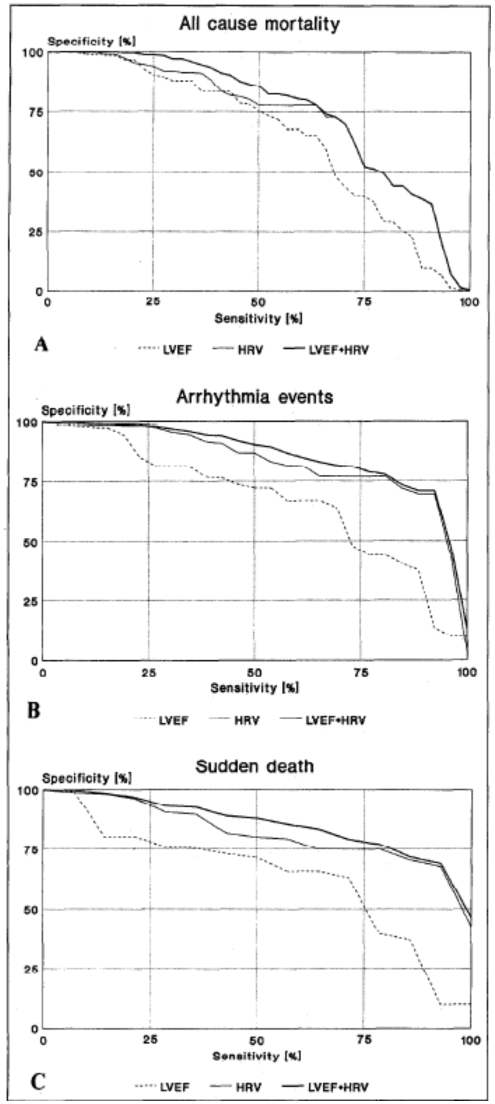
Low-frequency peak
Mid-frequency peak
High-frequency peak
Power spectrum of HR fluctuations
Parasympathetic blockade
Total autonomic blockade
Frequency (Hz)
β-Sympathetic blockade
Parasympathetic blockade
Area of low-frequency peak
increasing parasympathetic activity
increasing β-sympathetic activity
BP (mm-Hg)
Renin-angiotensin blockade
Baseline
Area under low-frequency peak (x10⁻³)
T
B
X

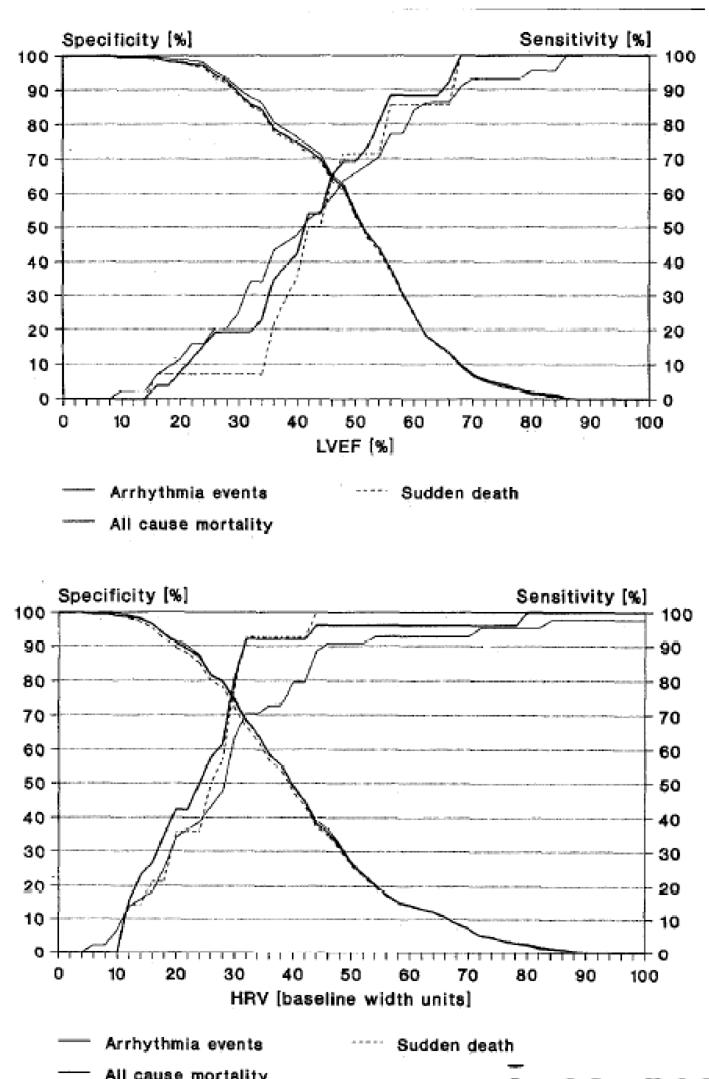


Para-sympathetic nervous system
Heart rate
Cardiac output Blood pressure
Renin-angiotensin system
Sympathetic nervous system

Clinical utilization

Survival predictor after AMI





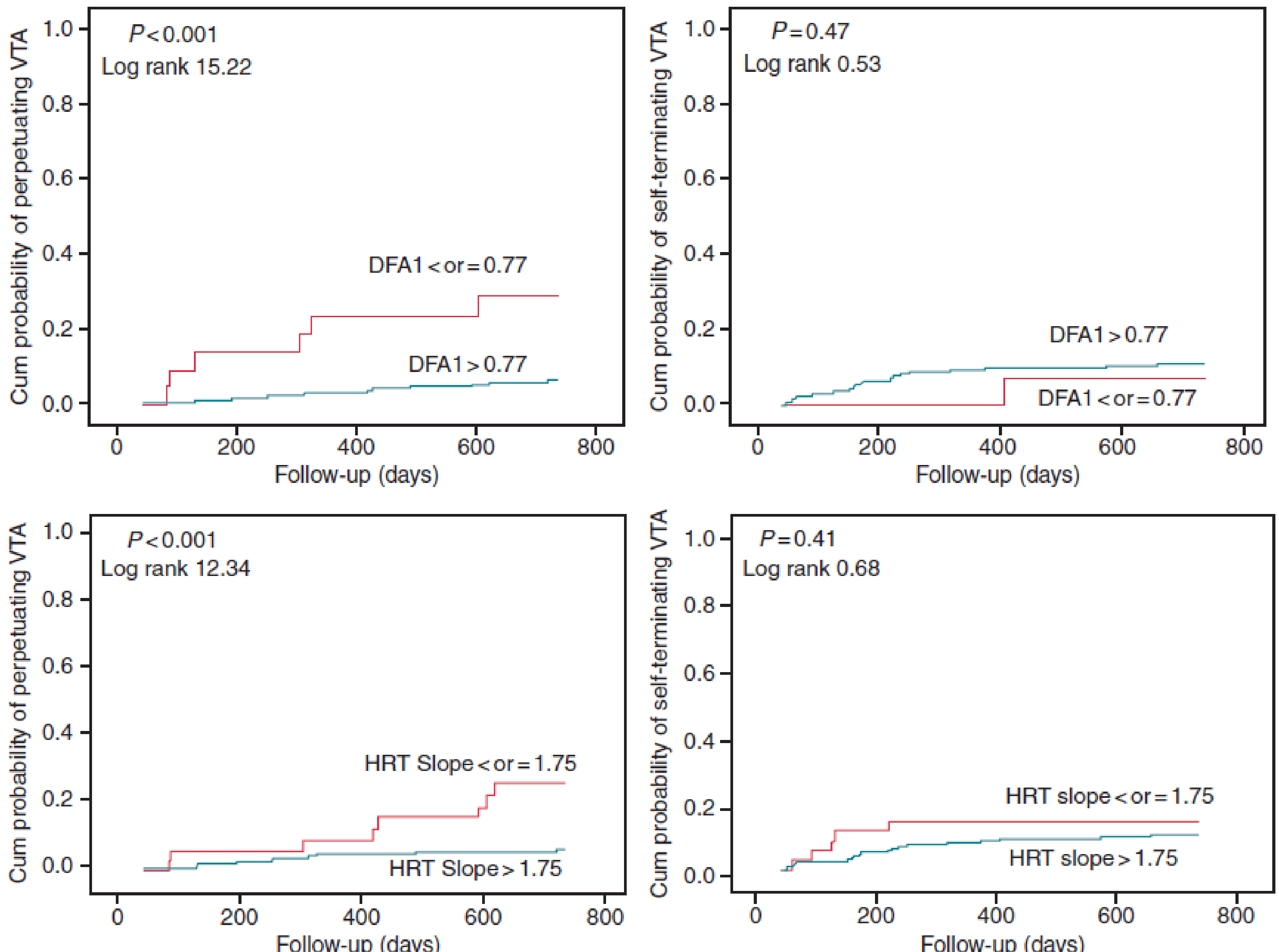
Am J Cardiol 1991;68:434–439

Risk factor of VT after AMI

	No VT (*n* = 245)	Self-terminating VT (*n* = 26)	Perpetuating VT (*n* = 21)	*P*
Inducibility during PES	21 (9)	4 (16)	6 (35)	0.004
SAECG				
Filtered QRS duration, ms	104 ± 15	109 ± 19	118 ± 19	0.002
Heart rate variability				
SDNN, ms	112 ± 35	114 ± 35	98 ± 40	0.25
HF spectral component	309 ± 507	368 ± 427	378 ± 463	0.76
LF spectral component	492 ± 674	430 ± 496	452 ± 568	0.89
VLF spectral component	1199 ± 935	1173 ± 1035	922 ± 1026	0.50
DFA1	1.16 ± 0.22	1.06 ± 0.17	1.01 ± 0.30	0.009
Heart rate turbulence				
Turbulence slope, ms/NN	8.14 ± 7.78	8.02 ± 10.03	4.17 ± 4.27	0.12
T-wave alternans (exercise/pacing combined)				0.69
Negative	90 (41)	7 (32)	6 (35)	
Positive	64 (29)	8 (36)	8 (47)	
Incomplete	36 (17)	5 (23)	2 (12)	
Indeterminate	28 (13)	2 (9)	1 (6)	
Non-sustained ventricular tachycardia on Holter	27 (12)	8 (31)	5 (26)	0.01

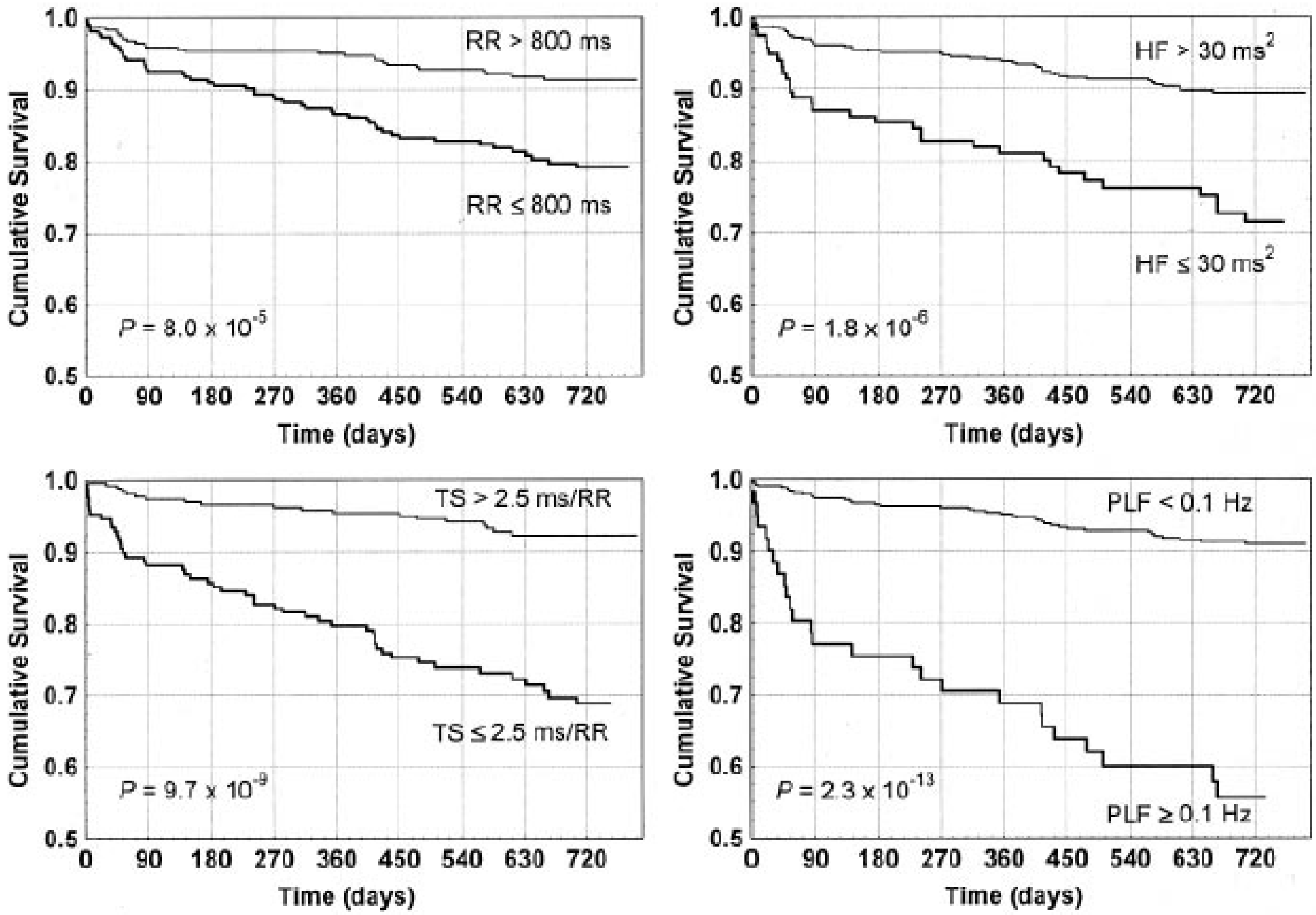
Europace (2011) 13, 1604–1611

Risk factor of VT after AMI



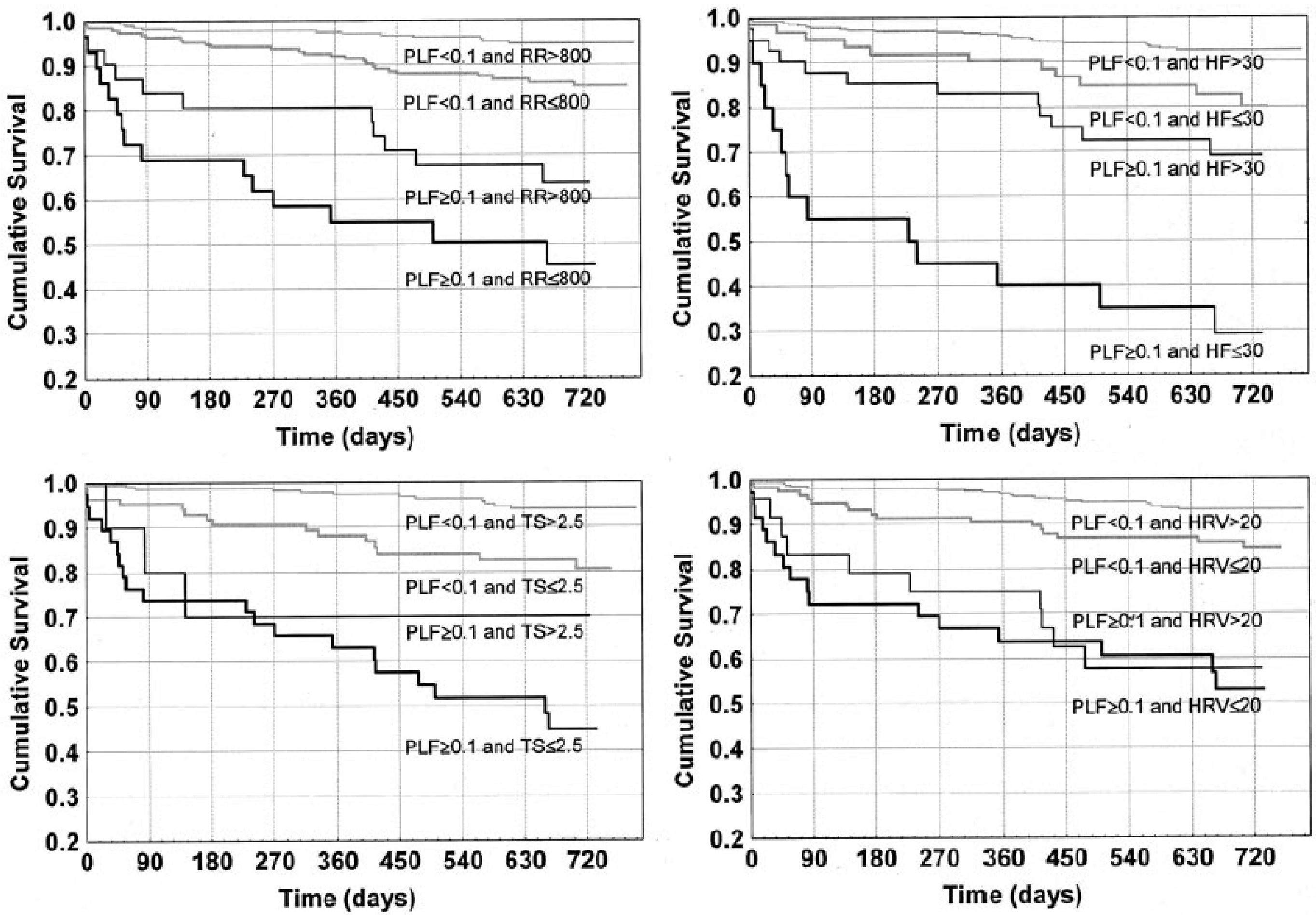
Europace (2011) 13, 1604–1611

EMIAT data



Circulation. 2004; 110:1183-1190

Prevalent low frequency oscillation



Circulation. 2004; 110:1183-1190

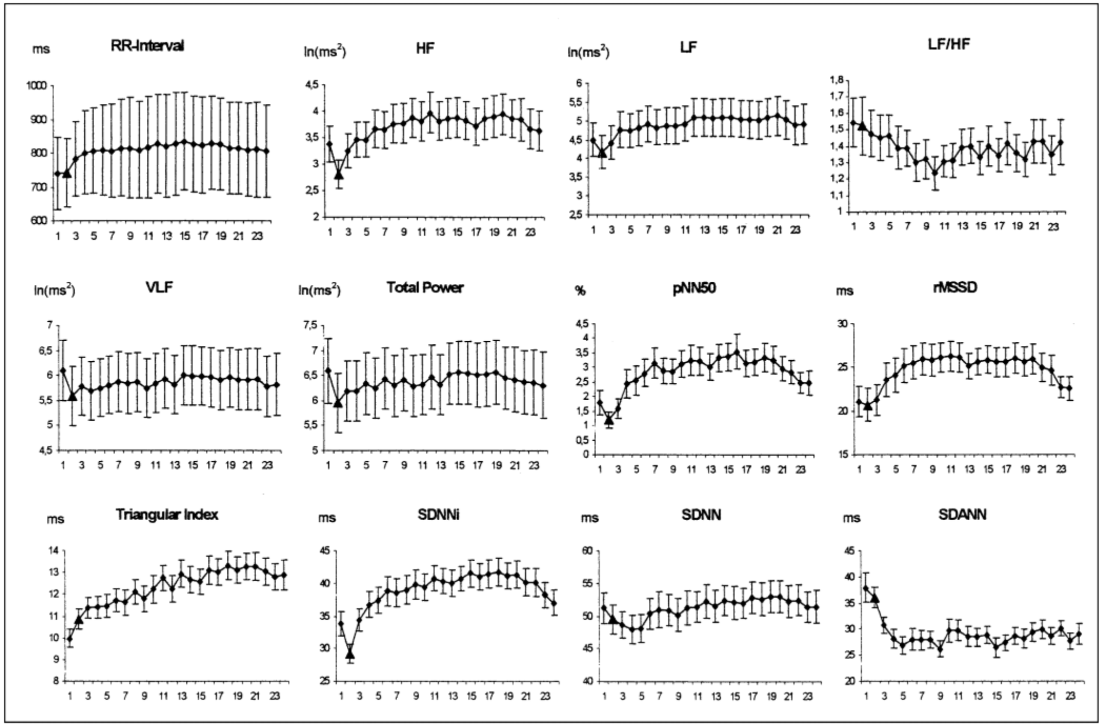
Predictors of improved heart rate variability after reperfusion in patient with LV dysfunction associated with acute myocardial infarction

Jum suk Ko, Nam Ho Kim, Jae young Cho, Sang Jae Rhee ,
Kyeong Ho Yoon, Eun Mi Lee, Seok Kyu Oh, Jin Won Jeong

Wonkwang University hospital and school of medicine

Background

- **Temporal changes of HRV parameters after reperfusion**



Am J Cardiol 2000;85:815–820

Method : study subjects

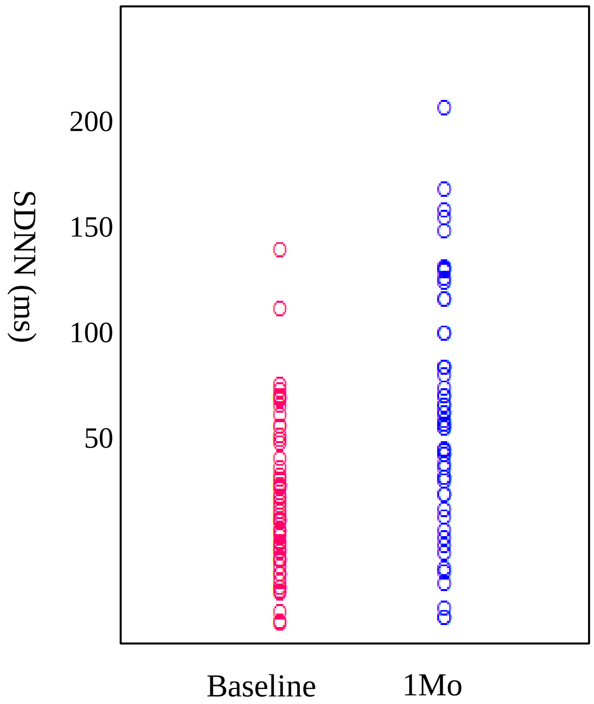
- **51 patients (male 82.4%, mean age 59.7±12.0) with acute myocardial infarction associated with significant LV dysfunction (LVEF<45%)**
- **All enrolled patients were underwent standard reperfusion therapy and medical treatment according to AHA/ACC guideline**

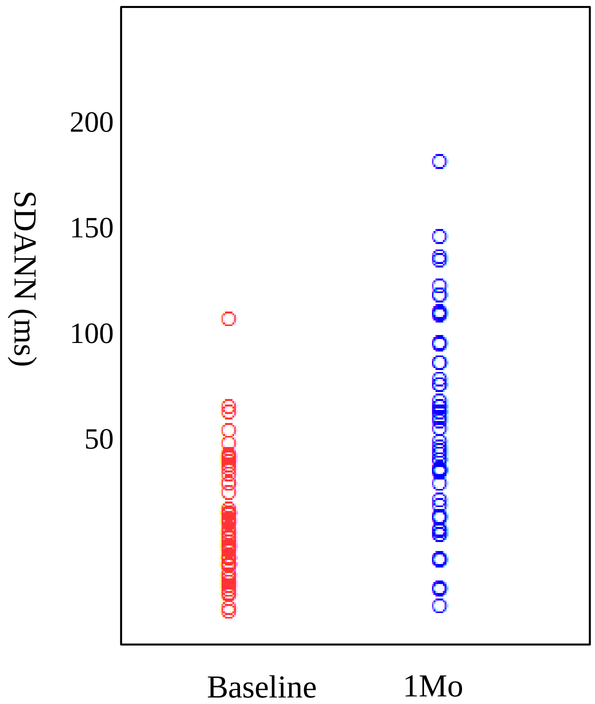
Method : data analysis

- **Collected data (baseline and 1 month follow up)**
  - clinical characteristics
  - laboratory findings
  - echocardiographic data
  - flow mediated dilatation (FMD)
  - 24 hour Holter parameters.

- **Enrolled patients were divided into two groups according to improvement of HRV (increased SDNN >20%) and various parameters were assessed**

Result : HRV parameters – baseline ad 1Mo





Result : HRV parameters – baseline ad 1Mo

	Baseline	1Mo FU	P value
SDNN	79.8±26.5	110.0±41.2	<0.05
SDANN	63.5±20.8	96.3±37.6	<0.05
ASDNN	43.1±18.0	45.0±17.6	<0.05
Max TWA	38.7±24.9	52.0±43.3	0.14

Result : Baseline characteristics

	Improved HRV (n=36)	Unimproved HRV (n=15)	P value
Age(yrs)	61.8±11.6	56.5±10.5	0.78
Gender(male%)	32(88.9%)	13(86.7%)	1.00
HTN	18(50.0%)	6(40.0%)	0.55
DM	6(16.7%)	4(26.7%)	0.45
Smoking	22(61.1%)	7(46.7%)	0.26
FHx	2(5.6%)	1(6.7%)	0.65
Old CVA	2(5.5%)	0(0%)	1.00
ESRD	1(2.8%)	0(0.0%)	1.00
Preivious PCI	3(8.3%)	0(0.0%)	0.54

Result : Laboratory data

	Improved HRV (n=36)	Unimproved HRV (n=15)	P value
Hgb	14.8±1.6	14.6±2.4	0.735
Creatinine	1.0±0.3	0.9±0.3	0.351
CRP	6.7±20.9	24.8±81.0	0.212
Na	140.2±137.4	137.4±4.2	0.056
K	4.1±0.5	4.1±0.4	0.962
Mg	2.1±0.2	1.8±0.3	0.037
LDL	112.8±38.6	137.5±55.6	0.078
Peak TnT	10.1±8.5	11.2±9.5	0.680
BNP	172.2±282.7	254.8±334.6	0.407

Result : Angiographic result

	Improved HRV (n=36)	Unimproved HRV (n=15)	P value
LAD culprit	25(69.4%)	12(80.0%)	0.653
Multivessel ds	14(38.9%)	5(33.3%)	0.840
Pre-TIMI 0	27(75.0%)	13(86.7%)	0.510
Post-TIMI 3	35(97.2%)	15(100%)	0.514
Complete-revasc	28(77.8%)	13(86.7%)	0.466

Result : Medical Tx

	Improved HRV (n=36)	Unimproved HRV (n=15)	P value
Aspirin	35(97.2%)	15(100%)	1.00
P2Y12 inhibitor	36(100%)	15(100%)	n/a
Cilostazol	3(8.3%)	1(6.7%)	1.00
Beta blocker	31(86.7%)	12(80.0%)	0.679
ACE inhibitor	19(52.8%)	3(20.0%)	0.031
ARB	13(36.1%)	10(43.5%)	0.056
Spironolactone	11(30.6%)	5(33.3%)	0.846
Statin	36(100%)	15(100%)	n/a

Result : Echocardiographic parameters

	Improved HRV (n=36)	Unimproved HRV (n=15)	P value
LVEF	40.5±5.2	39.3±3.6	0.426
LVEDD	54.3±4.6	52.7±3.6	0.233
E/E’	11.9±4.1	13.7±8.5	0.313
LVEF(1Mo)	46.4±7.3	45.6±10.8	0.774
LVEDD(1Mo)	54.0±4.5	53.8±7.6	0.892
E/E’(1Mo)	11.9±4.1	13.7±8.5	0.036

Result : ECG parameters

	Improved HRV (n=36)	Unimproved HRV (n=15)	P value
QRSd	98.3±17.0	102.2±29.4	0.547
QRSd1Mo	99.6±9.8	99.4±22.8	0.200
QTc	458.3±45.1	474.6±64.4	0.305
QTc 1Mo	465.1±28.5	460.7±32.4	0.629
QTd	399.1±56.4	397.0±50.6	0.904
QTd 1Mo	425.5±35.3	405.5±49.3	0.108

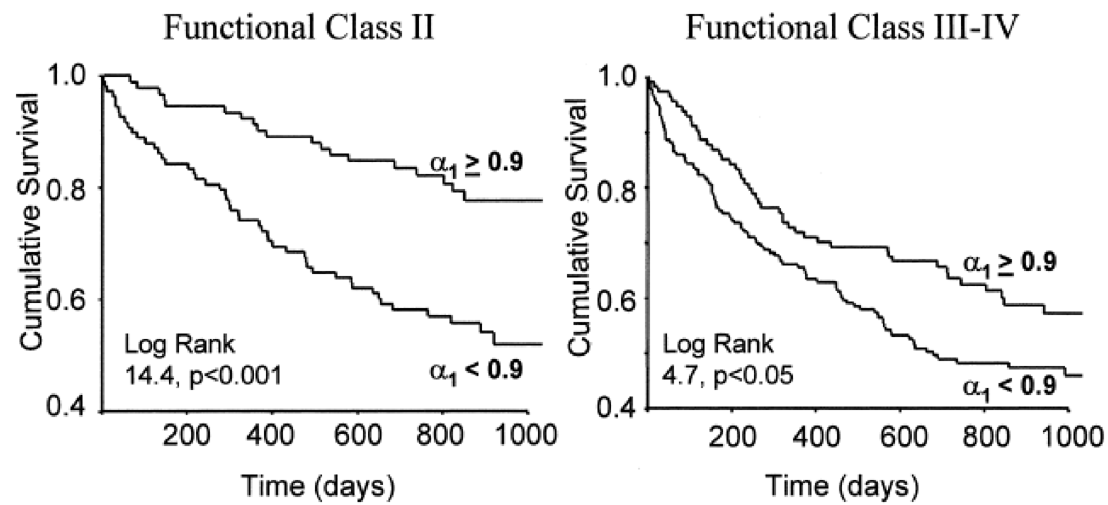
Result : FMD

	Improved HRV (n=36)	Unimproved HRV (n=15)	P value
FMD%	6.2±4.9	4.9±7.1	0.035
FMD% 1Mo	5.9±4.5	5.8±4.0	0.968

Fractal analysis in CHF patients

	Unadjusted Relative Hazard (95% CI)	Adjusted Relative Hazard (95% CI)
Mortality in total population (n = 499)		
α_1 <0.9	1.9 (1.4–2.5)*	1.4 (1.0–1.9)‡
SDNN <80 ms	1.7 (1.3–2.3)*	1.2 (0.9–1.9)
Mean HR >75 beats/min	1.5 (1.1–1.9)†	1.2 (0.9–1.7)
HRVI <22	1.6 (1.2–2.1)†	1.1 (0.8–1.6)
ln VLF <6.4	1.7 (1.3–2.2)*	1.2 (0.8–1.8)
Mortality in NYHA class II (n = 210)		
α_1 <0.9	2.7 (1.6–4.6)*	2.3 (1.2–4.2)†
SDNN <80 ms	2.5 (1.4–4.4)†	1.5 (0.6–3.5)
Mean HR >75 beats/min	2.0 (1.3–3.4)†	1.5 (0.9–2.8)
HRVI <22	2.2 (1.4–3.6)†	1.4 (0.7–2.5)
ln VLF <6.4	2.5 (1.5–4.1)*	1.3 (0.6–2.9)
Mortality in NYHA class III–IV (n = 289)		
α_1 <0.9	1.5 (1.0–2.1)‡	1.1 (0.8–1.6)
SDNN <80 ms	1.1 (0.8–1.6)	1.3 (0.7–1.9)
Mean HR >75 beats/min	1.2 (0.8–1.6)	1.0 (0.7–1.5)
HRVI <22	1.2 (0.9–1.7)	0.9 (0.6–1.4)
ln VLF <6.4	1.3 (0.9–1.8)	1.2 (0.8–1.9)

*p <0.00; †p <0.01; ‡p <0.05.
§Adjustments made for age, NYHA class, wall motion index, medication, and creatinine concentration. Cut-off point values of each variable are optimized to this population. NYHA class used here was evaluated at the time of randomization.
CI = 95% confidence intervals; other abbreviations as in Table 2.



Am J Cardiol 2001;87:178–182

Autonomic marker in CHF (GISSI-HF)

Cardiovascular death

Population/events		Unadjusted		Adjusted[a]	
		P-value	HR (95% CI)	P-value	HR (95% CI)
388/57	SDNN (per 12 ms decrease)	0.018	1.23 (1.02–1.24)	0.024	1.17 (1.01–1.23)
349/52	Ln VLFP (per 0.27 ln ms^2 decrease)	0.0002	1.31 (1.06–1.21)	0.0004	1.13 (1.05–1.20)
349/52	Ln LFP (per 0.37 ln ms^2 decrease)	<.0001	1.19 (1.11–1.29)	0.0004	1.17 (1.07–1.27)
388/57	DFA (per 0.08 unit decrease)	0.0001	1.17 (1.08–1.26)	0.030	1.10 (1.01–1.20)
339/54	TO (per 0.51% increase)	0.005	1.27 (1.04–1.22)	0.175	1.07 (0.97–1.17)
339/54	TS (per 0.91 ms/RR decrease)	0.0003	1.28 (1.12–1.47)	0.017	1.19 (1.03–1.38)
388/57	DC (per 0.76 ms decrease)	0.013	1.10 (1.02–1.19)	0.08	1.07 (0.99–2.25)

European Journal of Heart Failure (2012) 14, 1410–1419

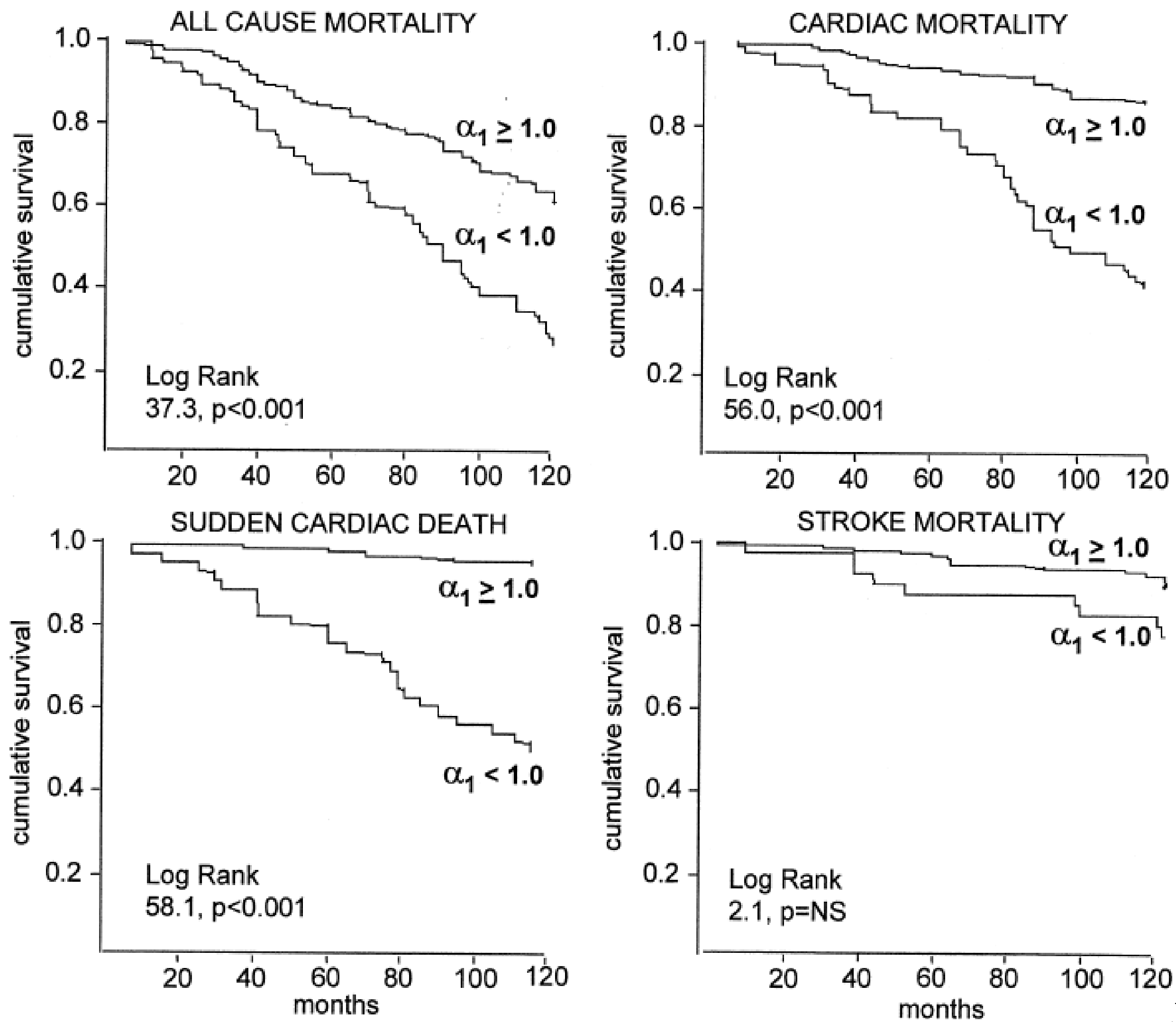
Autonomic marker in CHF (GISSI-HF)

Arrhythmic event

Population/events		Unadjusted		Adjusted[a]	
		P-value	HR (95% CI)	P-value	HR (95% CI)
388/47	SDNN (per 12 ms decrease)	0.049	1.11 (1.00–1.23)	0.066	1.10 (0.99–1.23)
349/41	Ln VLFP (per 0.27 ln ms^2 decrease)	0.029	1.10 (1.01–1.19)	0.020	1.10 (1.01–1.19)
349/41	Ln LFP (per 0.37 ln ms^2 decrease)	0.020	1.12 (1.02–1.23)	0.046	1.10 (1.00–1.21)
388/47	DFA (per 0.08 unit decrease)	0.061	1.09 (1.00–1.19)	0.159	1.07 (0.97–1.17)
339/44	TO (per 0.51% increase)	0.206	1.06 (0.97–1.17)	0.378	1.05 (0.95–1.15)
339/44	TS (per 0.91 ms/RR decrease)	0.016	1.17 (1.03–1.33)	0.034	1.15 (1.01–1.30)
388/47	DC (per 0.76 ms decrease)	0.089	1.08 (0.99–1.18)	0.127	1.07 (0.98–1.17)

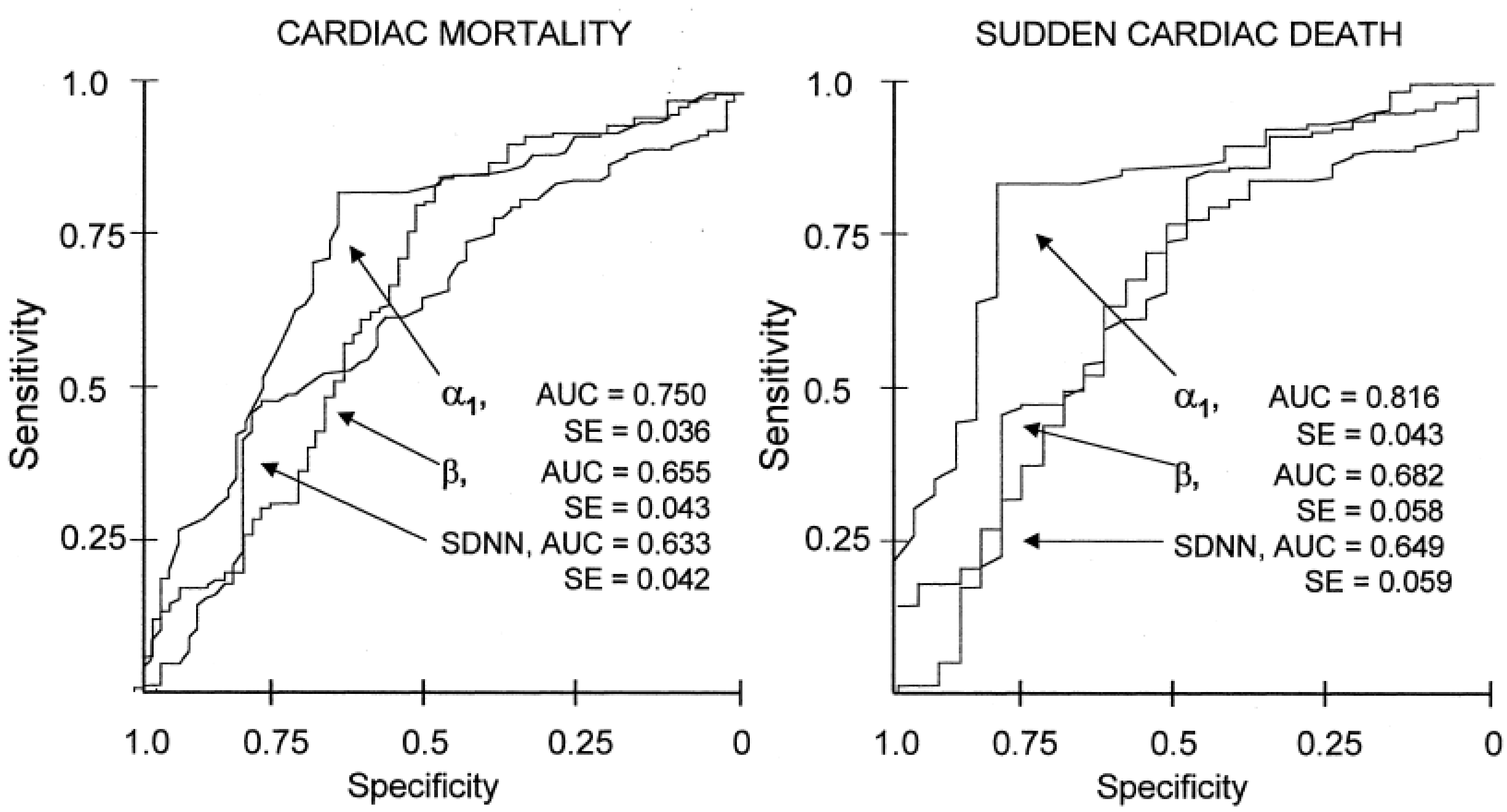
European Journal of Heart Failure (2012) 14, 1410–1419

SCD predictor in elderly subjects



J Am Coll Cardiol 2001;37:1395– 402

SCD predictor in elderly subjects



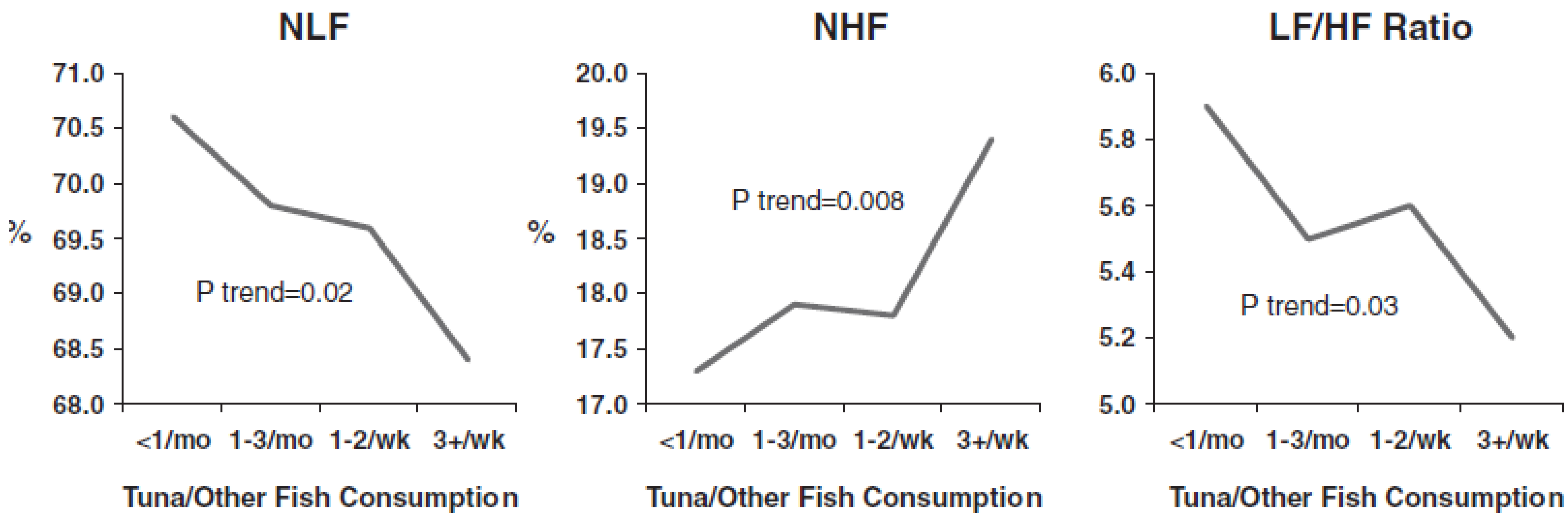
J Am Coll Cardiol 2001;37:1395– 402

omega-3 Fatty Acid Consumption and Heart Rate Variability in Adults

	Frequency of Consumption				
	<1/mo (n=111)*	1–3/mo (n=280)*	1–2/wk (n=632)*	≥3/wk (n=229)*	*P* for Trend
Time-domain indices					
SDNN, ms	118.8 (13.2)	113.7 (11.4)	118.0 (10.8)	118.6 (10.9)	0.69
rMSSD,† ms	19.1 (1.8)	18.4 (1.9)	18.6 (1.8)	19.4 (2.1)	0.06
SDNNIDX, ms	40.6 (4.8)	40.9 (4.5)	41.8 (4.4)	43.0 (4.6)	0.07
Frequency-domain indices					
NLF,† %	70.6 (1.4)	69.8 (1.5)	69.6 (1.5)	68.4 (1.3)	0.02
NHF,† %	17.3 (1.2)	17.9 (1.1)	17.8 (1.1)	19.4 (1.1)	0.008
VLF, ms^2	946 (253)	936 (243)	1000 (248)	1058 (269)	0.02
ULF, 1000 ms^2	12.2 (2.8)	10.9 (2.2)	12.1 (2.2)	12.3 (2.3)	0.44
Nonlinear indices					
Poincaré ratio (SD12)	0.26 (0.03)	0.26 (0.03)	0.25 (0.02)	0.24 (0.02)	0.02
DFA1	1.02 (0.07)	1.03 (0.07)	1.06 (0.06)	1.07 (0.06)	0.005

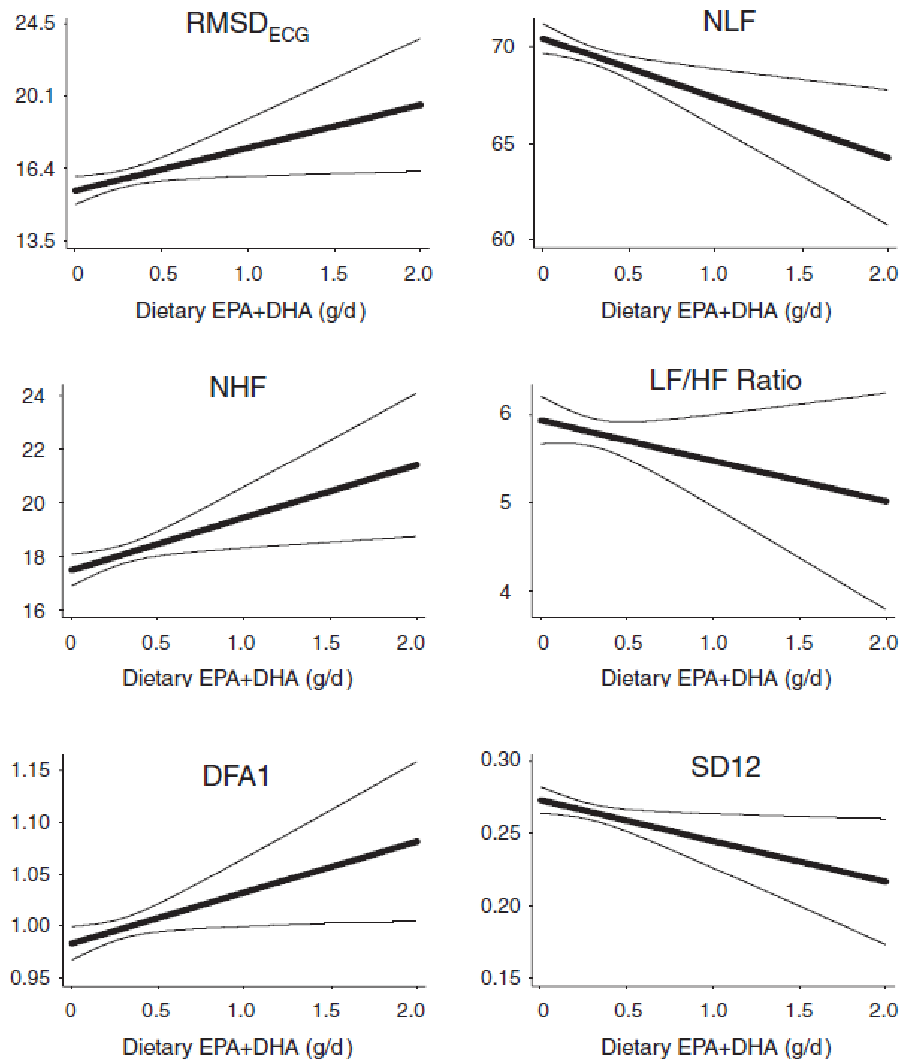
Circulation. 2008;117:1130-1137

omega-3 Fatty Acid Consumption and Heart Rate Variability in Adults



Circulation. 2008;117:1130-1137

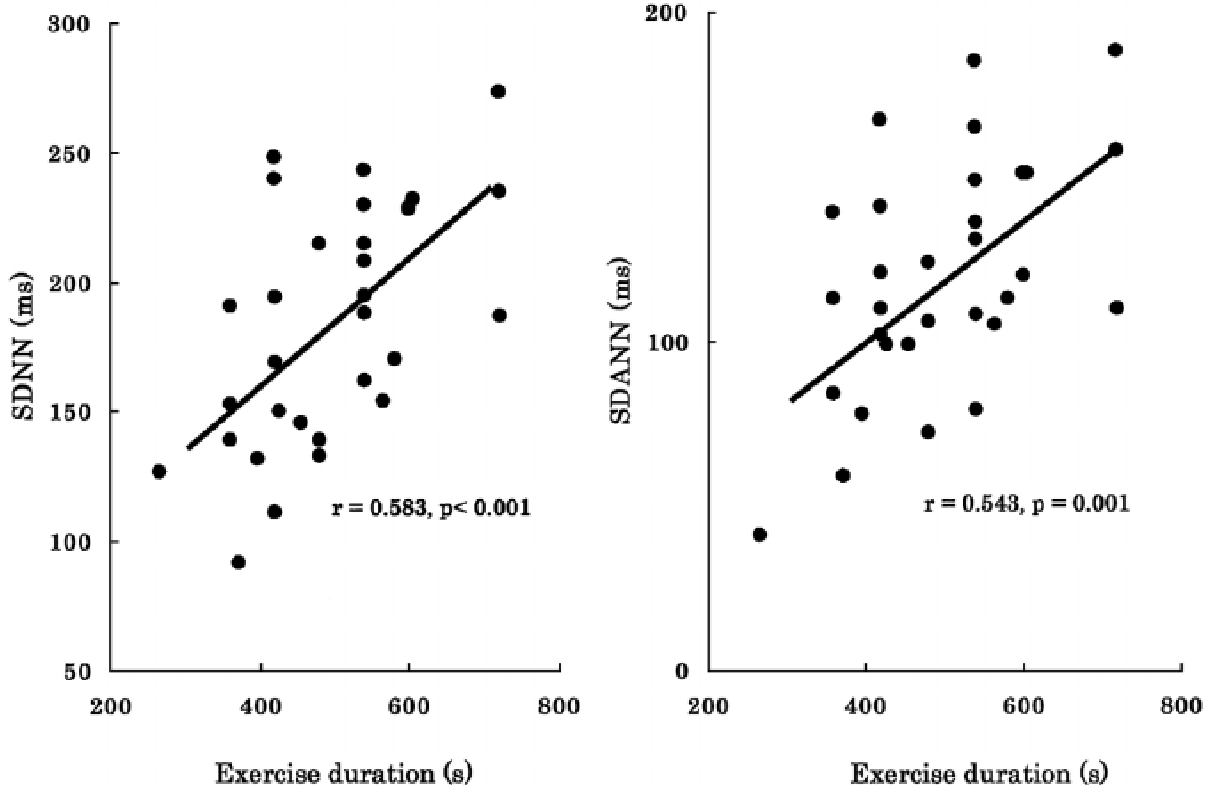
omega-3 Fatty Acid Consumption and Heart Rate Variability in Adults



Circulation. 2008;117:1130-1137

HRV in AF patients

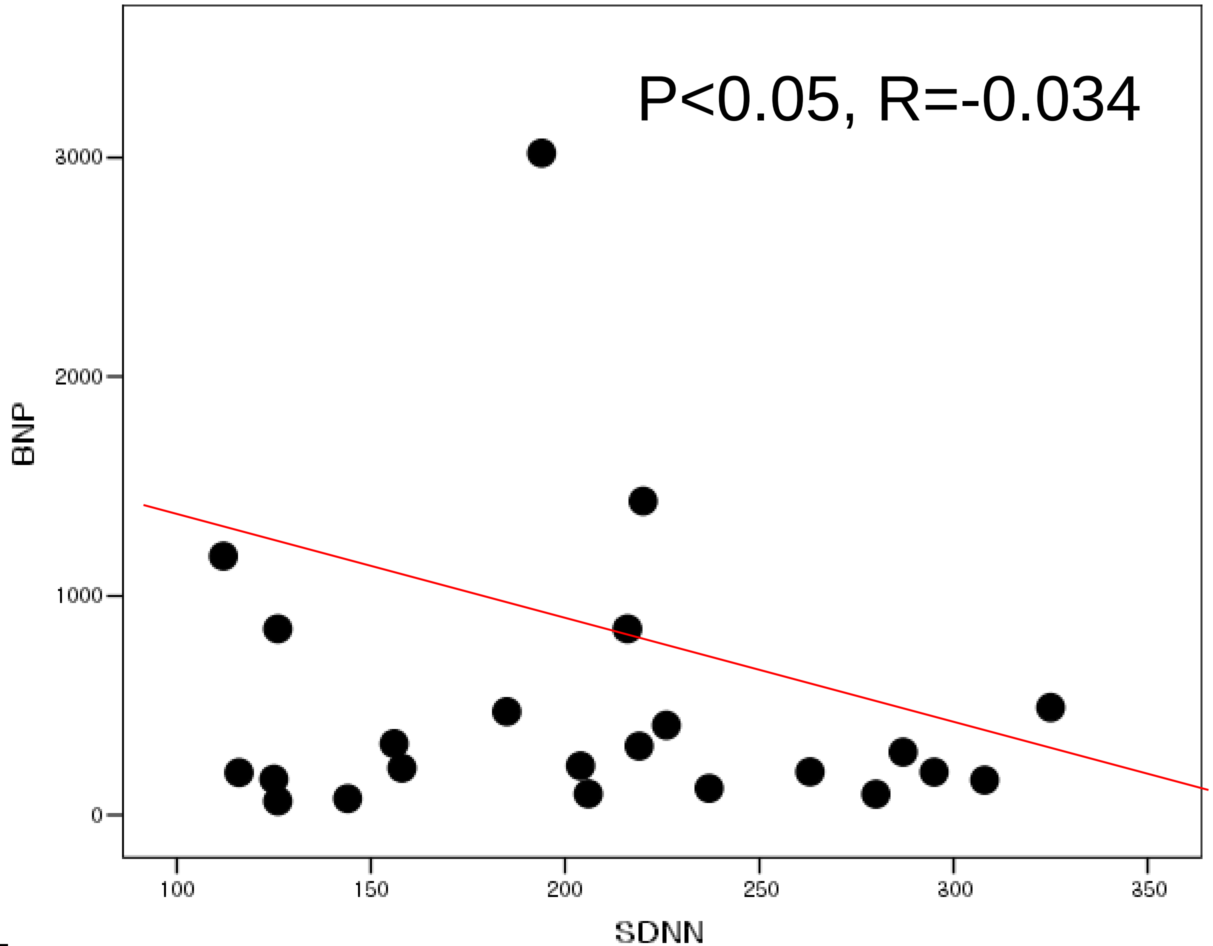
■ **Reduced HRV was associated with impaired exercise capacity in AF**



Miwa et al, Circ J 2004; 68: 294 –296

HRV in AF patients

- **BNP level reversely correlated with SDNN**



Take home massage

- **HRV is useful tool for assessing variation of autonomic nervous system.**
- **HRV has potential to predict adverse event in patients with cardiovascular disease**
- **Large prospective longitudinal studies are needed to determine the sensitivity, specificity, and predictive value of HRV in the identification of individuals at risk for subsequent morbid and mortality**

Thank you for your attention