Prediction of AF episodes in patients with lone atrial fibrillation

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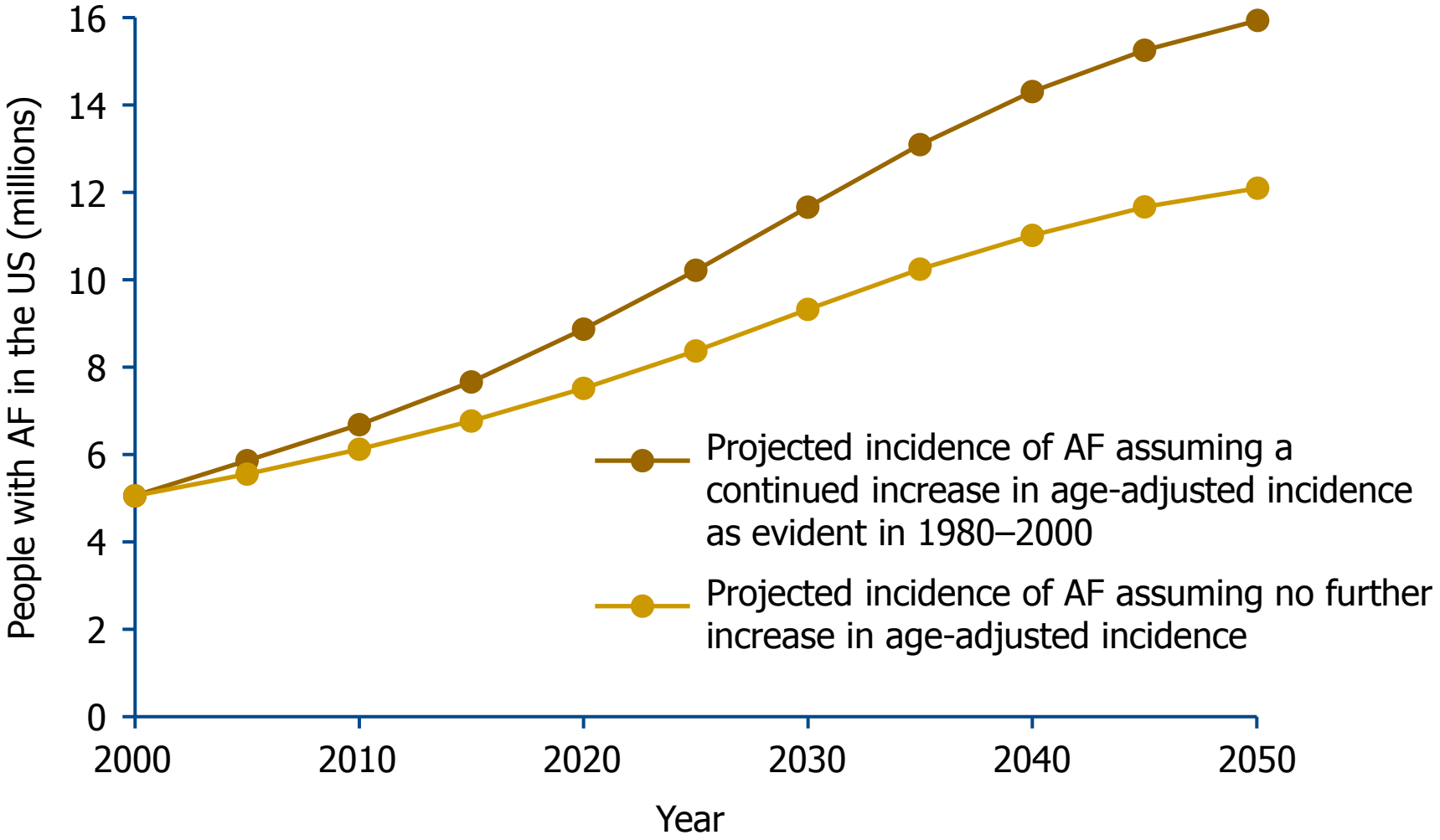
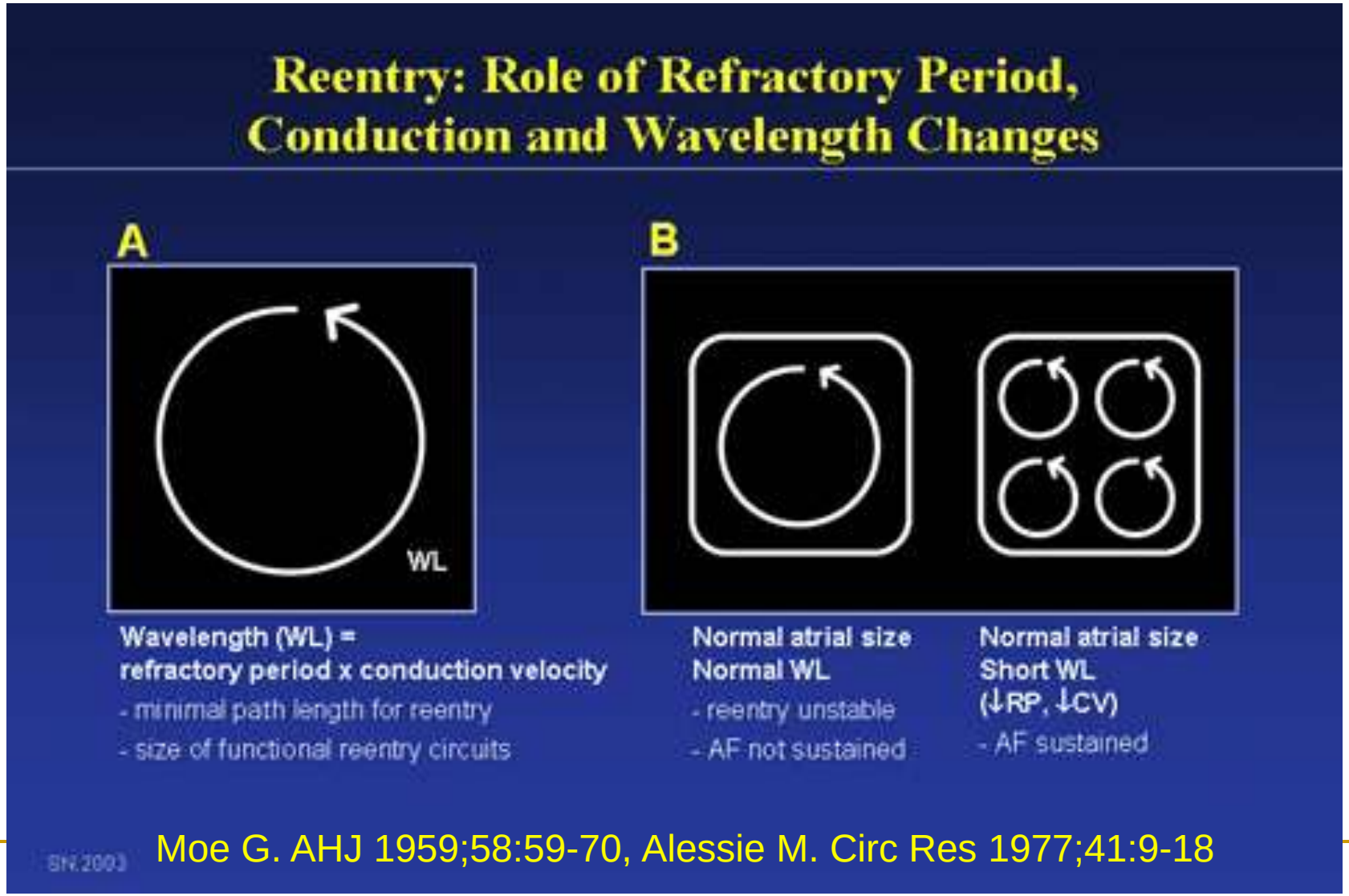
Prevalence of AF predicted to more than double by 2050



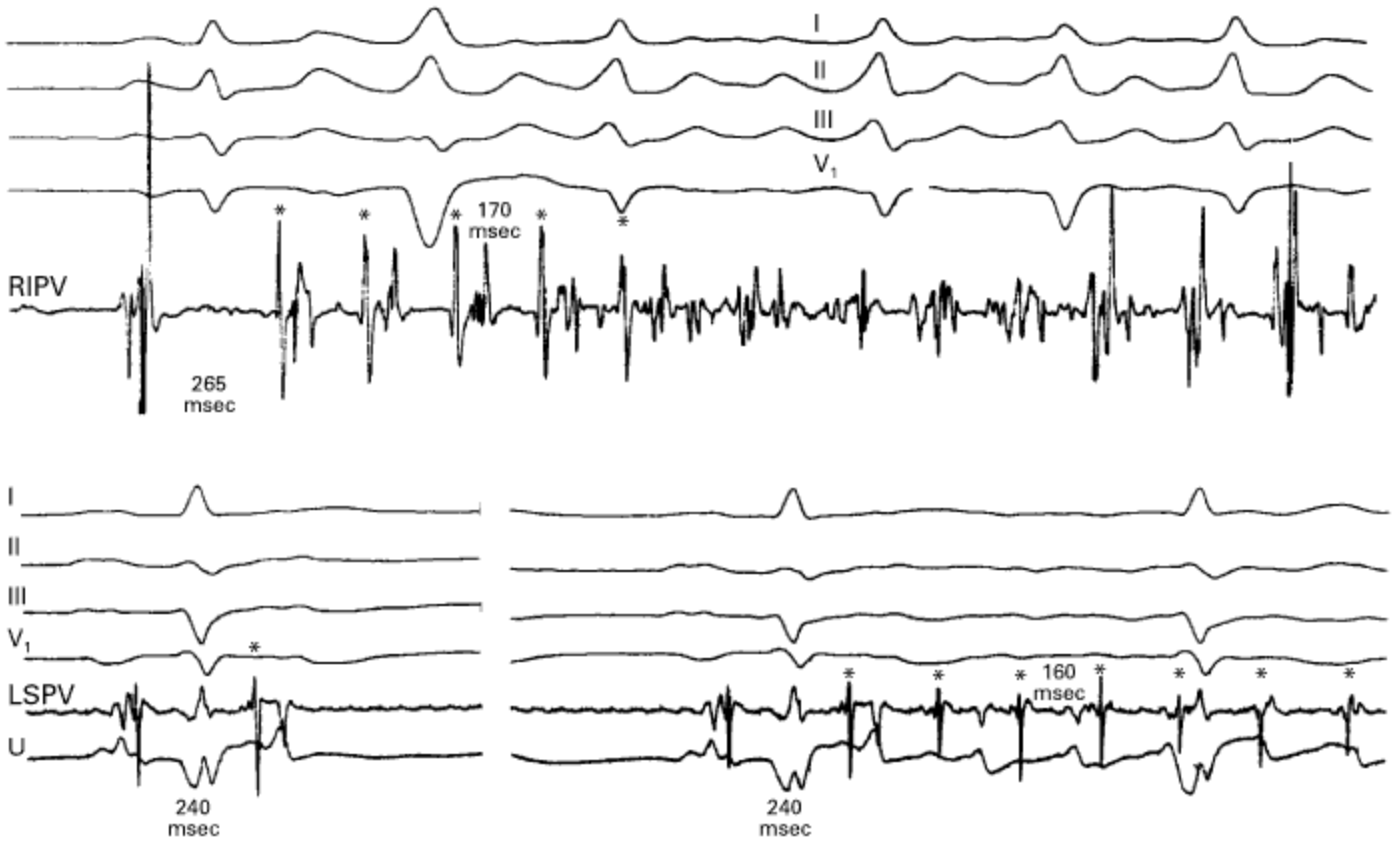
Miyasaka Y et al. Circulation 2006;114:119–25

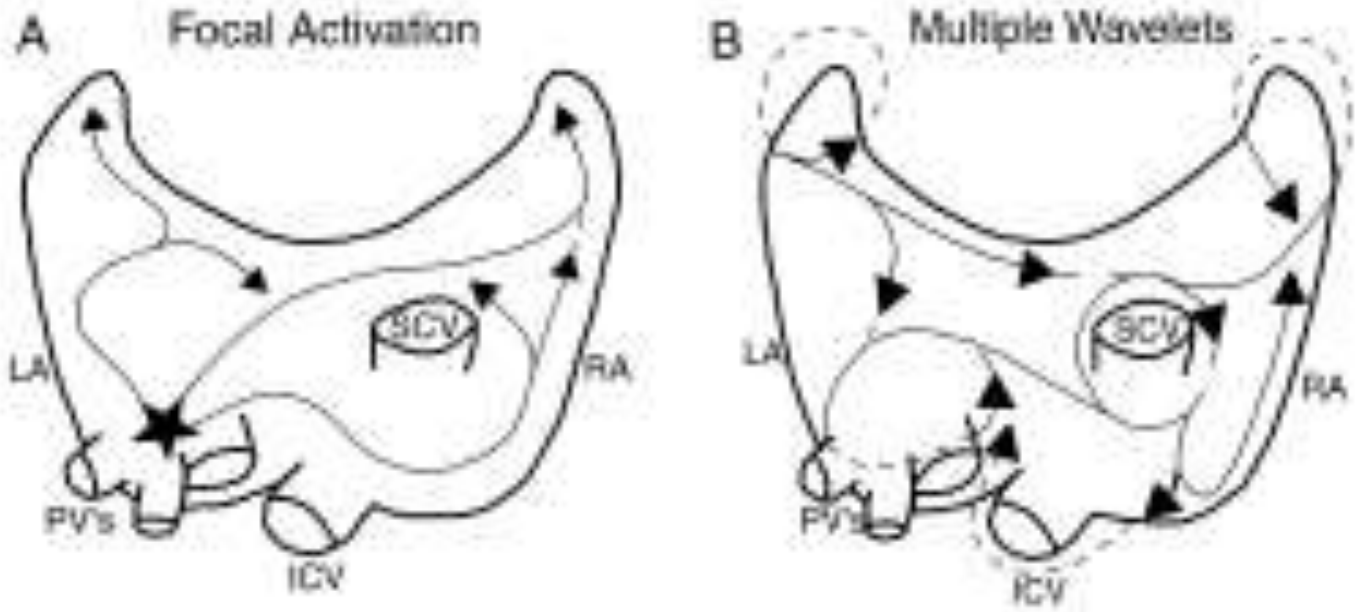
Leading circle- functional re-entry



Moe G. AHJ 1959;58:59-70, Alessie M. Circ Res 1977;41:9-18

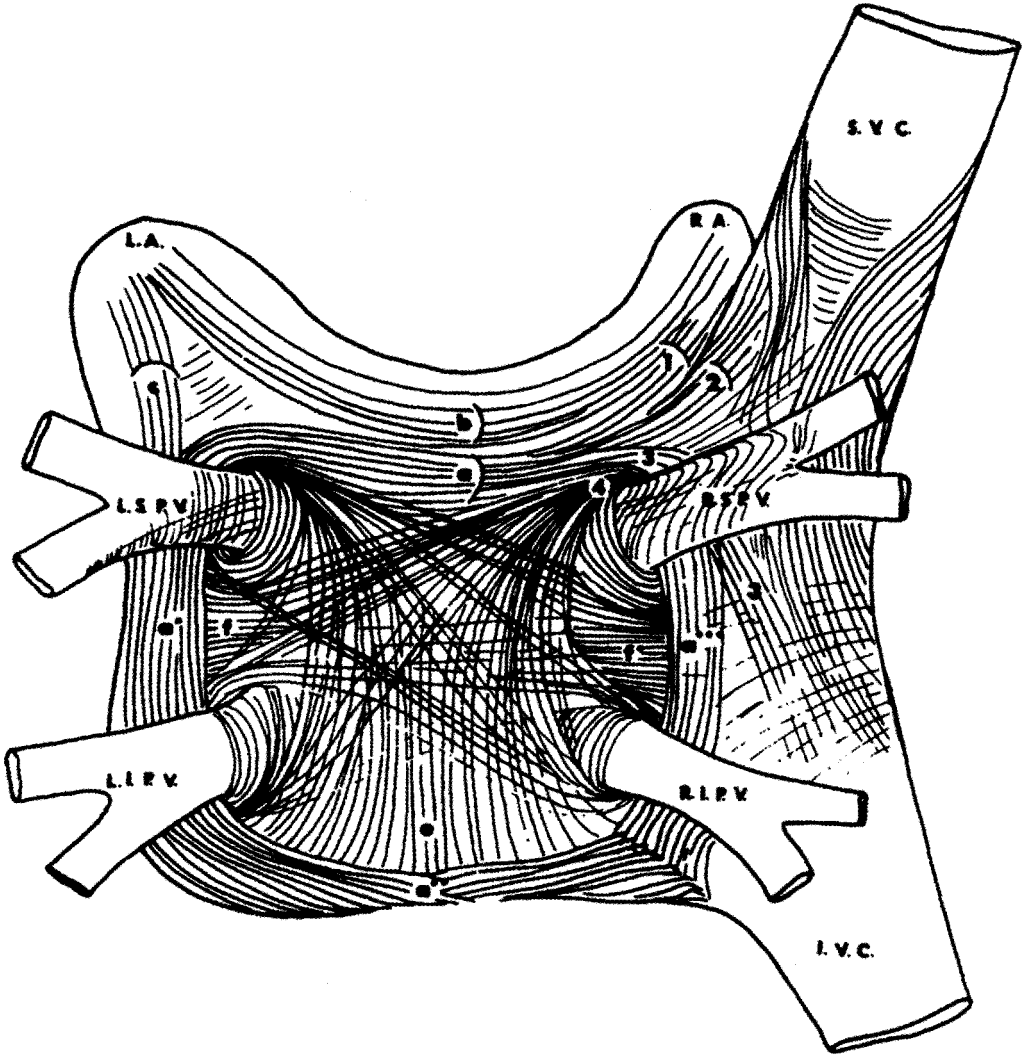
PAFib initiation



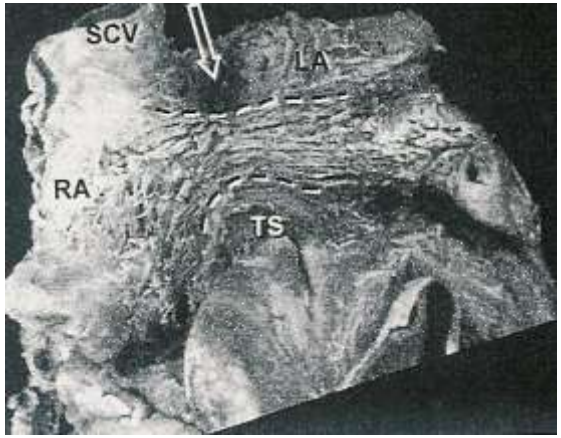

A
Focal Activation
SCV
LA
RA
PV's
ICV
B
Multiple Wavelets
SCV
LA
RA
PV's
ICV

Atrial musculature

Nathan and Eliakim. Circulation 1966

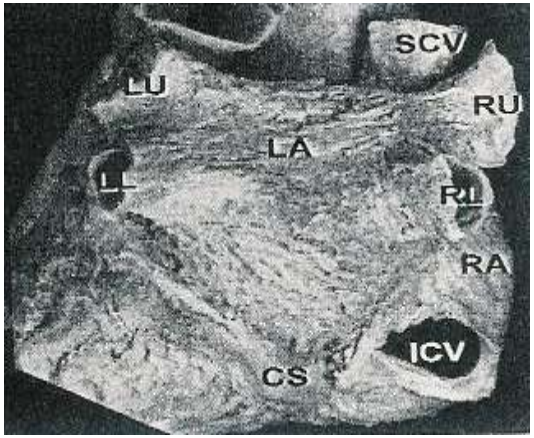


Anatomy



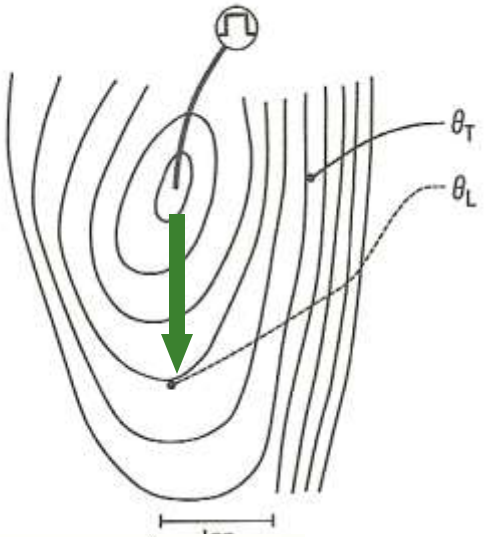
Bachmann's Bundlle

- Delayed conduction
- Block
- Inhomogeneous anisotropic conduction



Posterior interatrial connections

- Delayed conduction



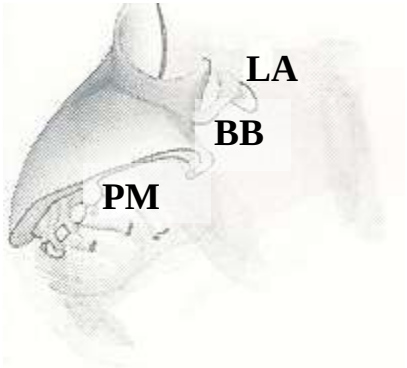
$\theta_L / \theta_T > 1$

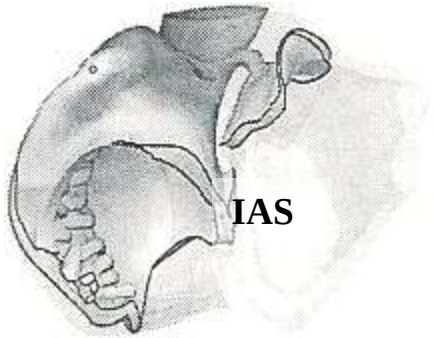
Anisotropic conduction

IASeptum

Anisotropic re-entry

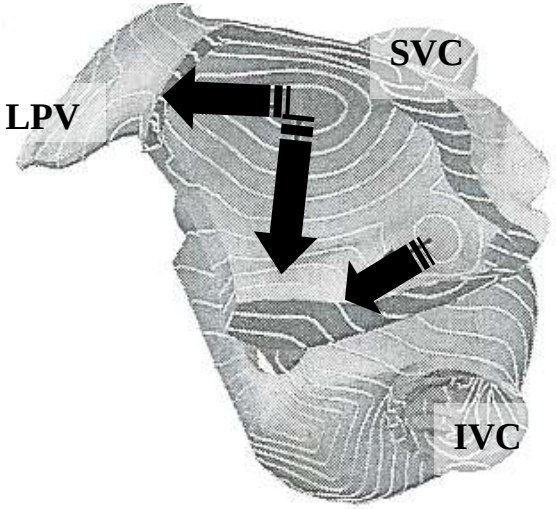
Intra-atrial septal activation





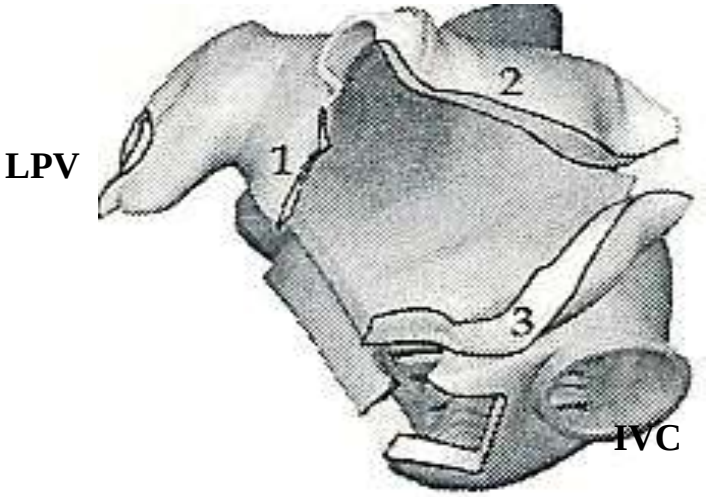
30 msec: left anterior IAAS activation through Bachmann's bunddle

51 msec: left anterior IAAS activation through foramen ovale

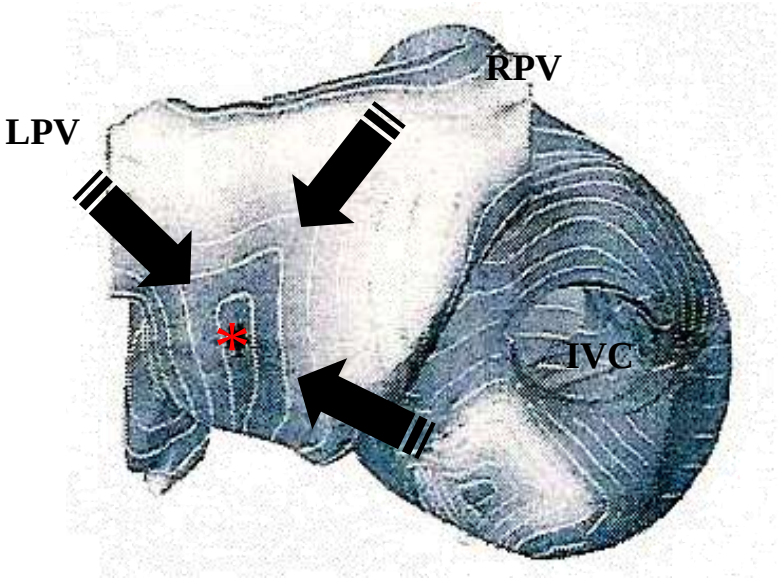


Left IAASeptum – left view. The double activation front. (Harrild et al, Circ Res 2000)

Postero-inferior left atrium



The 3 activation fronts



* Postero-inferior view - LA

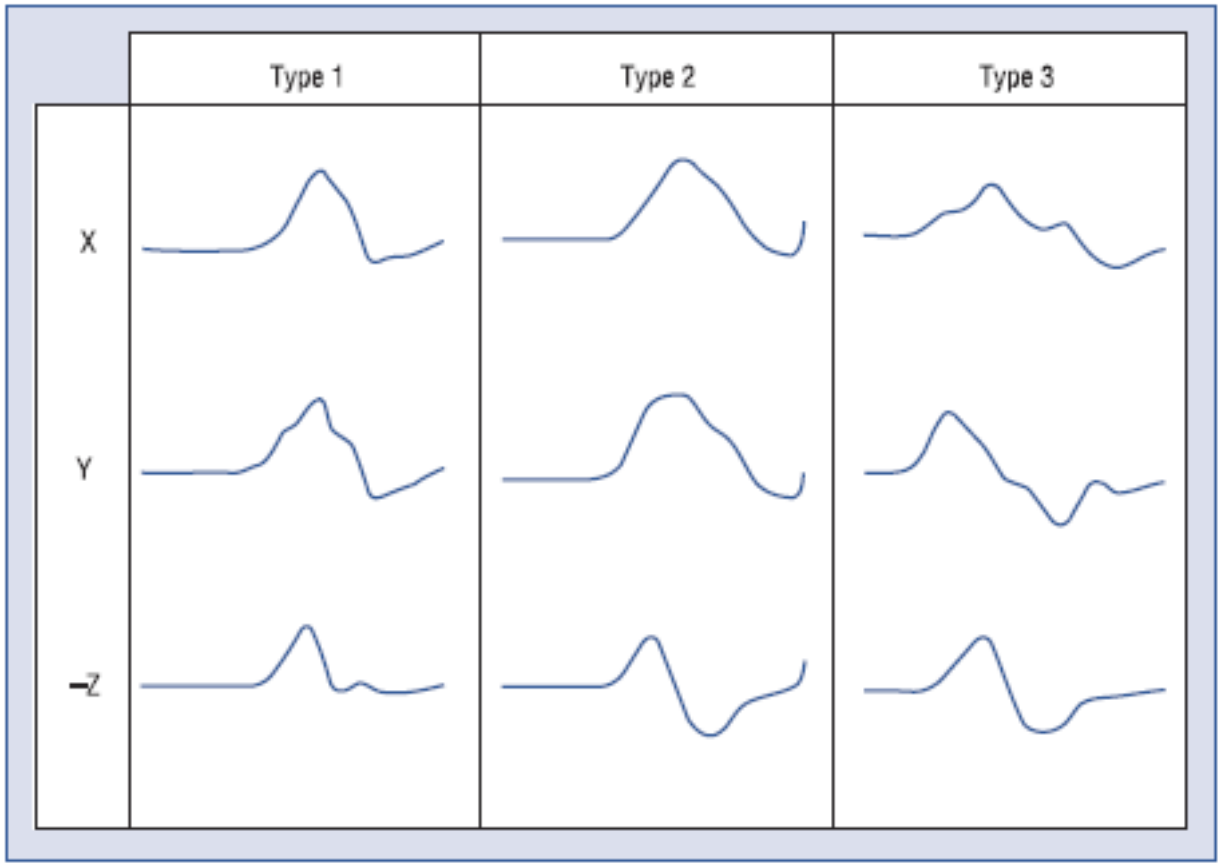
(Harrild et al, Circ Res 2000).

Non invasive methods

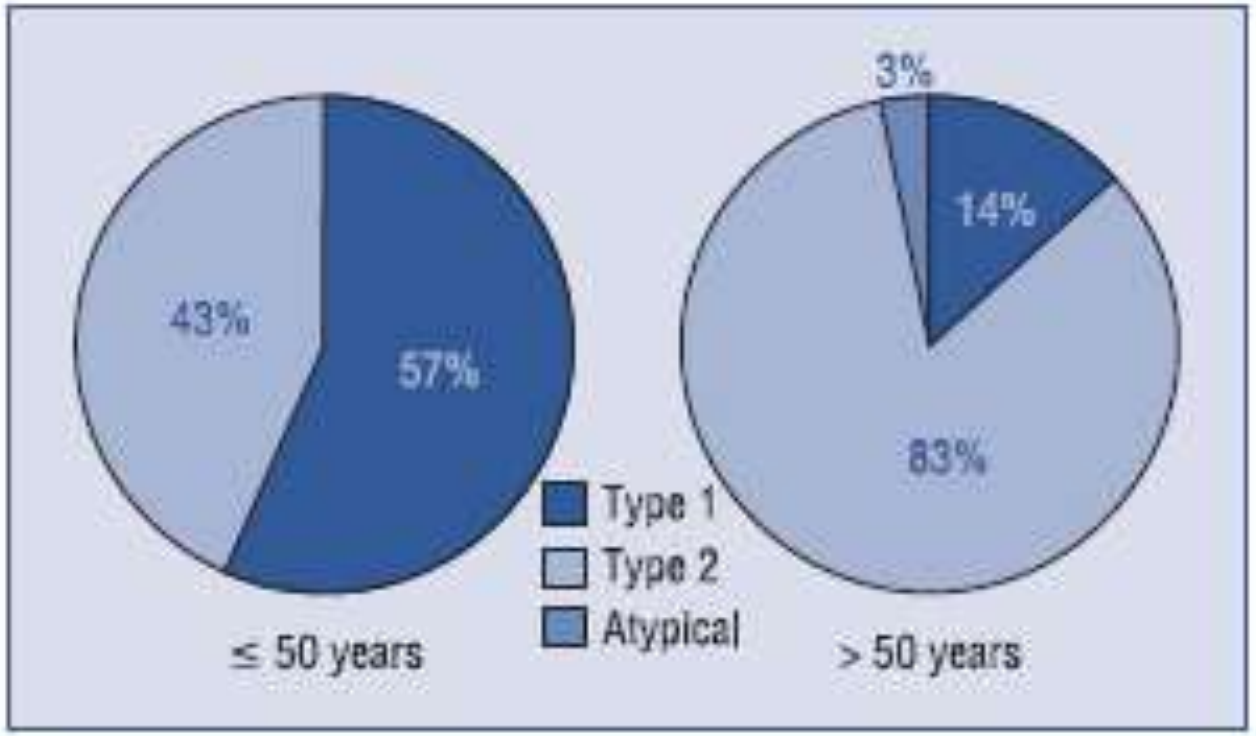
- P-wave duration
- P-wave dispersion
- P-wave SAECG
- P-wave wavelet analysis

normal

PAF **Adv IAA block**



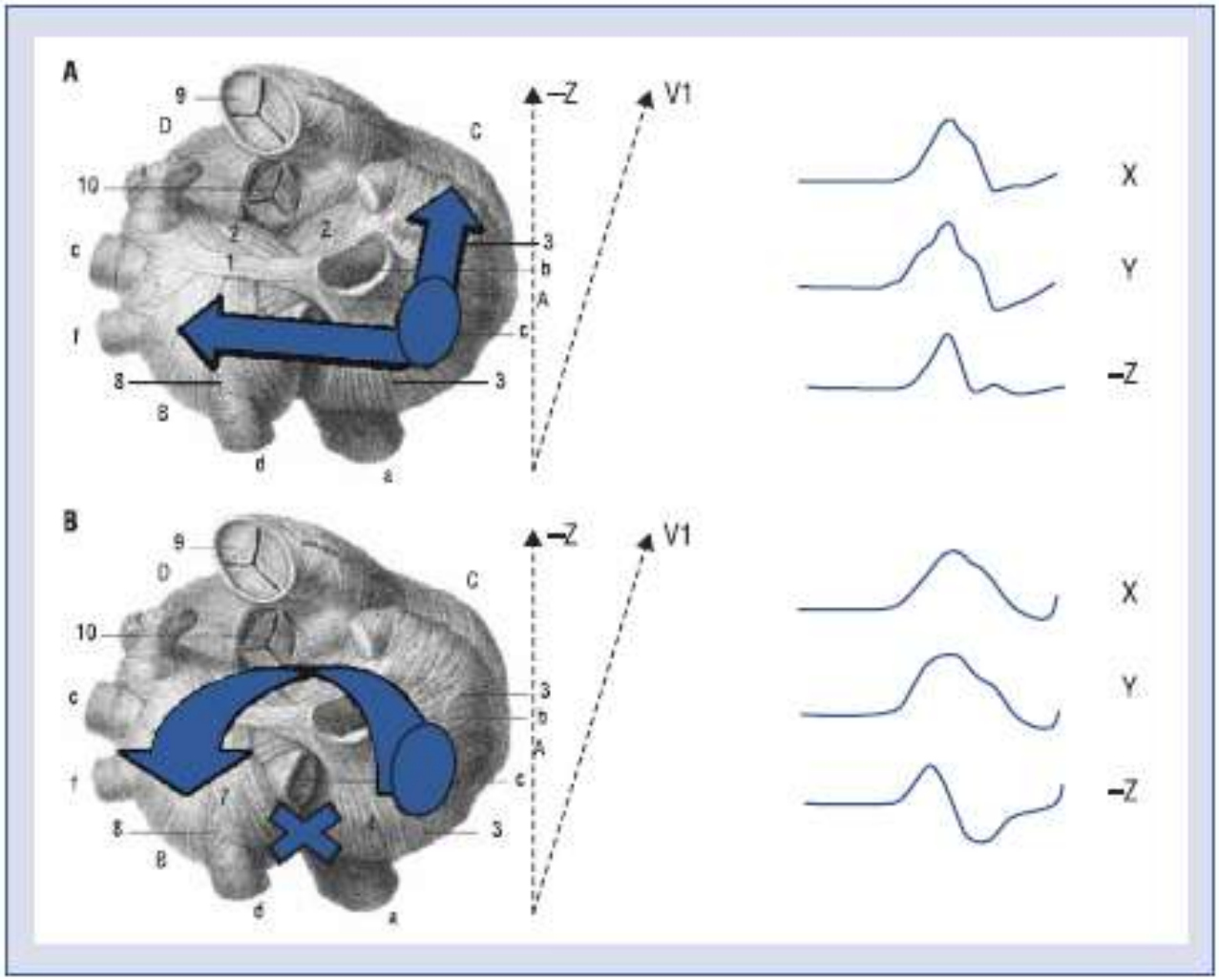
Platonov, Card J, 2008



Platonov, Card J, 2008

Posterior IAA connections

Bachmann's bundle



Holmqvist F et al. Ann Noninvasive Electrocardiol, 2007; 12: 227–236

- Time-domain analysis
- Frequency-domain analysis
- Time-frequency domain analysis

Prediction of atrial fibrillation in patients with cardiac dysfunctions†

P wave signal-averaged ECG and chemoreflexsensitivity in atrial fibrillation

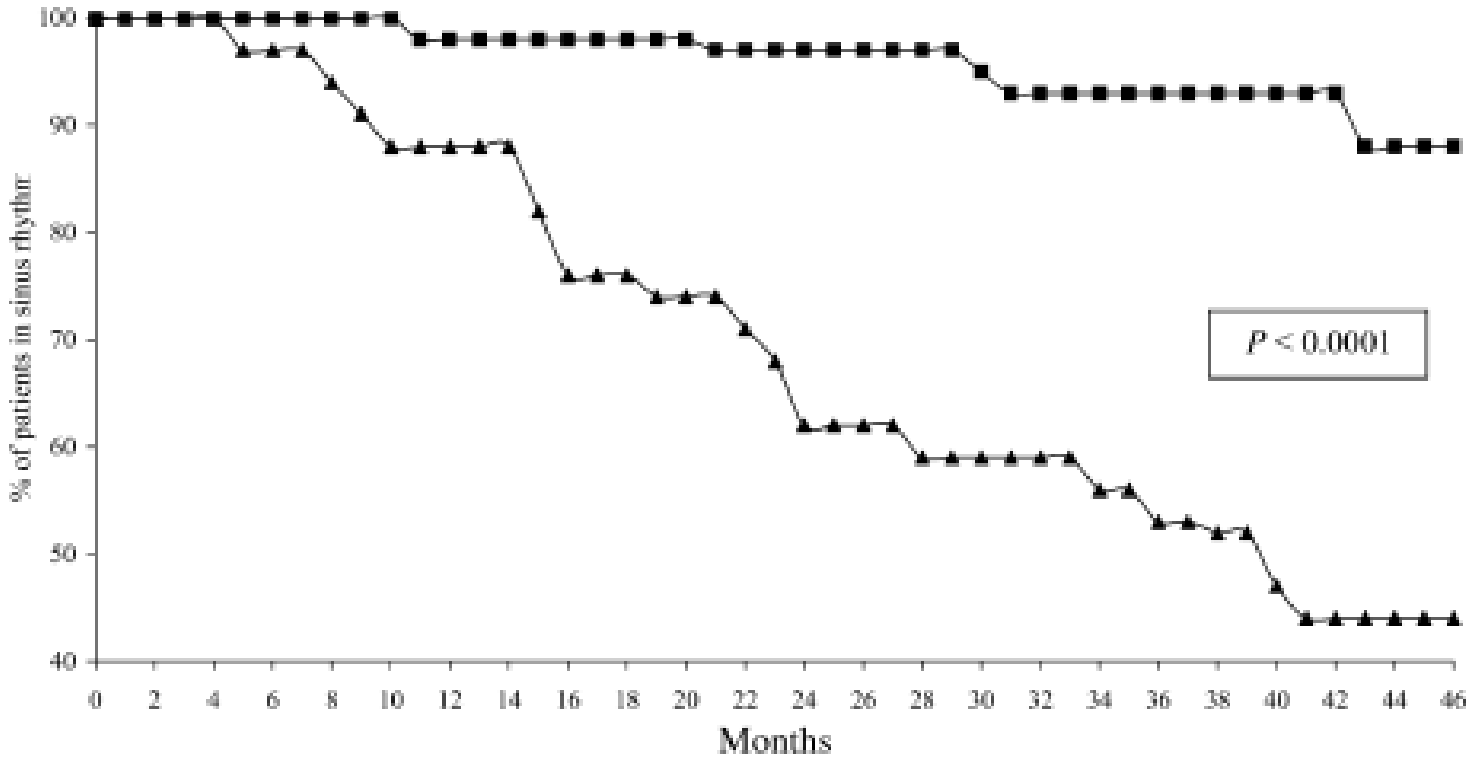
Table 4 Univariate and multivariate predictors of atrial fibrillation

	Univariate			Multivariate		
	OR	95% CI	*P*-value	OR	95% CI	*P*-value
FPD ≥125 ms and RMS 20 ≤3.3 μV	9.63	4.23–21.91	<0.0001	18.71	4.85–72.16	<0.0001
Ejection fraction ≤20%	2.43	1.14–5.18	0.022	6.60	1.42–30.62	0.02
Left atrial size ≥44 mm	3.72	1.68–8.23	0.001	1.90	0.55–6.63	0.32

FPD, filtered P wave duration; RMS 20, root mean square voltage of the last 20 ms of the P wave.

Budeous et al EuroPace 2007

Afib occurrence (FPD>125ms and RMS 20<3.3µV



Budeous et al EuroPace 2007

Prediction of atrial fibrillation in patients with cardiac dysfunctions†

P wave signal-averaged ECG and chemoreflexsensitivity in atrial fibrillation

Table 2 Predictive values of the measurements of P-SAECG and echocardiography

	Specificity	Sensitivity	PPV	NPV	Accuracy
FPD ≥125 ms and RMS 20 ≤3.3 μV	77	79	54	92	78
CHRS ≤3.0 ms/mmHg	57	54	30	78	56
Left atrial size ≥44 mm	74	46	38	80	67
Ejection fraction ≤20%	86	38	47	80	73

NPV, negative predictive value; PPV, positive predictive value.

Budeous et al EuroPace 2007

- Wavelet analysis is a spectro-temporal technique which can reveal dynamic changes within each frequency band during the duration of the cardiac cycle length

Morlet transformation wavelet

$$W(u,a)=\frac{1}{\sqrt{a}}\int f(t)^{*}\varphi(\frac{t-u}{a})dt \ , \ \varphi(t)=\frac{1}{\sqrt{2\pi}\sigma}e^{-j\omega t}e^{-t^{2}/2\sigma^{2}}$$

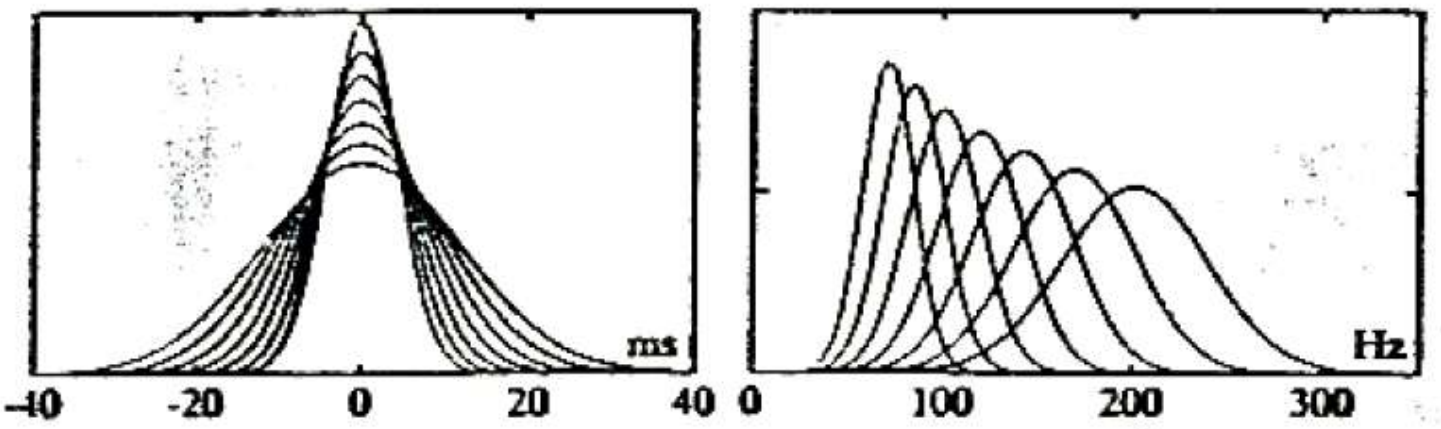
where φ(t) is the Morlet mother wavelet

a: scale, u: time

Short time Fourier analysis (STFT) vs Wavelet analysis Window used for the signal analysis

- Constant window for all frequencies
- Inverse relation between time – frequency

- Dynamic window (analyzed wavelet)
- Time (window width-time)
- Scale (frequency amplitude)
- Best application for temporary signals which transform during time, i.e. ECG


ms
-40
-20
0
20
40
Hz
0
100
200
300

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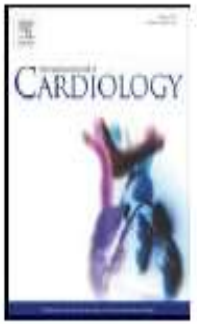


Novel non-invasive P wave analysis for the prediction of paroxysmal atrial fibrillation recurrences in patients without structural heart disease
A prospective pilot study

Vassilios Vassilikos [a], George Dakos [a], Yiannis S. Chatzizisis [a,*], Ioanna Chouvarda [b], Charalambos Karvounis [a], Charles Maynard [c], Nicos Maglaveras [b], Stylianos Paraskevaidis [a], George Stavropoulos [a], Charalambos I. Styliadis [a], Sotirios Mochlas [a], Ioannis Styliadis [a]

[a] 1st Cardiology Department, AHEPA University Hospital, Aristotle University Medical School, Thessaloniki, Greece
[b] Medical Informatics Laboratory, AHEPA University Hospital, Aristotle University Medical School, Thessaloniki, Greece
[c] Department of Health Services, University of Washington, Seattle, WA, United States

Materials and methods

- Standard 12 lead ECG
- Echocardiogram
- P wave wavelet analysis with the Morlet wavelet during sinus rhythm

Materials and methods

- Morlet wavelet analysis:

  3 channel digital recorder

  Frank orthogonal leads X, Y, Z

  Sampling frequency of 1000Hz

- The **vector magnitude** was calculated:

$$VM=\sqrt{X^2+Y^2+Z^2}$$

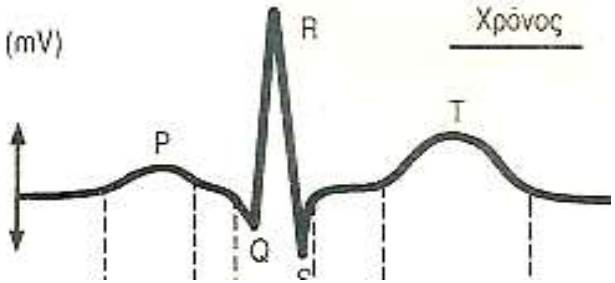
- Custom made software for wavelet signal decomposition

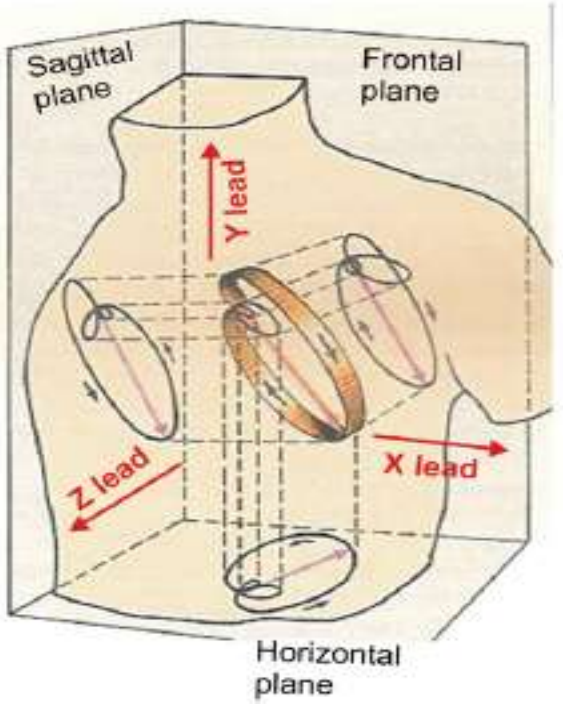
Wavelet parameters

- ***Mean energy (MN)*** which corresponds to the area under the spectral curve during the P wave

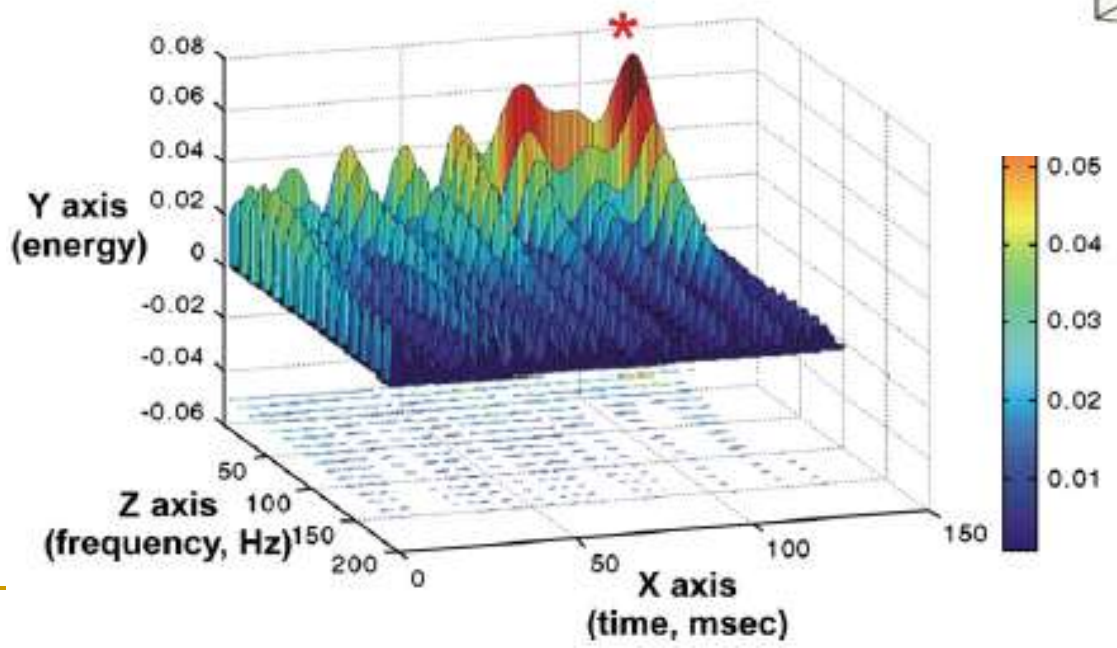
$$Ea = \sum_{i=beg}^{end} W(i,a) * W(i,a)$$

- The ***Maxima (MX)*** corresponding at the global maximum energy of the spectral curve under the P wave
- MN and MX were calculated in three frequency bands (200-160Hz [1], 150-100Hz [2], 90-50Hz [3])





P wave wavelet analysis



Methods

- Group A (<5 AF episodes/year)
- Group B (>5 AF episodes/year)
- Group C (Normal controls)

Echo parameters

Echocardiographic parameters of the study subjects at baseline.

	Group A ($n=33$, <5 episodes/year)	Group B ($n=17$, >5 episodes/year)	p	Groups A & B ($n=50$)	Group C ($n=50$, control)	p
Lald (cm)	4.98 ± 0.7	5.33 ± 0.3	0.055	5.09 ± 0.6	4.69 ± 0.6	**0.012**
Latd (cm)	2.91 ± 0.5	3.32 ± 0.7	0.026	3.04 ± 0.6	3.14 ± 0.5	0.510
Lals (cm)	4.24 ± 0.6	4.69 ± 0.5	**0.011**	4.39 ± 0.6	4.18 ± 0.6	0.170
Lats (cm)	2.36 ± 0.5	2.54 ± 0.6	0.193	2.39 ± 0.5	2.59 ± 0.5	0.130
LVDD (mm)	49.5 ± 4	49.3 ± 5	0.937	49.4 ± 4	46.5 ± 5	**0.019**
LVSD (mm)	28.5 ± 7	28.4 ± 10	0.207	28.4 ± 7	28.1 ± 7	0.380
EF (%)	66 ± 3	66 ± 3	0.656	66 ± 3	65 ± 5	0.160

Values are presented as mean ± SD. Lald: left atrial longitudinal diameter in end-diastole, Latd: left atrial transverse diameter in end-diastole, Lals: left atrial longitudinal diameter in end-systole, Lats: left atrial transverse diameter in end-systole, LVDD: left ventricular diastolic dimension, LVSD: left ventricular systolic dimension, EF: ejection fraction.

P wave at baseline

P wave duration at baseline.

	Group A ($n=33$, <5 episodes/year)	Group B ($n=17$, >5 episodes/year)	p	Groups A & B ($n=50$)	Group C ($n=50$, control)	p
PdurX (msec)	70±8	71±18	0.801	70.4±12	70.7±12	0.870
PdurY (msec)	81.6±13	88.1±14	0.117	83.8±14	80±12	0.130
PdurZ (msec)	85.8±13	87.7±13	0.630	86.4±13	71.5±15	**<0.001**
PdurVM (msec)	88.4±14	91.2±11	0.425	89.3±13	81.8±15	**0.008**

Pdur: P wave duration, X: X lead, Y: Y lead, Z: Z lead, VM: vector magnitude.

Mean and Max P wave energy

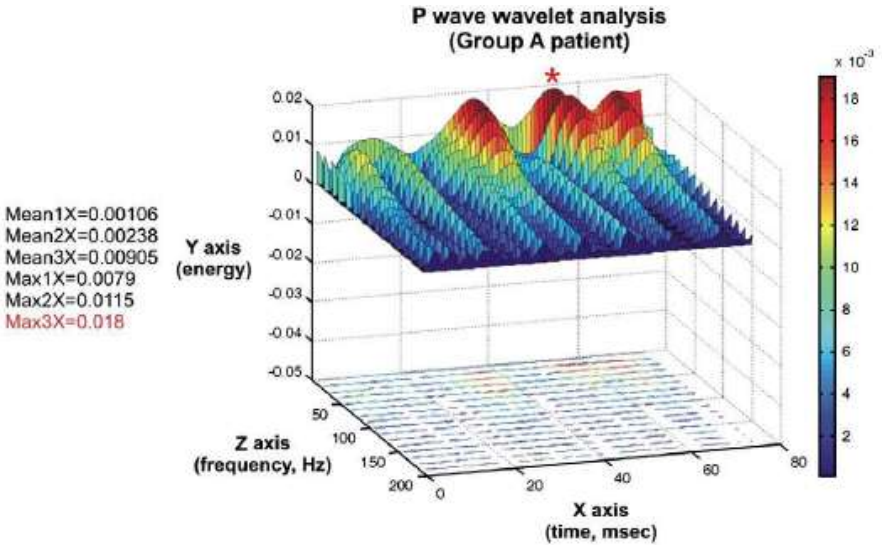
Mean and maximum P wave energy values at baseline.

	Group A ($n=33$, <5 episodes/year)	Group B ($n=17$, >5 episodes/year)	p	Groups A & B ($n=50$)	Group C ($n=50$, control)	p
Mean1X	1.55 ± 1	2.07 ± 0.9	0.081	1.73 ± 0.9	2.16 ± 1.2	0.059
Mean2X	3.18 ± 1.9	4.31 ± 2.1	0.077	3.56 ± 2.1	4.68 ± 2.6	0.020
Mean3X	14.1 ± 7.3	17.7 ± 17.2	0.309	15.3 ± 11.6	24.2 ± 15.7	**0.002**
Max1X	8.96 ± 2.9	11.1 ± 2.5	**0.013**	9.7 ± 2.9	10.8 ± 3.2	0.090
Max2X	12.3 ± 3.3	14.5 ± 3.5	0.041	13.1 ± 3.5	15 ± 4.3	0.020
Max3X	22.5 ± 5.9	27.7 ± 6.9	**0.014**	24.3 ± 6.7	29.3 ± 9.5	**0.003**
Mean1Y	2.25 ± 1.3	2.59 ± 1.8	0.503	2.36 ± 1.5	2.35 ± 1.4	0.960
Mean2Y	4.86 ± 2.9	5.67 ± 4.2	0.481	5.14 ± 3.4	5.34 ± 3.3	0.760
Mean3Y	27.8 ± 15.1	23.2 ± 17.2	0.337	26.2 ± 15.8	30.9 ± 23.1	0.240
Max1Y	10.5 ± 3.3	10.8 ± 4	0.721	10.6 ± 3.5	10.7 ± 3	0.890
Max2Y	14.6 ± 4.8	15.2 ± 6.7	0.772	14.8 ± 5.5	15.2 ± 4.3	0.690
Max3Y	29.7 ± 9	26.2 ± 10.2	0.223	28.5 ± 9.5	31.6 ± 10.3	0.120
Mean1Z	3.02 ± 2.2	3.58 ± 1.8	0.376	3.2 ± 2.1	2.09 ± 1.1	**0.001**
Mean2Z	7.39 ± 6.5	7.82 ± 4.3	0.808	7.54 ± 5.8	4.84 ± 2.9	**0.005**
Mean3Z	35.1 ± 21.9	44.6 ± 27.3	0.224	38.3 ± 24.1	27.9 ± 15.9	**0.012**
Max1Z	12.1 ± 3.9	13.2 ± 3.4	0.310	12.5 ± 3.8	10.5 ± 3	**0.005**
Max2Z	17.5 ± 5.8	18.5 ± 5.2	0.545	17.8 ± 5.6	15.2 ± 4.8	**0.013**
Max3Z	34.5 ± 10.4	38.7 ± 11.5	0.203	36 ± 10.8	31.4 ± 9.9	0.031
Mean1VM	2.26 ± 0.5	2.73 ± 1.5	0.222	2.42 ± 0.9	2.11 ± 09	0.100
Mean2VM	4.4 ± 1.6	4.06 ± 2.1	0.532	4.29 ± 1.8	4.22 ± 1.9	0.090
Mean3VM	17.9 ± 6.9	16.9 ± 11.9	0.747	17.6 ± 8.8	19.8 ± 12.9	0.320
Max1VM	9.7 ± 1.4	10.7 ± 3.1	0.235	10 ± 2.1	9.88 ± 2.1	0.720
Max2VM	13.6 ± 2.8	14.9 ± 4.9	0.334	14 ± 3.7	13.5 ± 3.4	0.460
Max3VM	25.8 ± 5.9	26.8 ± 9.8	0.666	26.1 ± 7.4	26.1 ± 6.8	0.960

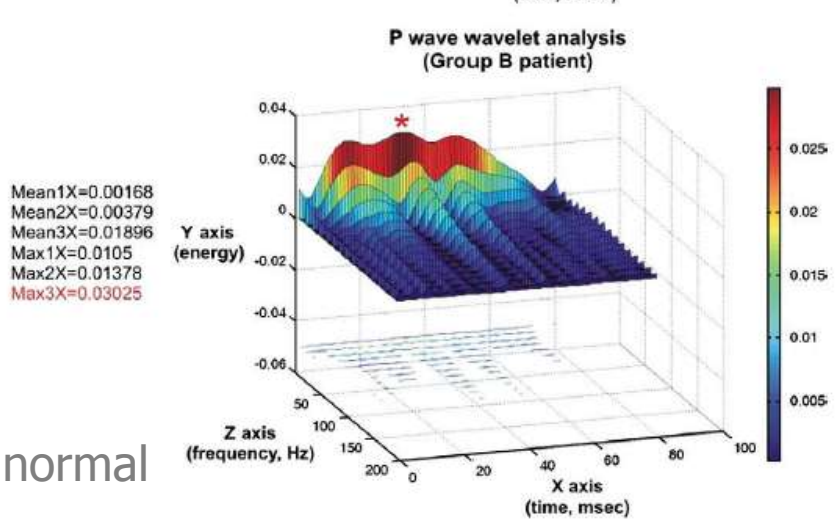
Mean1, 2 and 3: mean energy value in the 1st, 2nd and 3rd frequency band, respectively, Max 1, 2 and 3: maximum energy value in the 1st, 2nd and 3rd frequency band, respectively, X: X lead, Y: Y lead, Z: Z lead, VM: vector magnitude. Energies are expressed in μV^2.

Wavelets in the 3 groups

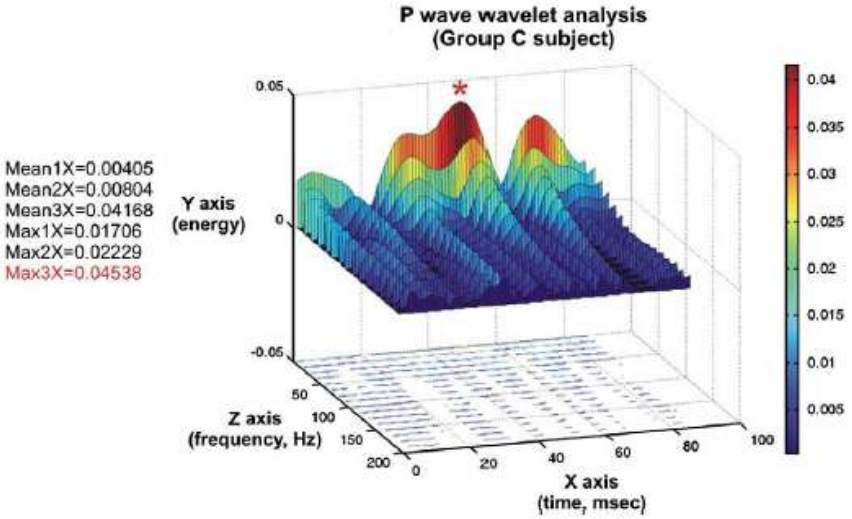
<5/year



>5/year



normal

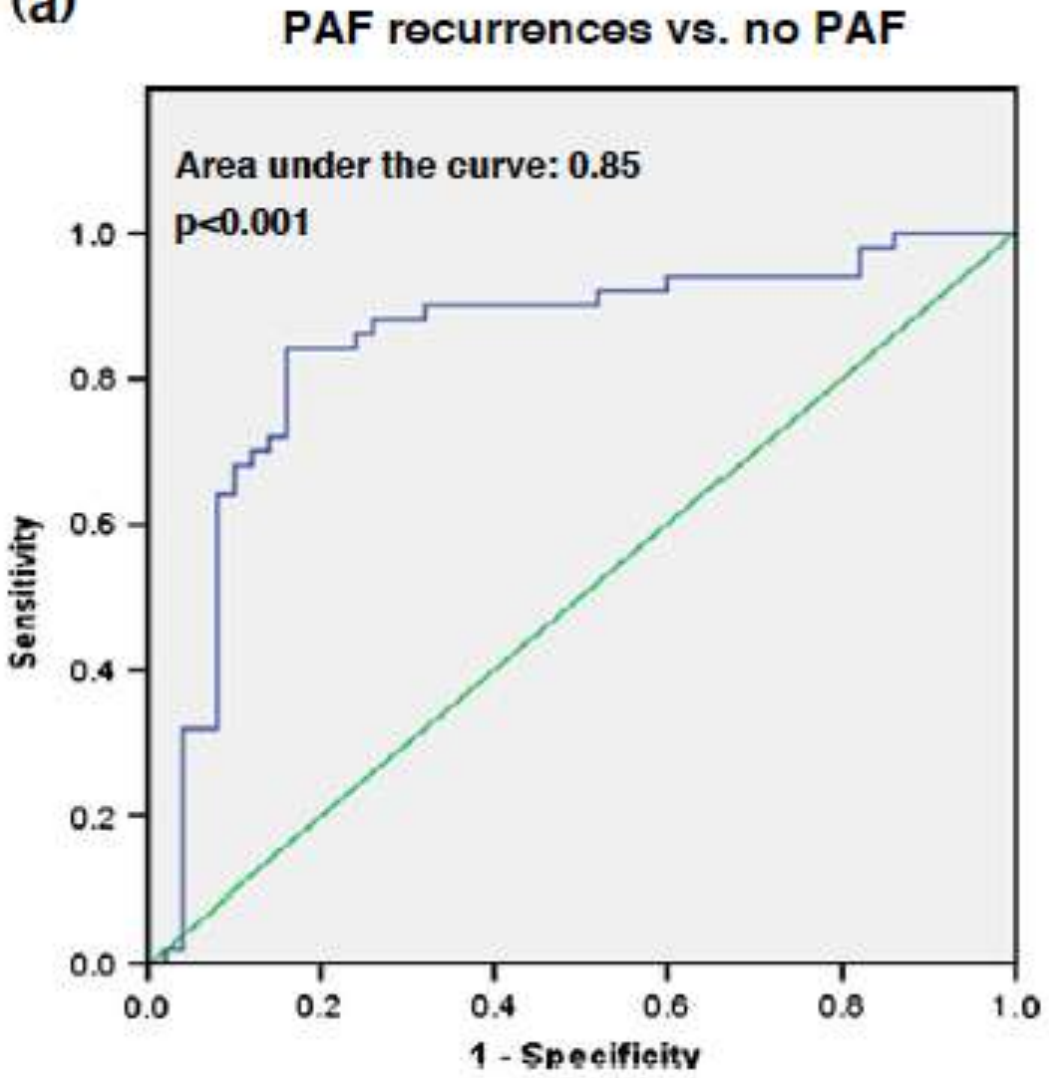


Logistic regression analysis for patients any number of PAF recurrences per year (Groups A and B) vs. healthy controls without history of PAF (Group C).

		B	SE	p
Step 1	PdurZ	76.892	17.563	<0.001
	Constant	−6.073	1.409	<0.001
Step 2	Mean3X	−66.93	22.567	**0.003**
	PdurZ	84.114	18.775	**<0.001**
	Constant	−5.361	1.460	<0.001

Mean3X: mean P wave energy at the 3rd frequency band in the X orthogonal lead, PdurZ: P wave duration in the Z lead.

(a)

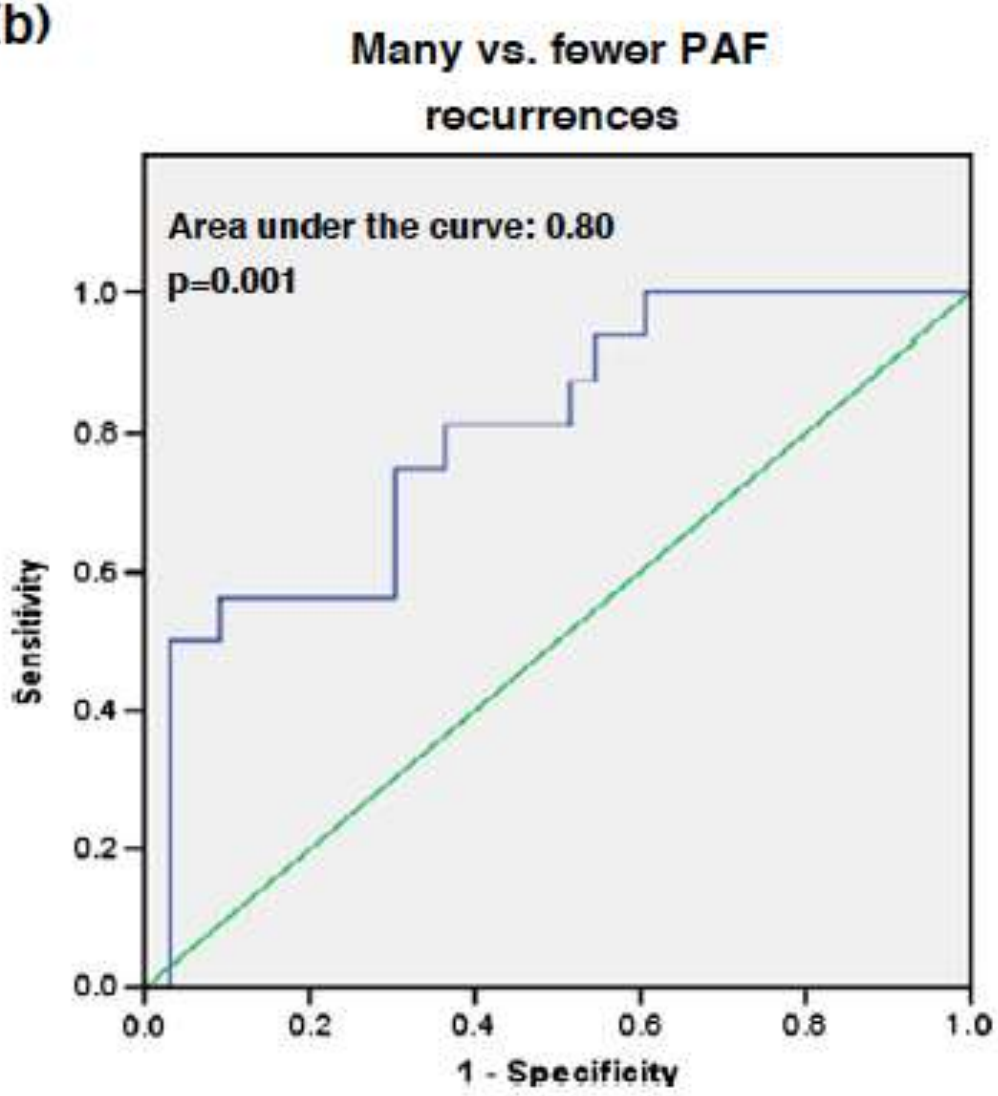

PAF recurrences vs. no PAF
Area under the curve: 0.85
p<0.001
Sensitivity
1 - Specificity
0.0
0.2
0.4
0.6
0.8
1.0

Logistic regression analysis for PAF patients with more than five recurrences per year (Group B) vs. patients with less than five recurrences per year (Group A).

		B	SE	p
Step 1	Max1X	293.710	126.888	0.021
	Constant	−3.675	1.342	0.006
Step 2	Lals	1.551	0.678	**0.022**
	Max1X	308.018	139.925	**0.028**
	Constant	−10.80	3.651	0.003

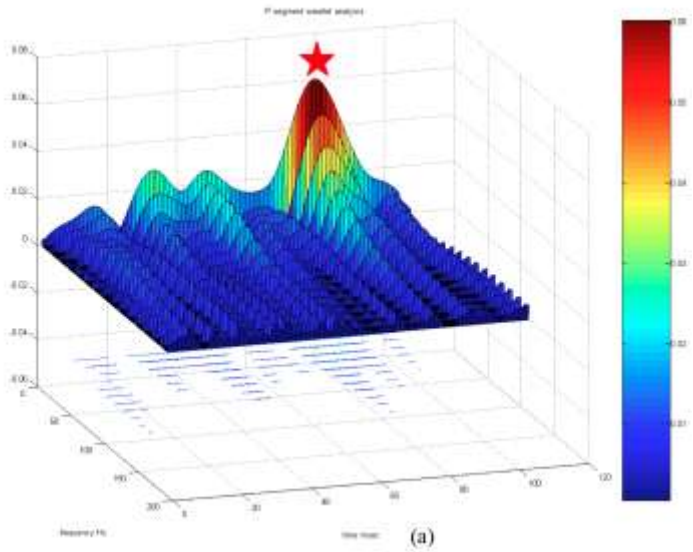
Max1X: maximum P wave energy at the 1st frequency band in the X orthogonal lead, Lals: left atrial longitudinal diameter in end-systole.

(b)

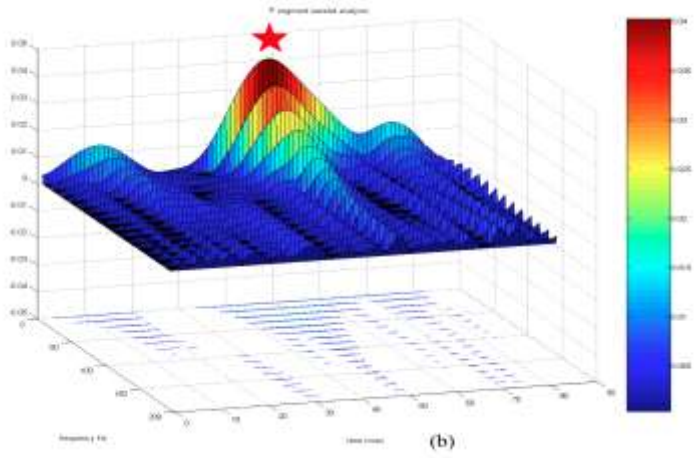

Many vs. fewer PAF recurrences
Area under the curve: 0.80
p=0.001
Sensitivity
1 - Specificity
0.0
0.2
0.4
0.6
0.8
1.0

Time-scale representations of the Morlet wavelet transform at Z axis

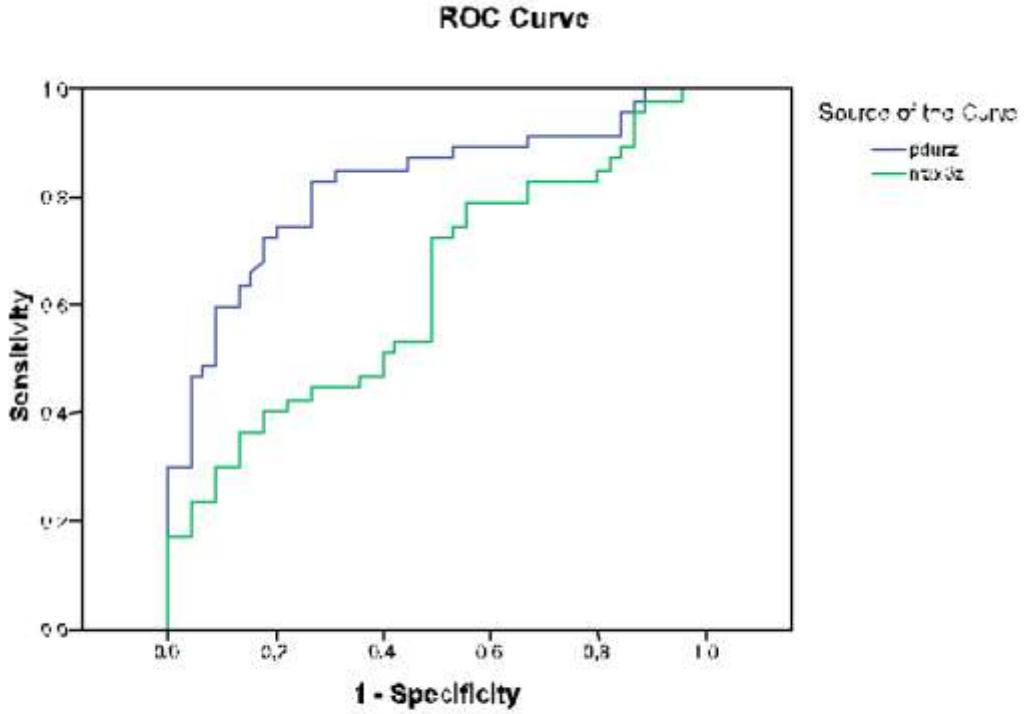
AF patient



Normal control



Dakos, Vassilikos et al. Unpublished data



	Area	SE	p
PdurZ	0.820	0.045	<0.001
Max3Z	0.627	0.058	0.035

Can P Wave Wavelet Analysis Predict Atrial Fibrillation After Coronary Artery Bypass Grafting?

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VASSILIKOS V., ET AL.: Can P Wave Wavelet Analysis Predict Atrial Fibrillation After Coronary Artery Bypass Grafting? *The purpose of this study was the evaluation of Morlet wavelet analysis of the P wave as a means of predicting the development of atrial fibrillation (AF) in patients who undergo coronary artery bypass grafting (CABG). The P wave was analyzed using the Morlet wavelet in 50 patients who underwent successful CABG. Group A consisted of 17 patients, 12 men and 5 women, of mean age 66.9 ± 5.9 years, who developed AF postoperatively. Group B consisted of 33 patients, 29 men and 4 women, mean age 62.4 ± 7.8 years, who remained arrhythmia-free. Using custom-designed software, P wave duration and wavelet parameters expressing the mean and maximum energy of the P wave were calculated from 3-channel digital recordings derived from orthogonal ECG leads (X, Y, and Z), and the vector magnitude (VM) was determined in each of 3 frequency bands (200–160 Hz, 150–100 Hz and 90–50 Hz). Univariate logistic-regression analysis identified a history of hypertension, the mean and maximum energies in all frequency bands along the Z axis, the mean and maximum energies (expressed by the VM) in the 200–160 Hz frequency band, and the mean energy in the 150–100 Hz frequency band along the Y axis as predictors for post-CABG AF. Multivariate analysis identified hypertension, ejection fraction, and the maximum energies in the 90–50 Hz frequency band along the Z and composite-vector axes as independent predictors. This multivariate model had a sensitivity of 91% and a specificity of 65%. We conclude that the Morlet wavelet analysis of the P wave is a very sensitive method of identifying patients who are likely to develop AF after CABG. The occurrence of post-CABG AF can be explained by a different activation pattern along the Z axis. (PACE 2003; 26[Pt. II]:305–309)*

CABG patients

Table I.

Patient Demographic and Clinical Data

	Group A	Group B	p
N	17	33	
Age (years ± SD)	66.9 ± 5.8	62.4 ± 7.8	0.059
Male sex	12	29	0.141
Previous MI	13	22	0.468
Hypertension	16	23	0.032
DM	4	12	0.350
Past AF	1	1	0.635
Beta-blocker	8	23	0.120
ACEI	8	16	0.924
Calcium antagonist	7	16	0.623
Digoxin	2	1	0.234
Diuretic	5	5	0.242
LA (mm ± SD)	41.5 ± 3.2	39 ± 6.1	0.306
LVDD (mm ± SD)	57.7 ± 6.9	57.8 ± 6.2	0.946
EF (% ± SD)	56 ± 12	49 ± 14	0.064
CBP time (min ± SD)	112 ± 68	82 ± 44	0.251
Clamp time (min ± SD)	65 ± 41	43 ± 28	0.181

MI = myocardial infarction, DM = diabetes mellitus, AF = atrial fibrillation, ACEI = angiotensin-converting enzyme inhibitor, LA = left atrium, LVDD = left ventricular diastolic dimension, EF = ejection fraction, CBP = cardiopulmonary bypass, SD = standard deviation.

Vassilikos, Dakos et al, PACE, 2003

CABG patients

Table II.

Univariate Associates with the Risk of Developing Atrial Fibrillation

	Group A	Group B	p
MEAN2-Y	3.4781	5.5107	0.028
PZ	86.4510	78.4628	0.081
MEAN1-Z	1.7711	1.2446	0.038
MEAN2-Z	3.6416	2.2511	0.003
MEAN3-Z	18.9990	12.4711	0.001
MAX1-Z	9.5439	7.6656	0.002
MAX2-Z	12.9006	10.6525	0.003
MAX3-Z	26.8923	20.4865	0.000
MEAN1-VM	1.8837	1.4869	0.035
MAX1-VM	8.5511	7.6898	0.022
MAX2-VM	11.4283	10.4926	0.074
MAX3-VM	21.5240	19.2208	0.067
Age (years)	66.9	62.4	0.073
HTN	16 (94%)	23 (70%)	0.043
EF (%)	56	49	0.071

Variables with p = 0.1 were included in the multivariate analysis.
MEAN1 = mean energy in the 200-160 Hz frequency band,
MEAN2 = mean energy in the 150-100 Hz frequency band,
MEAN3 = mean energy in the 90-50 Hz frequency band,
MAX1 = maximum energy in the 200-160 Hz frequency band,
MAX2 = maximum energy in the 150-100 Hz frequency band,
MAX3 = maximum energy in the 90-50 Hz frequency band,
Y = Y axis, Z = Z axis, VM = vector magnitude, PZ = P-wave duration on the Z axis, HTN = hypertension, EF = ejection fraction.

Vassilikos, Dakos et al, PACE, 2003

CABG patients

Table III.

Multivariate Model of the Most Significant Associates of Developing Postoperative Atrial Fibrillation

	P	Coefficient	S.E.
Model overall	<0.001		
MAX3-Z	0.006	0.434	0.159
MAX3-VM	0.066	0.293	0.160
HTN	0.014	4.232	1.721
EF	0.014	0.116	0.048

This model had a sensitivity of 91% and a specificity of 65%. MAX3-Z = maximum energy for the 90-50 Hz frequency band on the Z axis, MAX3-VM = maximum energy for the 90-50 Hz frequency band in vector magnitude, HTN = hypertension, EF = ejection fraction.

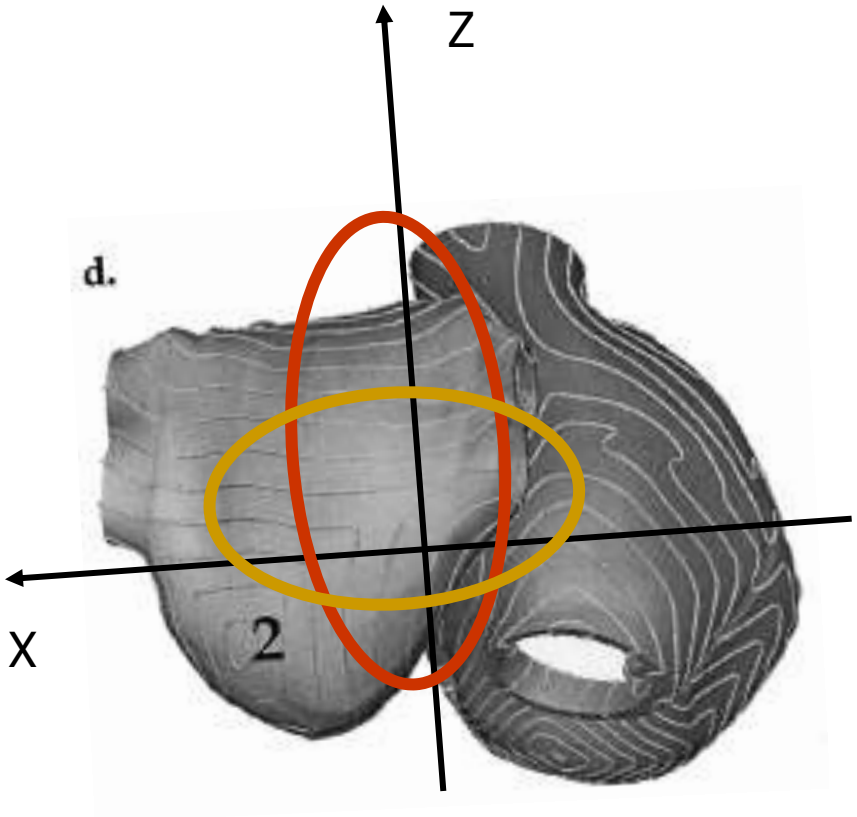
Vassilikos, Dakos et al, PACE, 2003

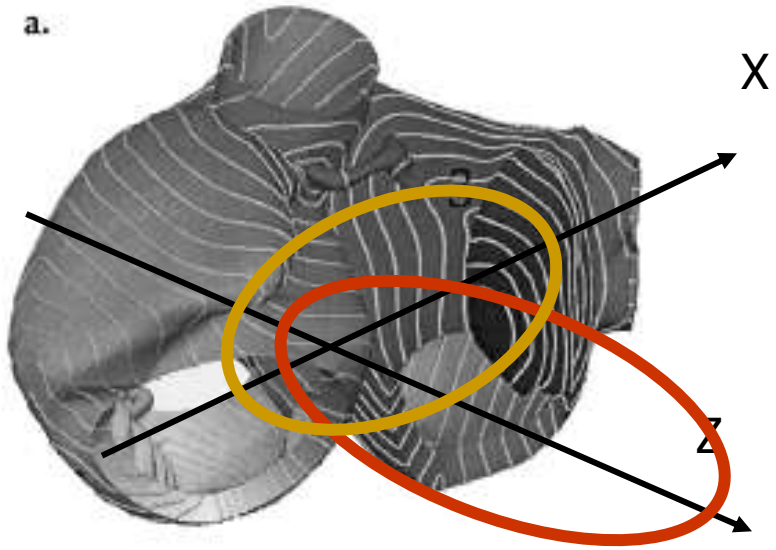
Conclusions

	Energy P wave	Duration P wave	Sn	Sp	TPV	PPV	NPV
PAF with <5/year	↓ X	↑ PdurZ PdurZ-X	76	83	80	80	80
PAF with >5/year	↑ Z	↑ PdurZ PdurZ-X	84	75	82	91	60
PAF post CABG	↑ Z,VM	↑ PdurZ	90	87	87	74	96

Postero-inferior

Antero-superior

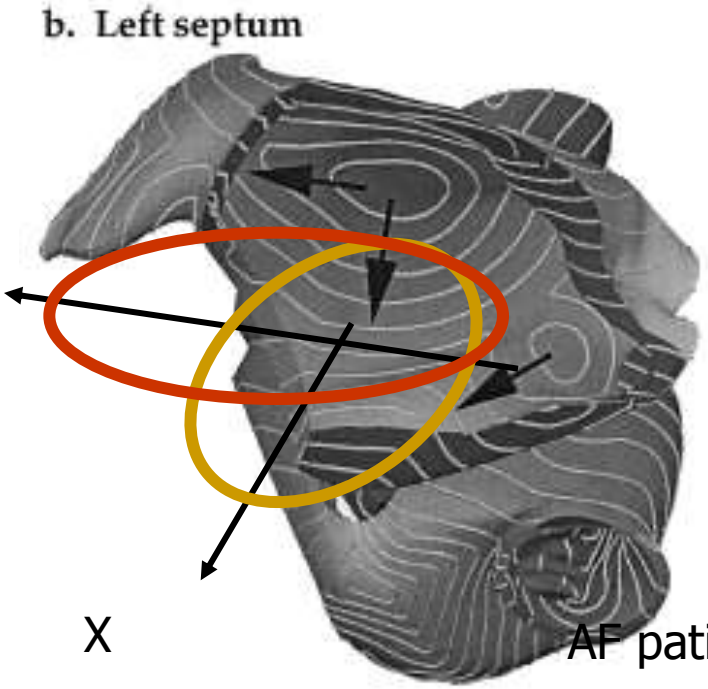




AF patients

Normal controls

Left septal activation



Anisotropic and slow conduction in IAAS

AF patients

Normal controls

Conclusions

- The P wave Morlet wavelet analysis in patients with PAF is indicative of a different activation along the postero-anterior direction.
- Anisotropic conduction and the possible presence of dispersion of refractoriness at the anterior and posterior-lower right atrium may explain this activation pattern.

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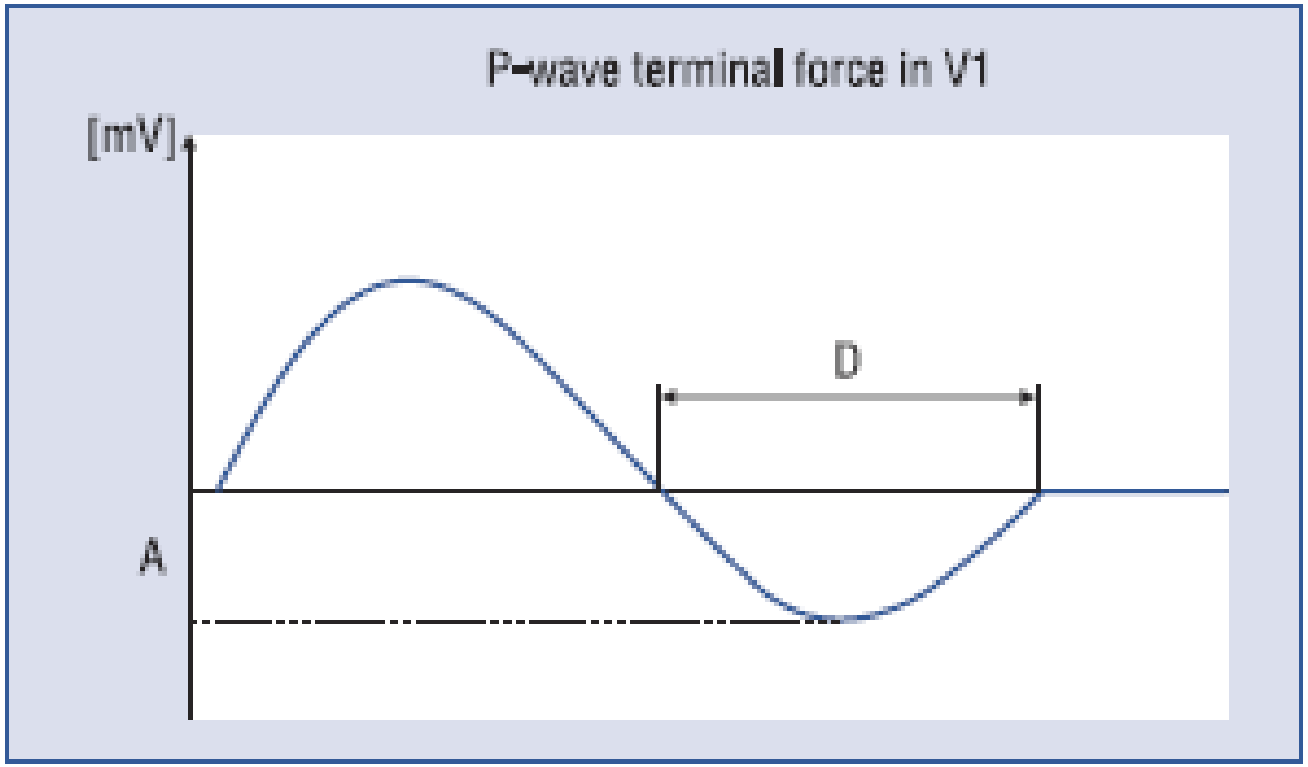
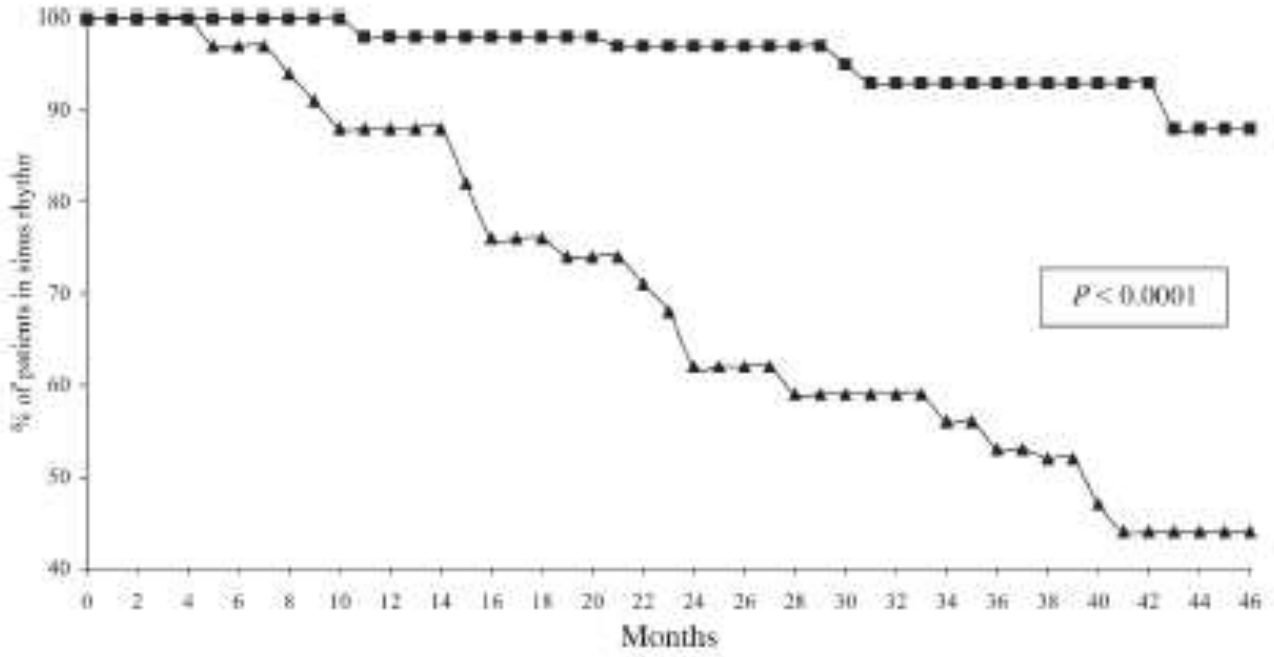


PTF > 0.04 mV . Ms has been found to be specific but less sensitive ECG marker of left atrial enlargement

Tsao et al J Cardiovasc Magn Res 2008

Prediction of atrial fibrillation in patients with cardiac dysfunctions†

P wave signal-averaged ECG and chemoreflexsensitivity in atrial fibrillation



Budeous et al EuroPace 2007

Logistic regression analysis Gr I vs Gr II

	B	**Std.Error**	**Wald**	**df**	**Sig.**
P dur Z	-74,721	21,415	12,174	1	**<0,001**
Mean2X	319,695	132,678	5,806	1	**0,016**
Mean1VM	-1291,463	584,412	6,181	1	**0,027**
Lalad	-1,159	0,567	4,179	1	**0,041**

Group with <5 episodes/year (Ia)
Group with >5 episodes/year (Ib)

	Group Ia (n=33)	**Group Ib (n=17)**	**p**
Lalad (cm)	4,98±0,7	5,43±0,3	**0,05**
Lasad(cm)	2,91±0,5	3,51±0,69	**0,006**
Lalas(cm)	4,24±0,6	4,85±0,56	**0,005**
Max3X (µV)	22,5±5,94	27,6±8,35	**0,037**
Mean2VM (µV)	4,4±1,63	3,05±1,78	**0,03**

Group with <5 episodes/year (Ia) Normal controls (II)

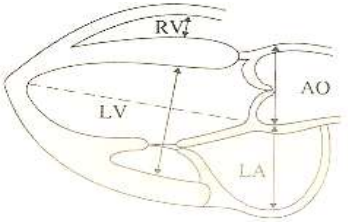
	Group Ia (n=33)	Group II (n=50)	p
Lapl(cm)	3,58±0,29	3,42±0,36	**0,046**
Lvdd(cm)	4,92±0,41	4,7±0,43	**0,037**
P dur Z(msec)	87,3±13	71,5±15	**<0,001**
P durVM(msec)	90,9±15	81,8±15	**0,005**
P dur Z-X(msec)	16,6±12	0,7±16	**<0,001**
Mean1X (µV)	1,48±0,9	2,16±1,2	**0,003**
Mean2X (µV)	3,23±1,9	4,68±2,6	**0,003**
Mean3X (µV)	17,2±14,2	24,2±15,7	**0,008**
Max1X (µV)	8,77±2,9	10,8±3,2	**0,003**
Max2X (µV)	12,3±3,4	15±4,3	**0,002**
Max3X (µV)	23,6±7,8	29,3±9,5	**0,003**
Mean2Z (µV)	7,14±6,1	4,84±2,9	**0,046**
Mean1VM(µV)	2,44±0,9	2,11±0,8	**0,028**

	R	R Square	Adj. R Square	Std.Error	R Square Change	F Change	df1	Sig. F Change
PdurZ-X	0,482	0,233	0,224	0,44	0,233	26,688	1	**0,000**
Max2X	0,566	0,321	0,305	0,42	0,088	11,260	1	**0,001**

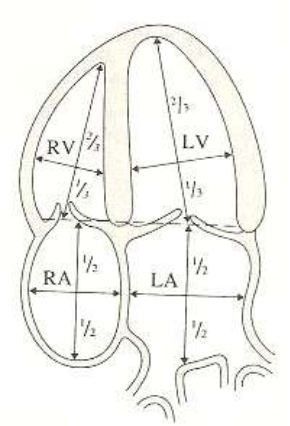
Group with >5 episodes/year (Ib) Normal controls (II)

	Ομάδα IB (n=17)	**Ομάδα II (n=50)**	**p**
Lalad(cm)	5,35±0,3	4,69±0,62	**0,004**
Lalas(cm)	4,73±0,57	4,18±0,59	**0,018**
P dur Z(msec)	87,3±14	71,5±15	**0,003**
P dur Z-X(msec)	11,8±13	0,7±16	**0,049**
Mean2Z (μV)	7,11±3,4	4,84±2,9	**0,036**
Mean3Z (μV)	43±21,7	27,9±15,9	**0,013**
Max1Z (μV)	12,7±3,7	10,5±3	**0,044**
Max3Z (μV)	39,2±10,7	31,4±9,9	**0,028**

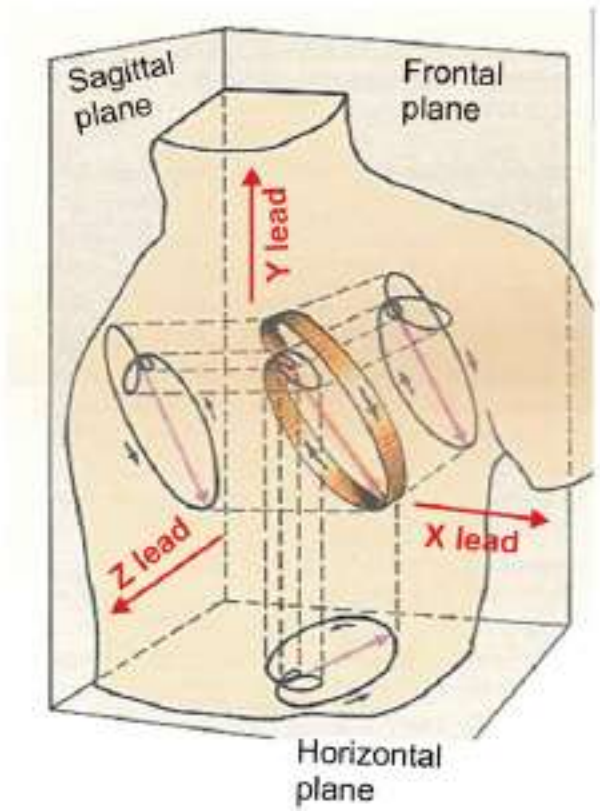
Echo parameters

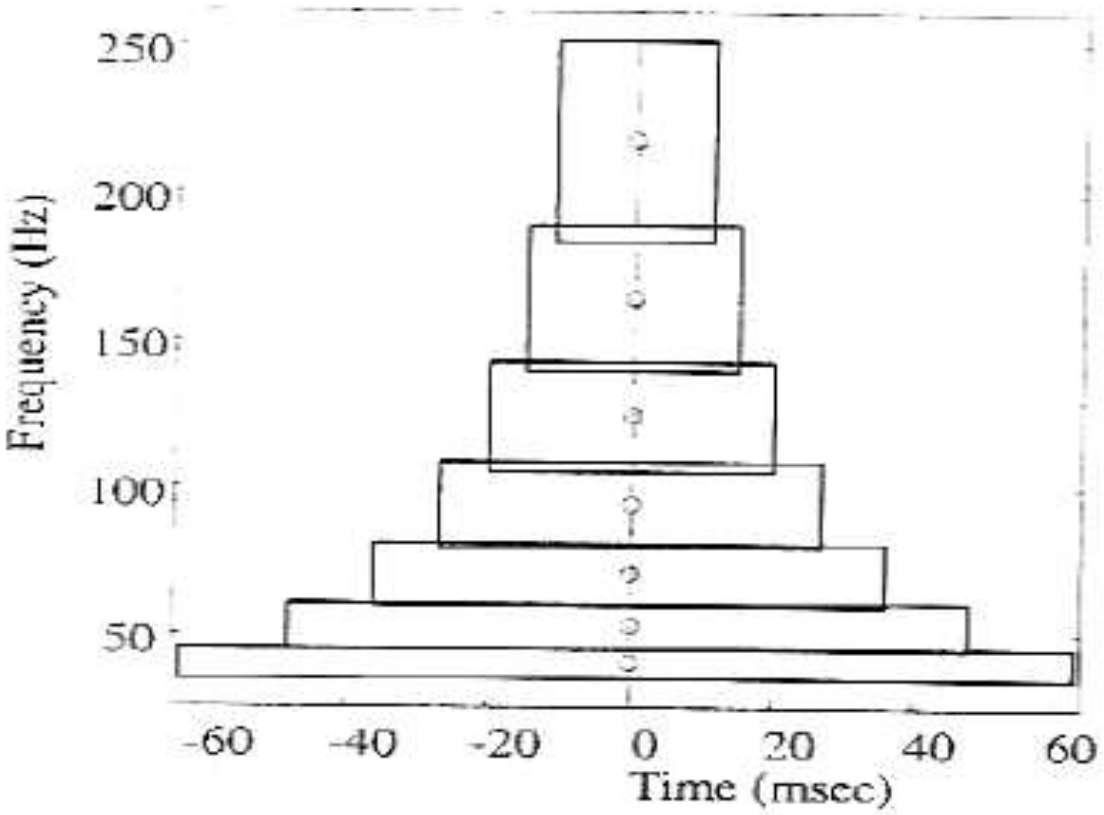


Left parasternal



Apical





Rubel P et al, 1996