St George's University of London

The RASE Brugada study: National Registry?

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British Heart Foundation

Study Hypothesis

A composite ECG-based score, derived from parameters of QRS and ST-T morphology and heterogeneity, their dynamic variation and heart rate variability, can better predict BrS patients at high risk of dying suddenly than available methods.

Study Design

Study type: Observational cohort which encompasses ongoing data collection.

Study Population: Patients diagnosed with BrS and subsequently followed up for manifestation of clinically significant cardiac events.

Project Centres

St George's: Elijah Behr

Belfast: Alison Muir/Pascal McKeown

Bart's: Pier Lambi

RBH: Jan Till

Imperial: Amanda Varnava

STH: Gerry Carr-White/Mike Cooklin

Kings: Nick Gall

Leeds: Steve Page

Liverpool: Derick Todd/Sagaar Mahida

ster: Cliff Garratt

h: Andrew Grace/Greg Mellor

Leicester: Andre Ng

Exeter: John Dean

Retrospective NIHR Adoption

Research Team

Senior Project Fellow:

Velislav Batchvarov

Research Nurses:

Victor Jardim

Helen Connolly

Criteria

- Inclusion criteria:
  a) informed consent provided (generic ICC ethics);
  b) spontaneous or drug-induced type 1 Brugada pattern observed in at least one of V1, V2, V1III, V2III, V1II and V2II.

- Exclusion criteria:
  a) significant coronary disease (>70% stenosis in at least one coronary artery and/or ischaemia on a functional test);
  b) significant cardiomyopathic disease (outside normal range ventricular function and structure on echocardiography and/or cardiac MRI);
  c) metabolic abnormality at time of type 1 ECG pattern (e.g. hyperkalaemia or hypercalcaemia);
  d) >10% ventricular pacing (patients with >10% atrial pacing will be excluded from assessment of autonomic function only).

Sample-Size

Four explanatory (independent) variables will be investigated for event occurrence and stratification of risk:

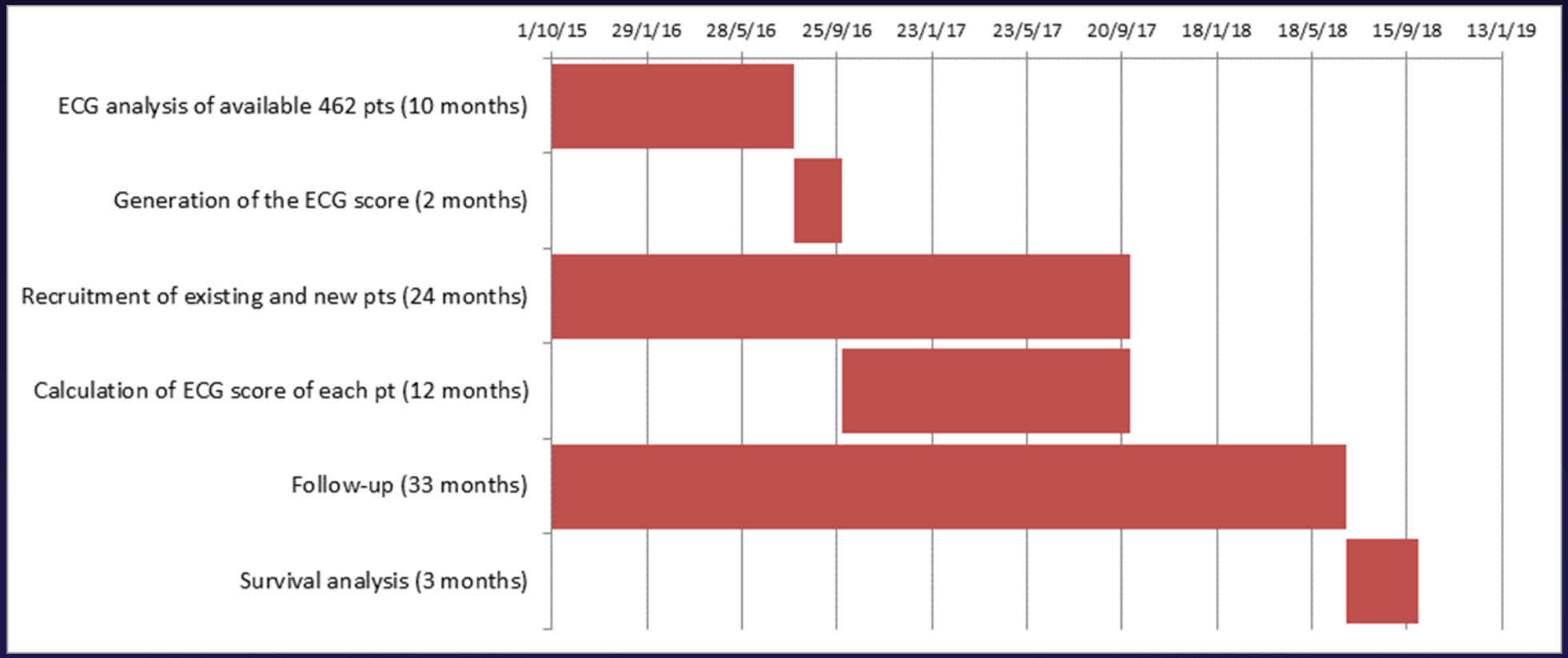
- Symptoms (syncope/cardiac arrest)
- Spontaneous type 1 ECG.
- ECG score
- Age at ECG acquisition

No of predictors	Total No of events needed	Approx. No of events in the cardiac arrest group	Approx. No of events in the syncope group	Approx. No of events in symptomatic BrS patients	Total No of *patient-years* needed	Total No of *patient-months* needed	Total No of patients needed if median follow-up is 37 months	Approx. No of patients in the cardiac arrest group	Approx. No of patients in the syncope group	Approx. No of patients in asympto-matic group
4	40	17	15	8	2488	29856	807	48	242	516

Expected Recruitment as of May 2015

Centre	Existing cases with digital ECG data (80% successful recruitment)	Existing cases without ECG data (80% successful recruitment)	Estimated new diagnoses annually	Maximal 2-year recruitment (80% successful recruitment)	Total for study (80% successful recruitment)
SGUL	362*	-	50	100 (80)	462 (442)
Heart/ Barts	-	238 (190)	40	80 (64)	318 (254)
RBH			45	90 (72)	90 (72)
Imperial	100 (80)	-	30	60 (48)	160 (128)
KHP		-	55	110 (88)	110 (88)
Belfast	12*	101 (81)	50	100 (80)	213 (173)
Total	474 (454)	339 (271)	270	540 (432)	1353 (1157)

Project Plan



Clinical data collection and follow-up

- Data collected by eCRF will include:
  a) demographics (date of birth, gender, ethnicity, family history),
  b) date and nature of presentation and symptoms,
  c) date of ECG, ajmaline test and Holter acquisition,
  d) date and nature of therapies, prior arrhythmias (atrial and ventricular) and;
  e) genotyping results (clinical, research and UK 100,000 Genomes [UK100KG] derived results if available).
  f) Follow-up will be recorded locally, patient questionnaire and enquiries to HSCIC:
    - sudden death, cardiac arrest, appropriate ICD shock
    - mortality
    - unexplained arrhythmogenic syncope,
    - documented arrhythmia,

RASE Brugada: Patient recruitment

CLINIC

- Brugada Syndrome Patient identified on Clinic list – new referral or follow-up:
  - CHECK inclusion and exclusion criteria – consent by RASE Research Nurse or Investigator

ECG

- High lead ECG on Cardiosoft Recorder
- Ajmaline test (if clinically indicated) according to RASE acquisition protocol
- Attach 12 lead Holter according to RASE protocol

DATA

- Research nurse to facilitate Cardiosoft data collection
- Download 12 lead Holter to core lab site (SGUL)
- Research Nurse to enter data into eCRF from local PC and scan presenting diagnostic ECG

DNA

- Research nurse to facilitate DNA/Blood collection at core lab site (SGUL) for cases requiring genotyping
  - DNA already extracted: request sample from local lab
  - DNA not extracted: fresh EDTA sample to transfer for extraction and storage at core lab site

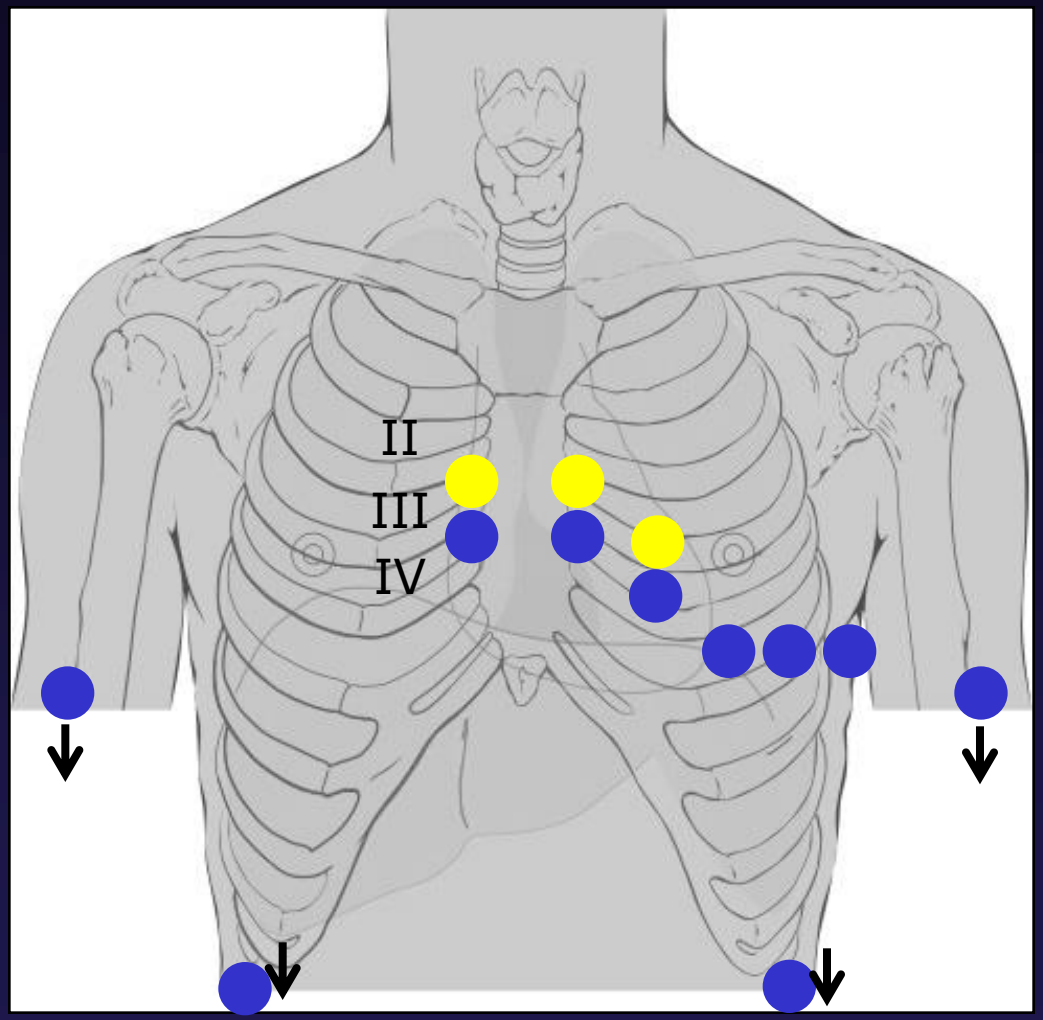
Acquisition of ECG data

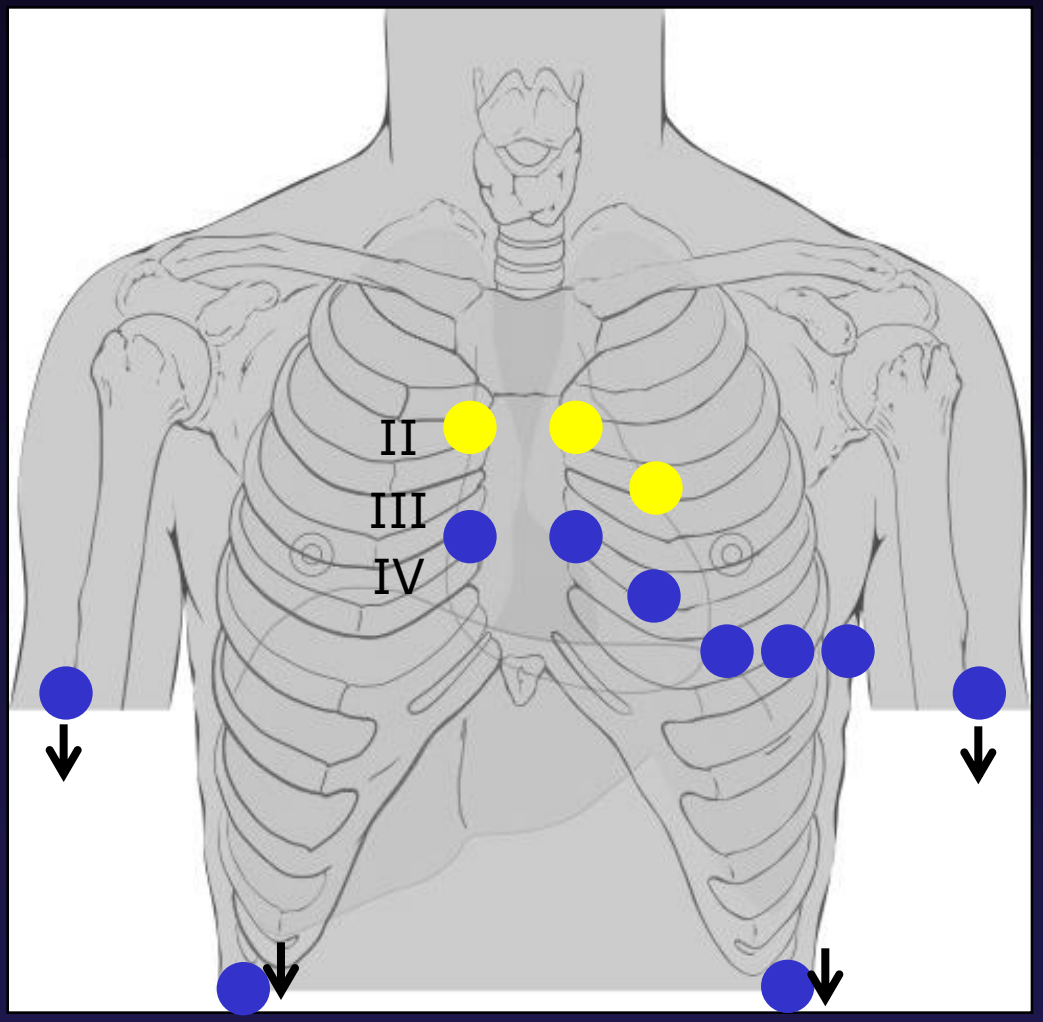
- Resting ECG and ajmaline testing:
  - CardioSoft laptop-based digital ECG recorder (500 samples/s, 5 μV amplitude resolution)

- 12-lead Holter recording:
  - Getemed (GE) or H-Scribe (Mortara), 1000 samples/s
  - Mortara downloads via card readers to SGUL.

- Scan and record the initial diagnostic ECGs of historical cases – spontaneous or ajmaline provoked – for diagnostic standardisation.

“Brugada” resting 15-lead ECG lead configuration

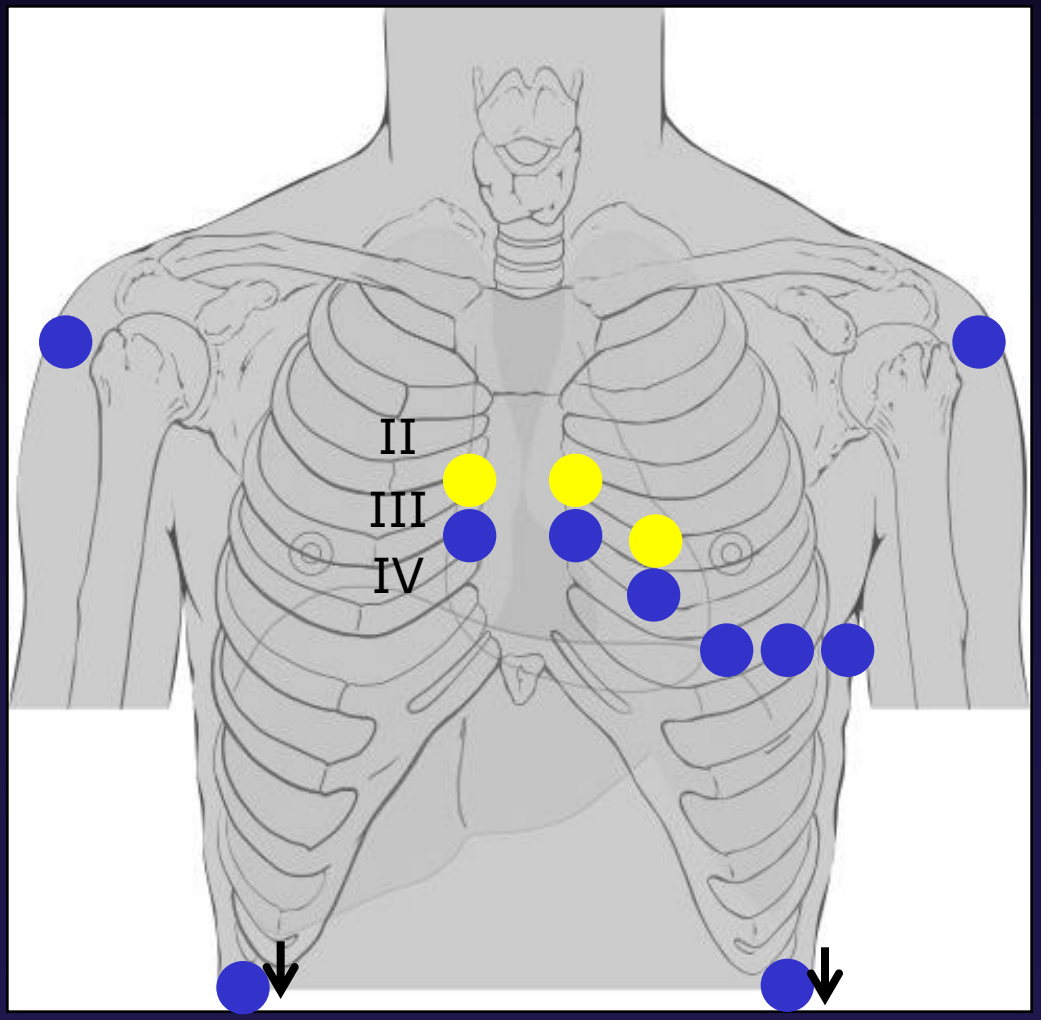




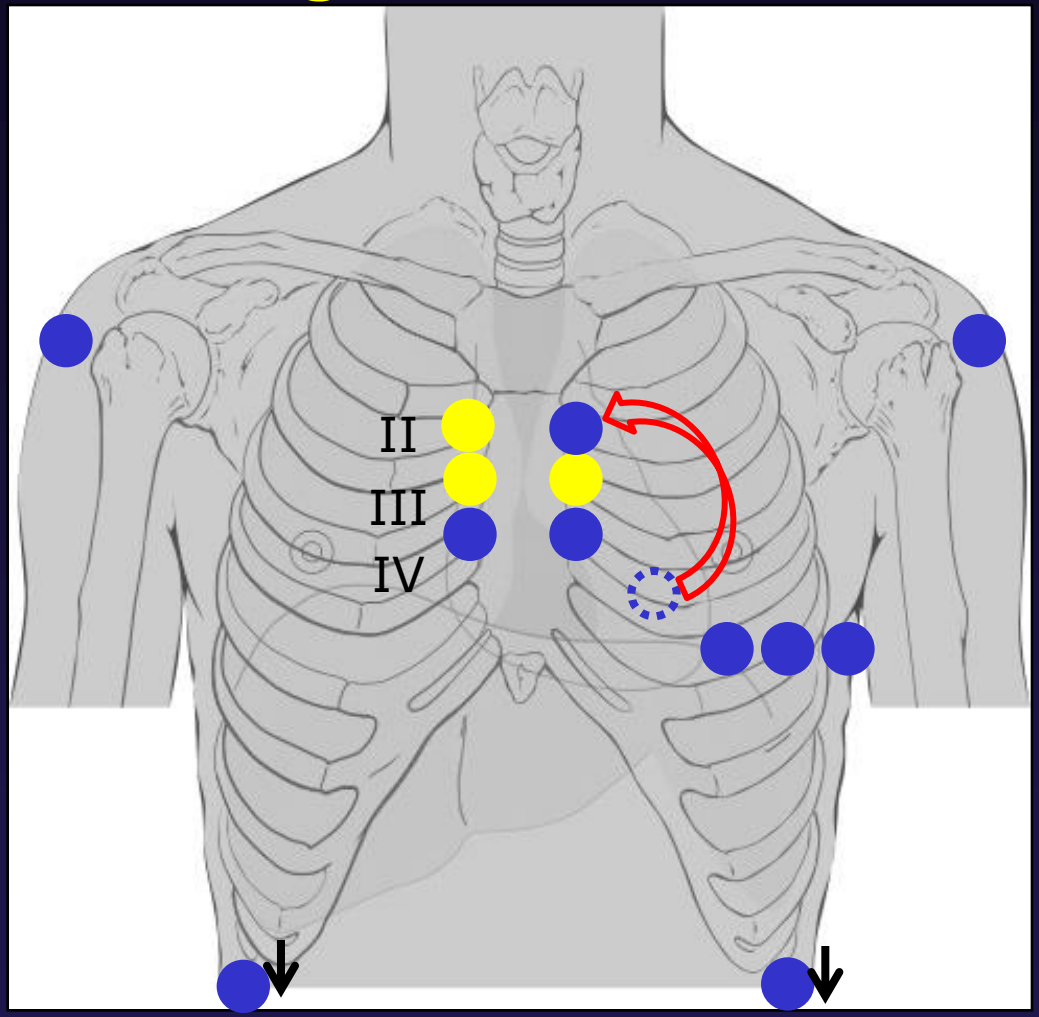
<u>Firstly record:</u>
12 standard leads + V1 to V3 one i.c. space higher (3rd space for V1 and V2)

<u>Then record:</u>
12 standard leads + V1 to V3 two i.c. spaces higher (2nd space for V1 and V2)

“Brugada” 15-lead ECG configuration for diagnostic ajmaline testing



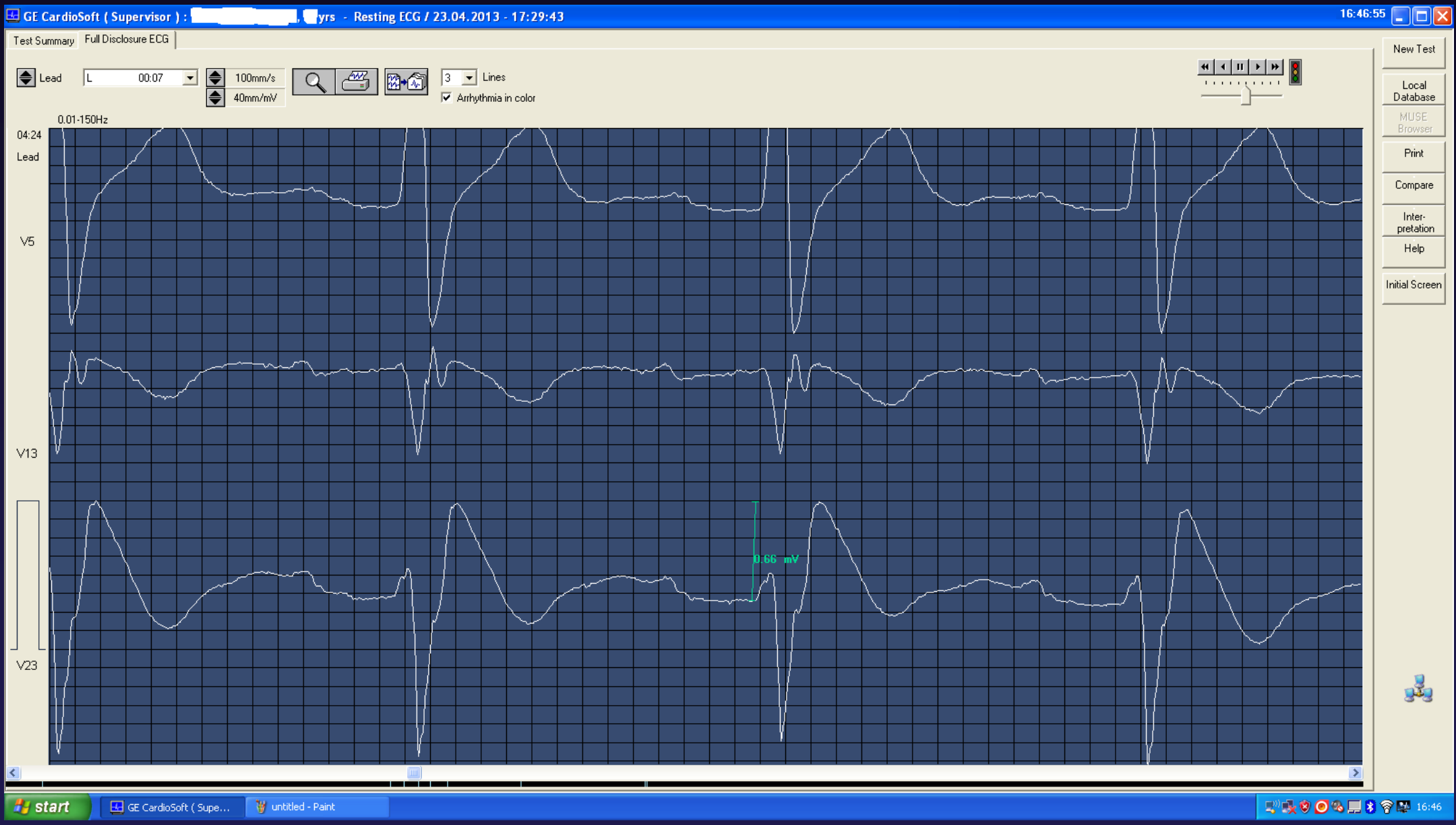
Recording before the test



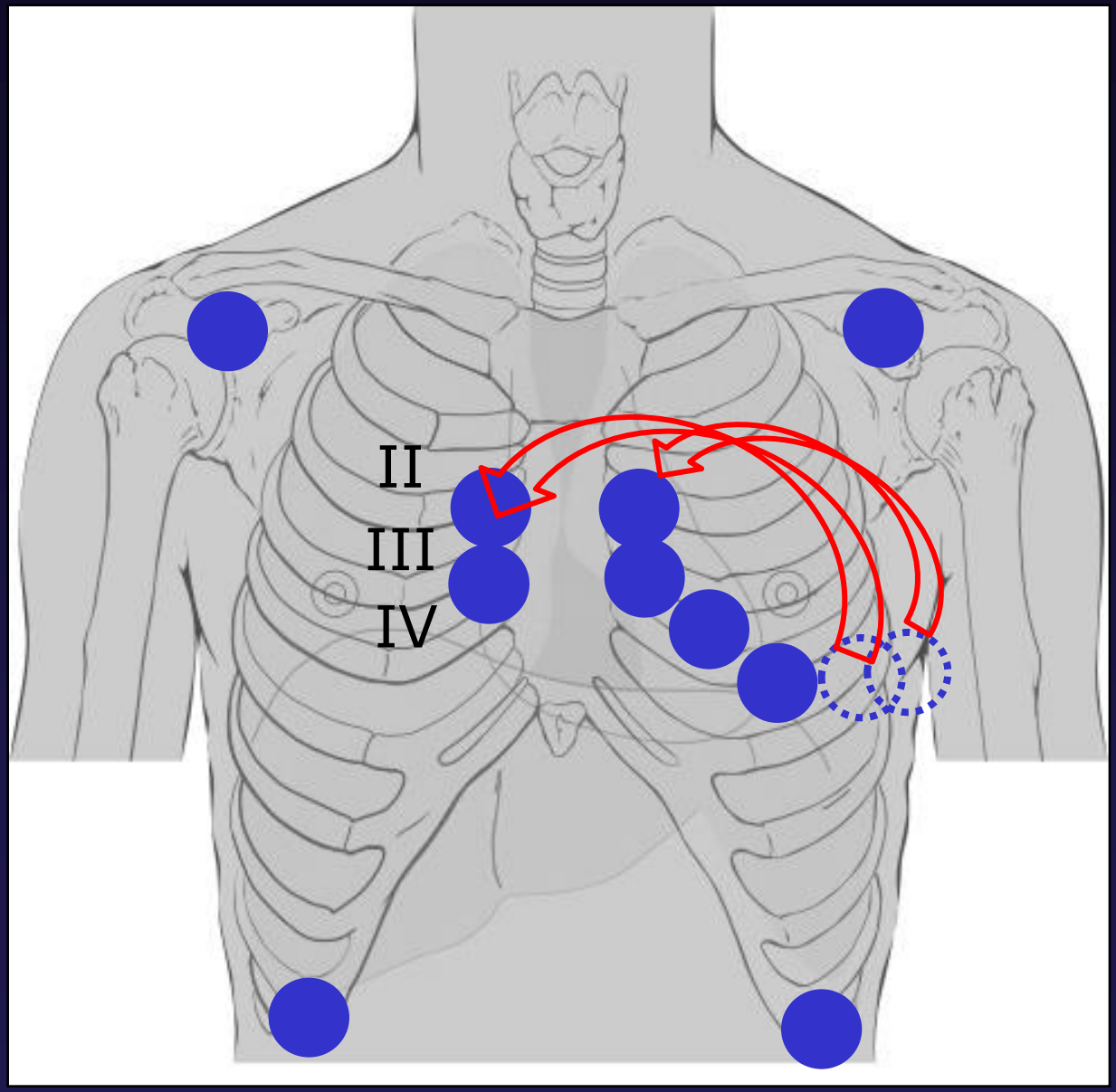
Recording during the test
(including 1 min before the start of ajmaline administration)

ECG recording during ajmaline testing

ECG recording during ajmaline testing

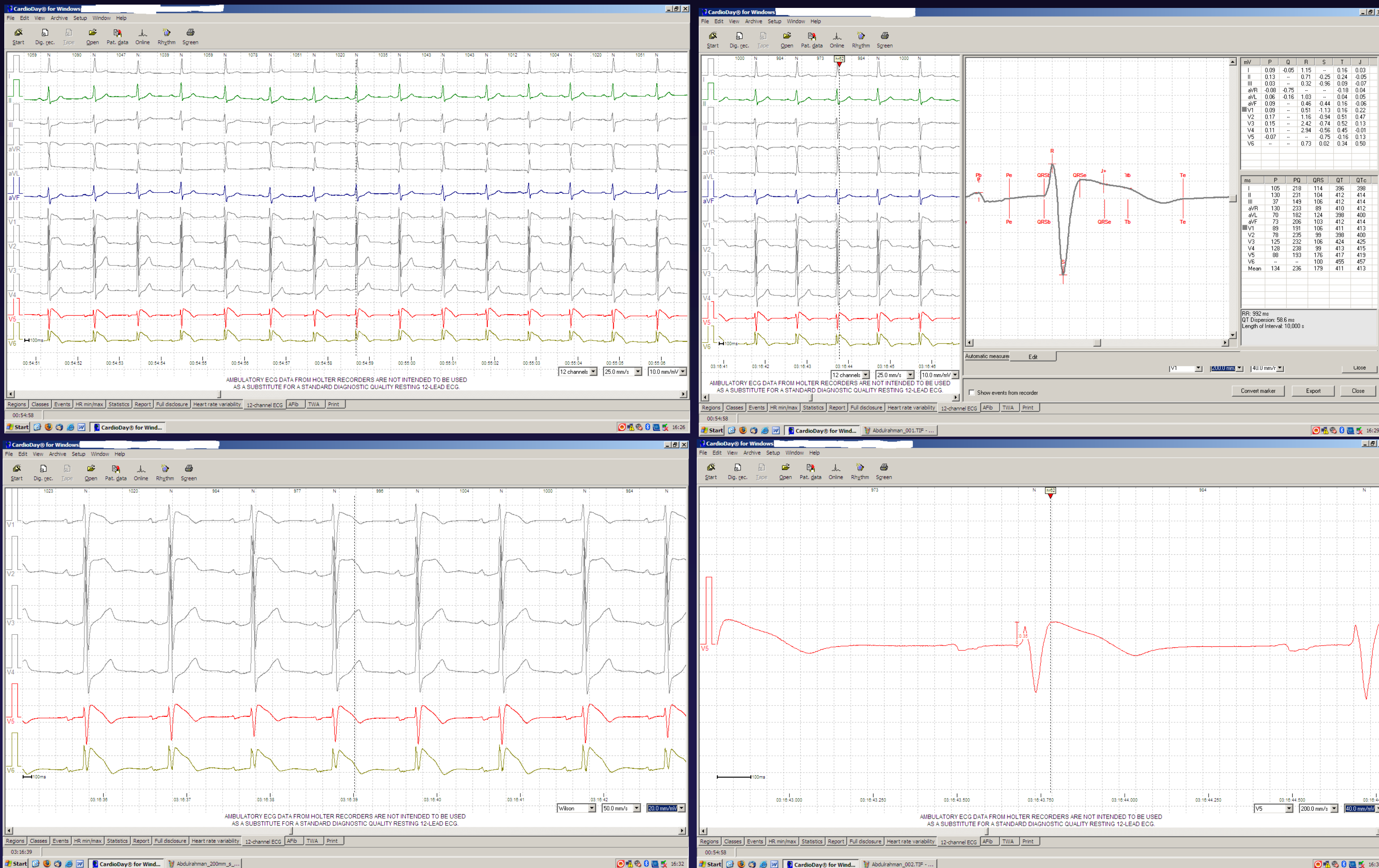


12 lead configuration for Holter monitoring in patients investigated for the Brugada syndrome

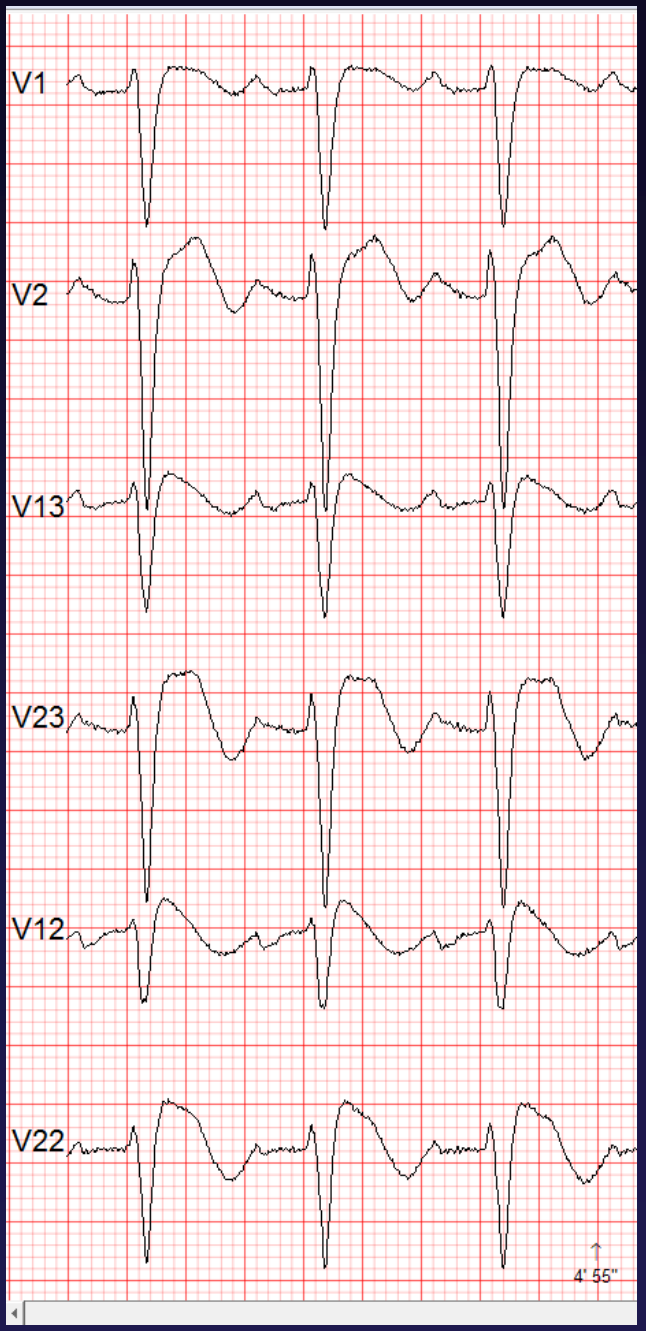


- Leads V5 and V6 are sacrificed in order to record leads V1 and V2 from “high” positions;
- Due to the large sticking area of the electrodes for continuous ambulatory recording, it is not possible to position electrodes both in the 2nd as well as 3rd i.c. space;
- Leads V3 and V4 are kept for general ECG analysis, for construction of precordial bipolar leads, etc.
- The peripheral electrodes are positioned according to the Mason-Likar configuration.

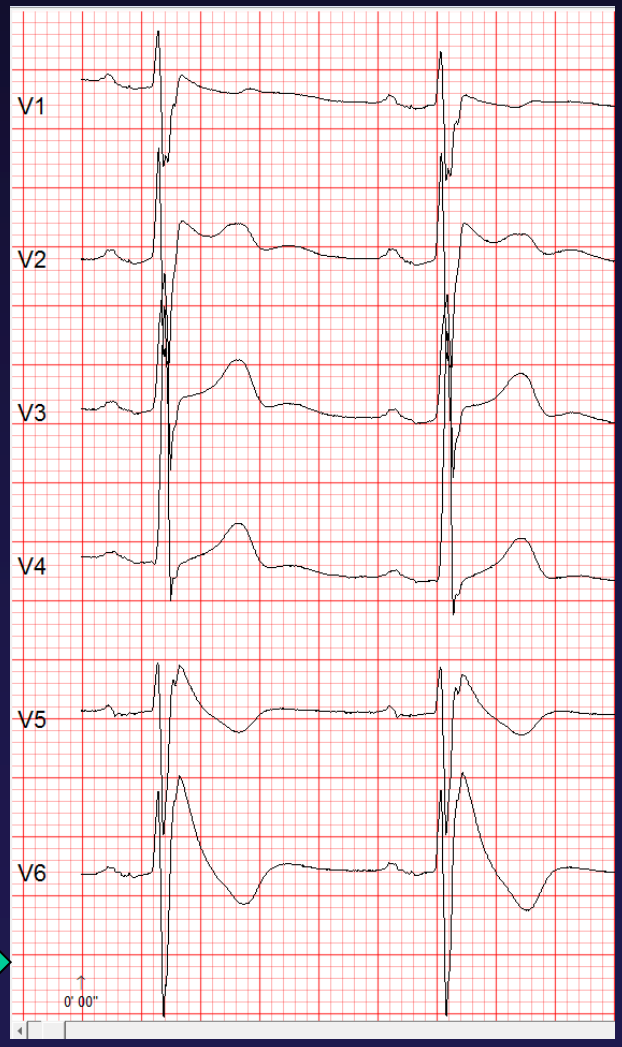
12-lead Holter recording (Getemed, GE)



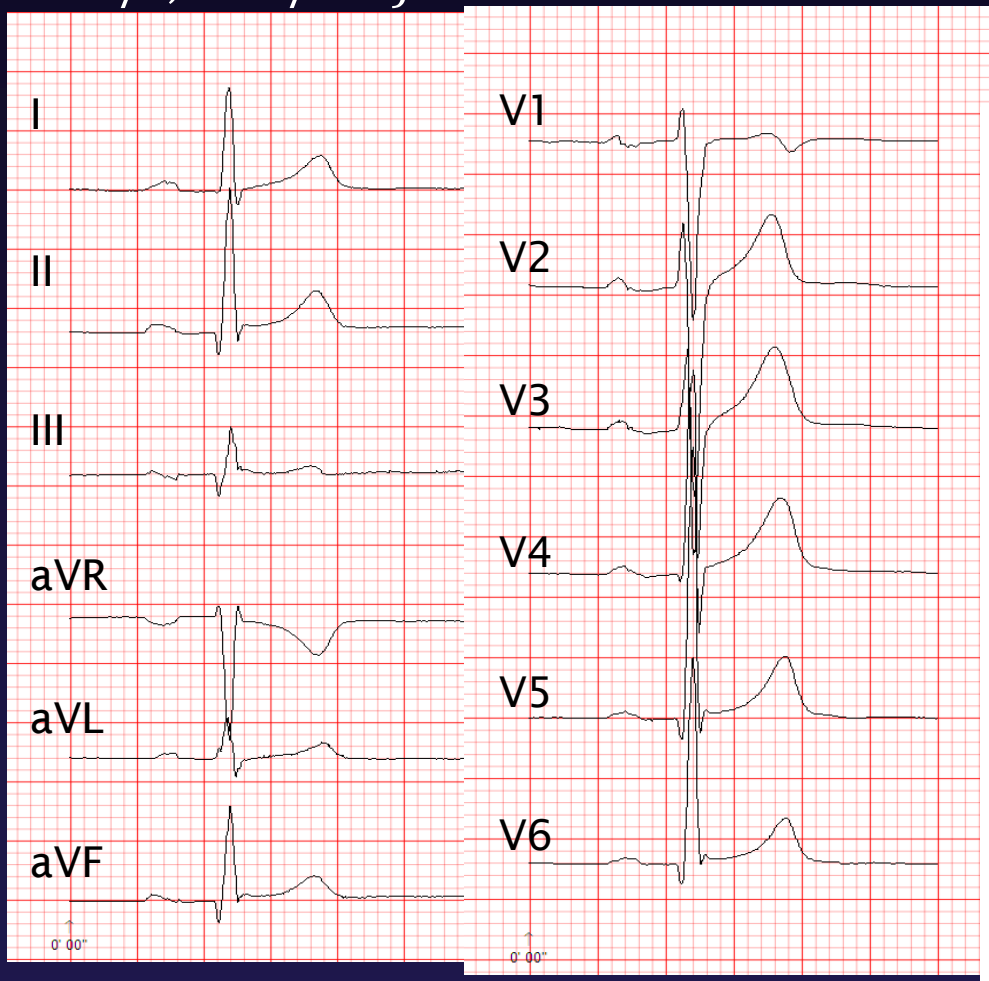
Resting & ajmaline 15L ECGs



12L Holter



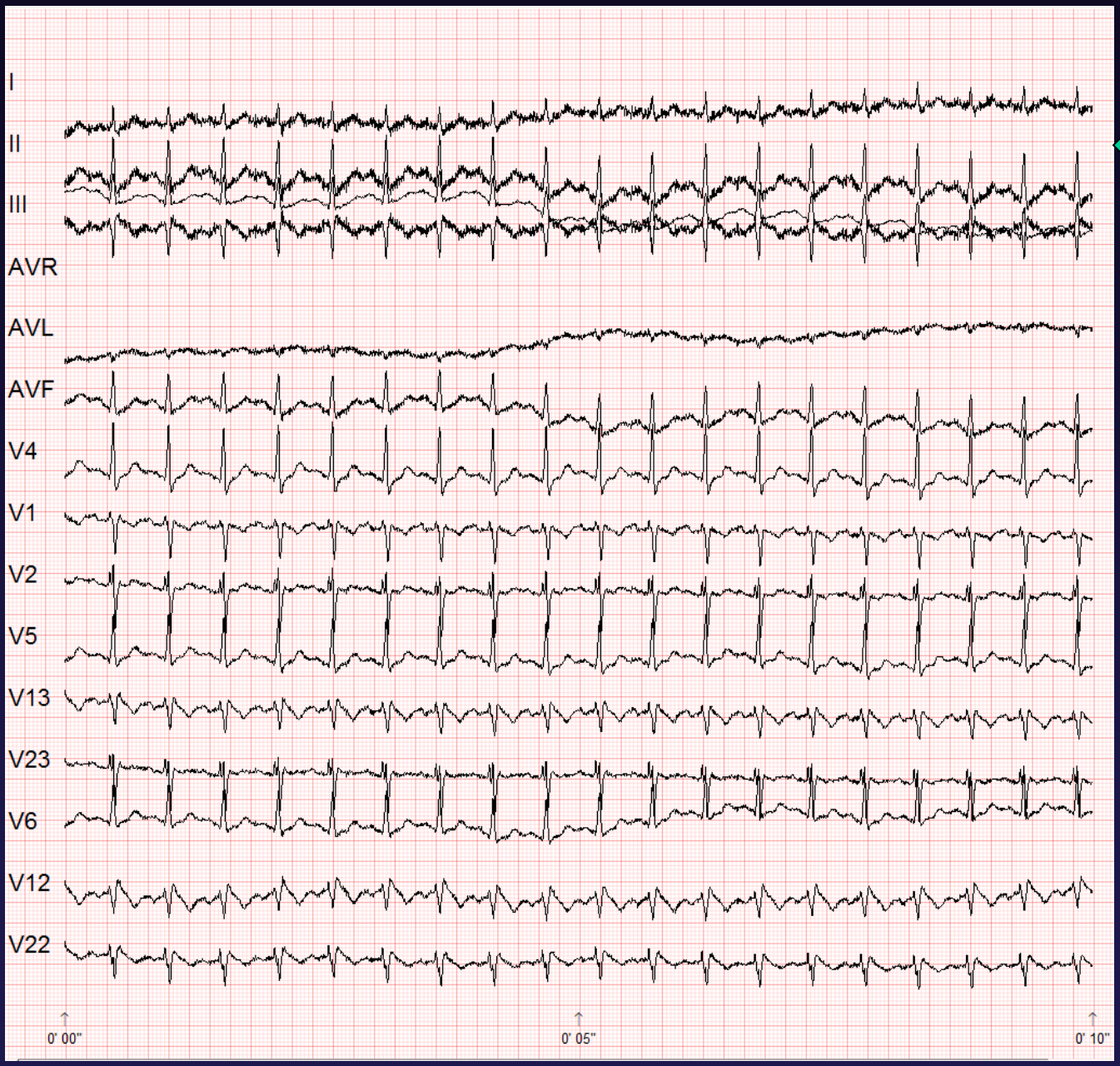
A 1.2-second 12-lead ECG recorded at 500 samples/s, displayed at 25 mm/s, 1cm/mV)



A "digital" ECG is just an array of numbers (the voltage values of each sample)

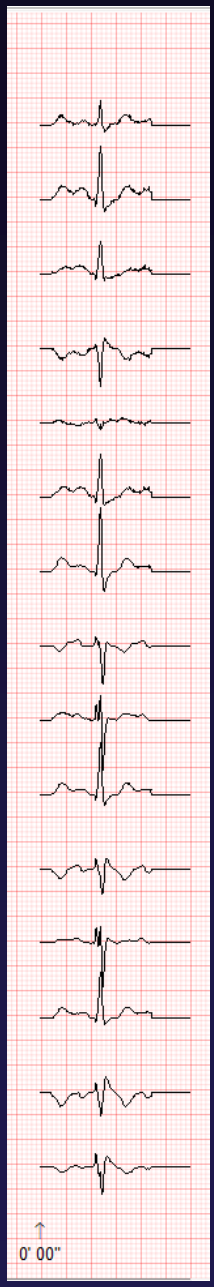
Time [ms]	I	II	V1	V2	V3	V4	V5	V6	III	aVR	aVL	aVF
0.000	0.0150	0.0050	-0.0150	-0.0100	0.0150	0.0100	0.0100	0.0100	II-I	(I+II)/(-2)	(I-III)/2	(II+III)/2
0.002	0.0150	0.0050	-0.0200	-0.0100	0.0150	0.0100	0.0100	0.0100	...	...	...	...
0.004	0.0150	0.0050	-0.0200	-0.0150	0.0100	0.0100	0.0100	0.0100	...	...	...	...
0.006	0.0100	0.0050	-0.0200	-0.0150	0.0100	0.0100	0.0100	0.0100	...	...	...	...
0.008	0.0100	0.0050	-0.0200	-0.0150	0.0100	0.0100	0.0100	0.0100				
...	...	...	...	...	...	...	...	...				
0.440	-0.0200	-0.0950	0.0900	0.1450	0.0450	-0.0350	-0.0850	-0.0800				
0.442	-0.0250	-0.1450	0.1500	0.2350	0.0850	-0.0500	-0.1250	-0.1250				
0.444	-0.0250	-0.1850	0.1950	0.3150	0.1200	-0.0600	-0.1600	-0.1550				
0.446	-0.0100	-0.1850	0.2150	0.3600	0.1600	-0.0500	-0.1650	-0.1650				
0.448	0.0000	-0.1850	0.2300	0.4000	0.1950	-0.0350	-0.1650	-0.1650				
0.45	0.0000	-0.1500	0.2450	0.4600	0.2400	-0.0050	-0.1650	-0.1650				
0.452	0.0150	-0.1000	0.2550	0.5050	0.3000	0.0350	-0.1350	-0.1550				
0.454	0.0500	-0.0350	0.2250	0.4950	0.3500	0.1000	-0.0850	-0.1150				
0.456	0.1050	0.0350	0.1550	0.4250	0.3850	0.1950	0.0150	-0.0300				
0.458	0.1900	0.1250	0.0450	0.3400	0.4250	0.3150	0.1500	0.0750				
0.460	0.2850	0.2400	-0.0700	0.2450	0.4950	0.4750	0.3200	0.2050				
0.462	0.3850	0.3650	-0.2000	0.1150	0.5650	0.6700	0.5350	0.3750				
0.464	0.5050	0.5000	-0.3200	-0.0350	0.6200	0.8900	0.7850	0.5650				
...	...	...	...	...	...	...	...	...				
1.186	0.0200	0.0500	-0.0150	-0.0200	0.0050	0.0100	0.0100	0.0000				
1.188	0.0200	0.0500	-0.0150	-0.0200	0.0050	0.0100	0.0100	0.0050				
1.19	0.0200	0.0500	-0.0150	-0.0200	0.0050	0.0100	0.0100	0.0050				
1.192	0.0200	0.0500	-0.0150	-0.0200	0.0050	0.0100	0.0100	0.0000				
1.194	0.0200	0.0500	-0.0150	-0.0200	0.0050	0.0100	0.0100	0.0000				
1.196	0.0200	0.0500	-0.0200	-0.0200	0.0050	0.0100	0.0000	0.0000				
1.198	0.0200	0.0500	-0.0150	-0.0200	0.0050	0.0100	0.0050	0.0000				

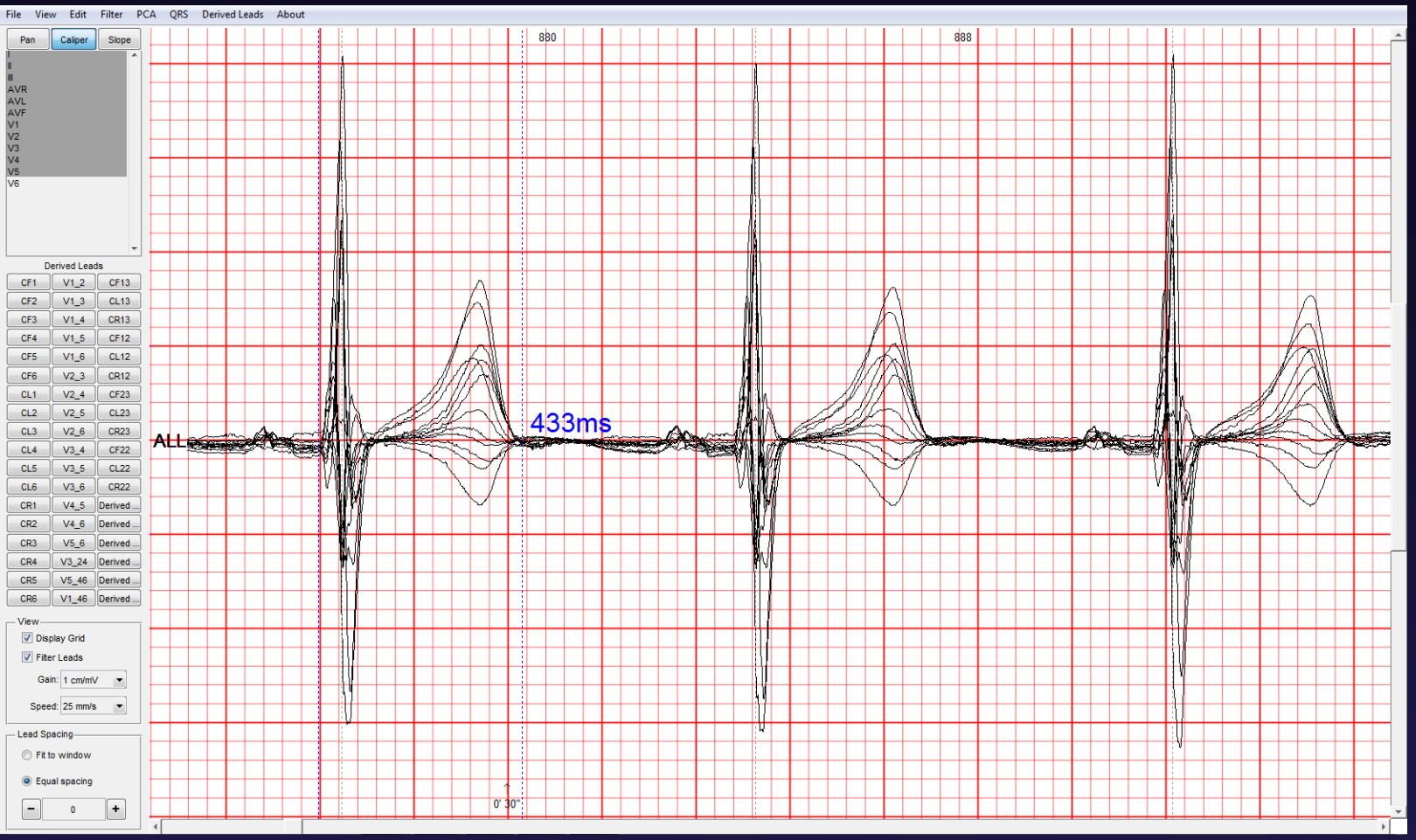
In digital form, this ECG is an array of 600 rows and 8 columns: each row is 1 sample (i.e. one value every 2 ms) and each column is the voltage value of the sample in each lead) – that is, the digital ECG is just 4,800 numbers (600 x 8) + some additional information

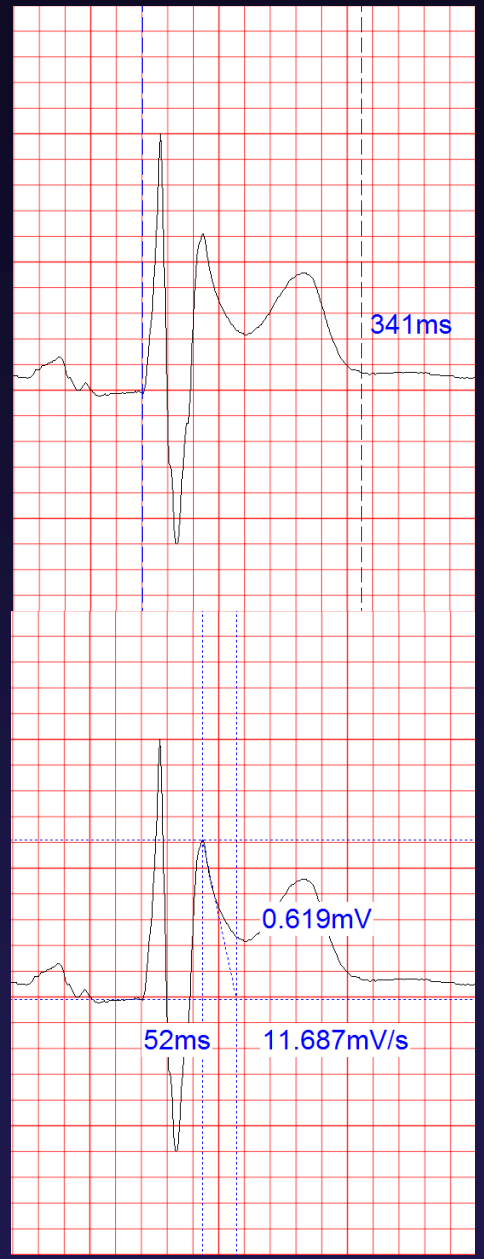


Original ("raw")
10-s ECG

"Median" ECG

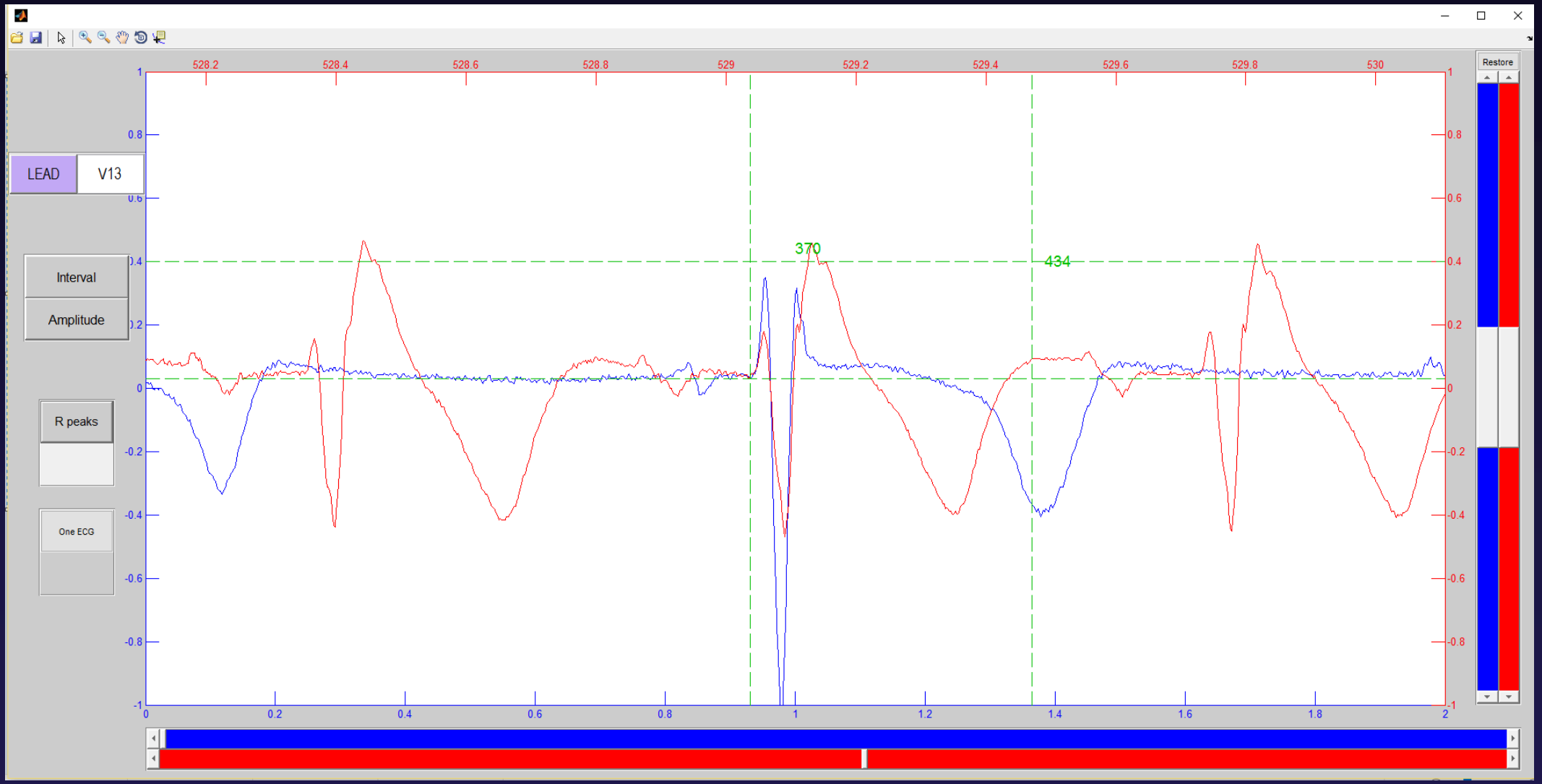






Allows very high magnification, filtering to remove noise, superimposition of leads (to detect better QRS/QT onset and offset), measurement of amplitudes, intervals and slopes with calipers, and much more…

Available software for visual assessment and measurement



Programme for superposition, alignment, and measurement of earlier and later segments of the same recording – to detect and measure dynamic changes in shape, duration and amplitude.

Analysis of ECG data

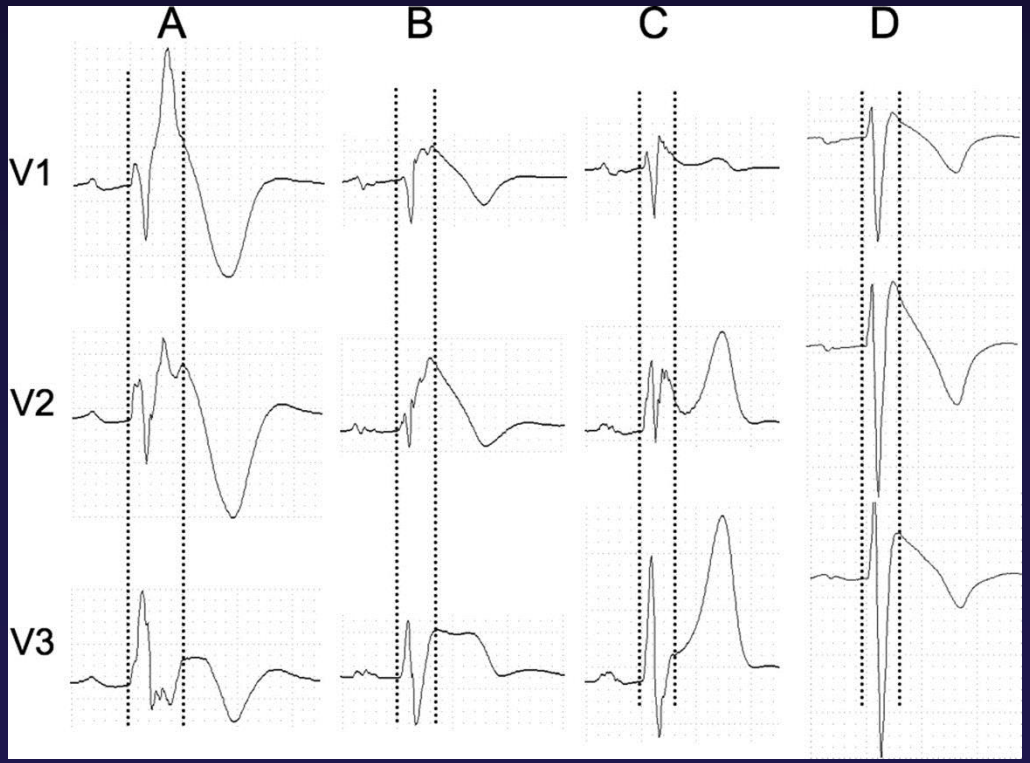
1. Assessment QRS, ST-T wave and QT interval duration /morphology/ heterogeneity:
   - Automatic QRS (R peak) detection → automatic detection of QRS onset & offset, T wave offset →measurement of the QRS/QT/QTc duration and J-point elevation;
   - Detection of type 1 Brugada ECG pattern (both visually & automatically);
   - Assessment of QRS morphology/heterogeneity:
     - Principal Component Analysis (PCA) of the QRS;
     - Wavelet Transform (WT) of the QRS;
     - Other methods (some of them developed but not tested)
     - Presence of early repolarisation (ER) with horisontal/descending ST.
   - Assessment of ST-T wave (J-point to T-end) heterogeneity (PCA, WT)
2. Computed bipolar/multipolar leads for:
   - Enhanced detection of type 1 pattern;
   - Detection of QRS notching/fractionation (visually & automatically)

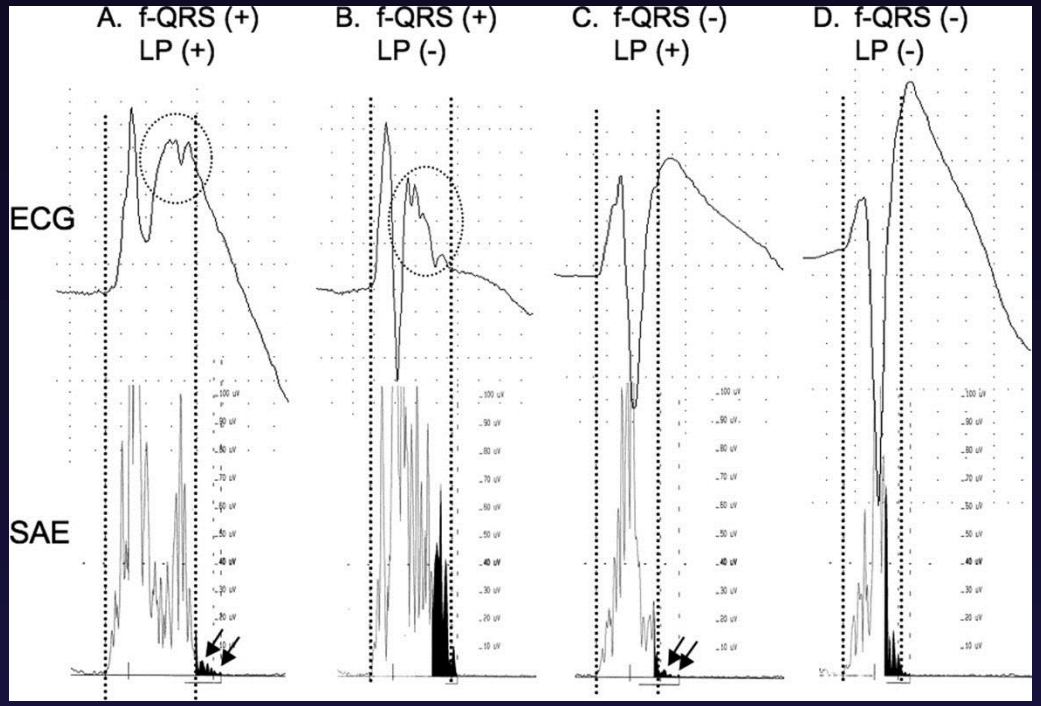
Analysis of ECG data (cont'd)

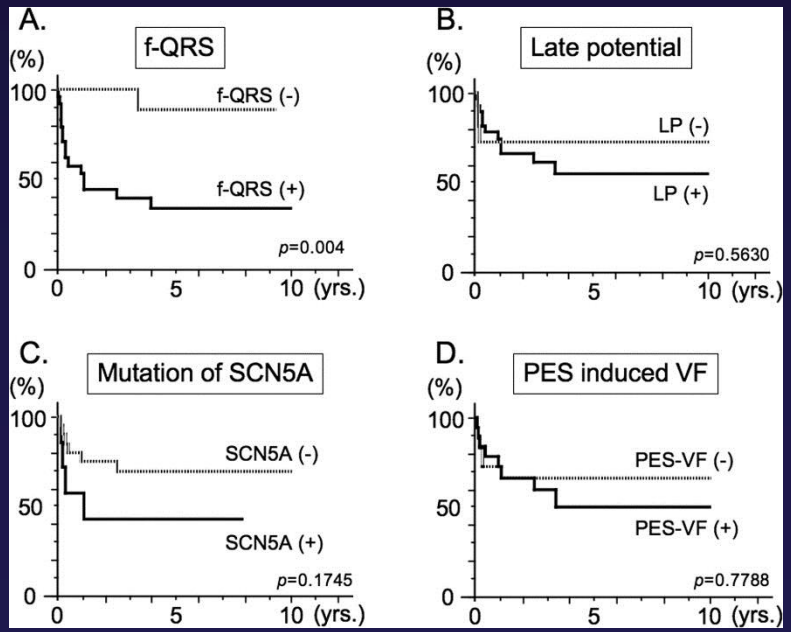
3. Dynamic variation of (some of) the parameters from 1. and 2.:
   - Circadian variation (day-night differences, dynamic profile of average hourly values);
   - Beat-to-beat variation from selected segments of Holter recordings, baseline (off-drug) and at maximum drug effect during positive ajmaline test:
     - beat-to-beat differences in parameters;
     - assessment of matrix consisting of automatically detected, superimposed and aligned ECG complexes.

   Dynamic variation can include QRS/QT/QTc duration, J-point elevation, PCA of the QRS & ST-T wave ($1^{st}/2^{nd}$ eigenvalue, non-dipolar components), WT-derived parameters, index of QRS fractionation, appearance of type 1 pattern, appearance / persistence of ER.
4. Heart rate variability (HRV), heart rate turbulence (HRT) and deceleration capacity (DC) from Holter recordings using proprietary software of the manufacturer's Holter analyser or custom software (to be developed)

QRS fractionation as a marker of arrhythmic risk in BrS

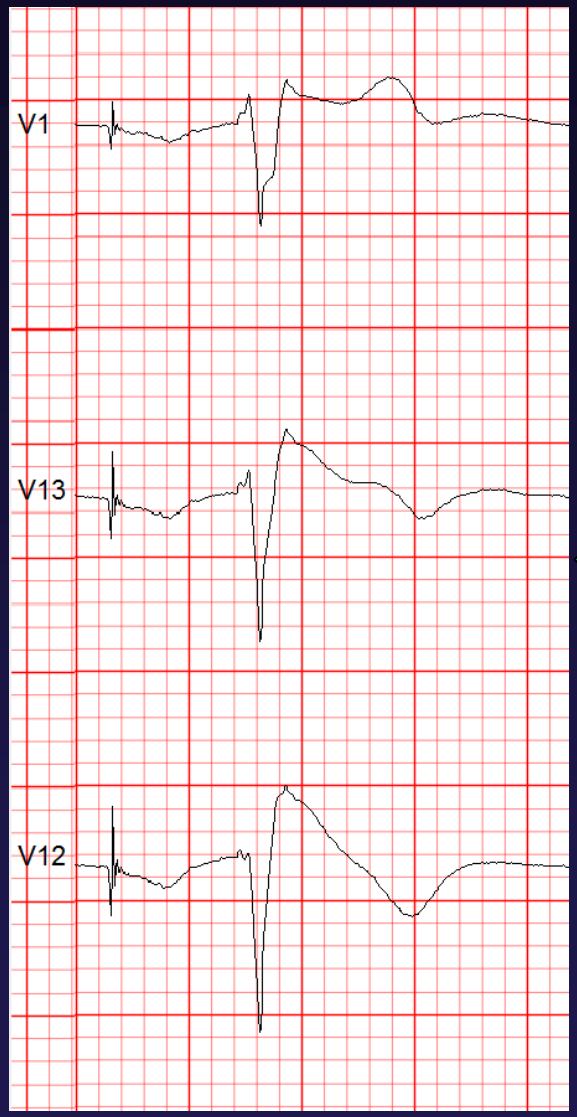






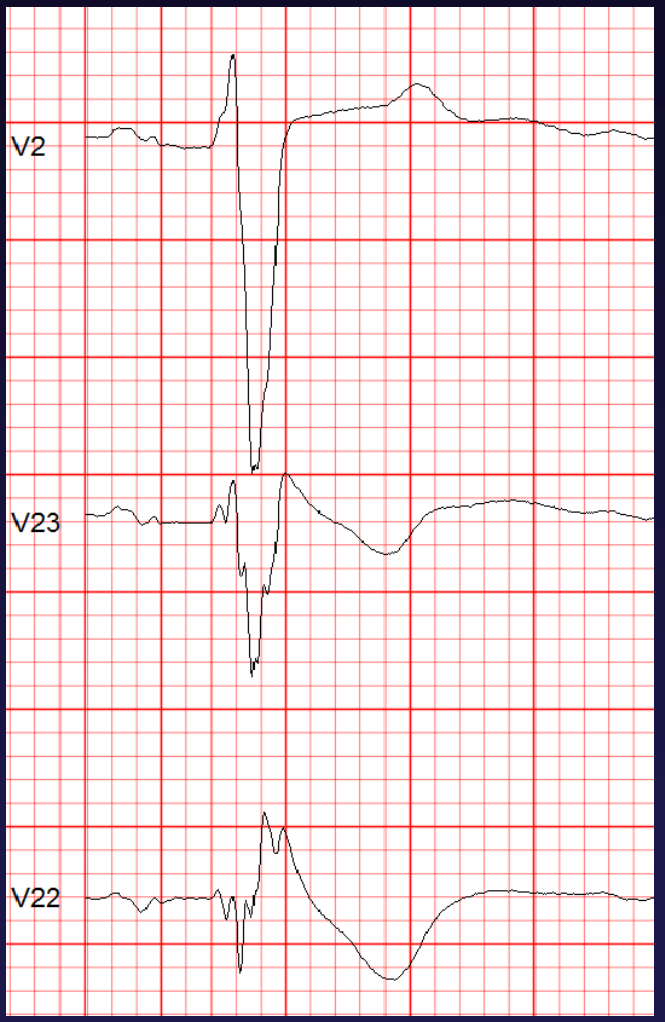
Morita H et al. Circulation 2008; 118:1697

Notching/fractionation of the QRS – not always indicative of risk

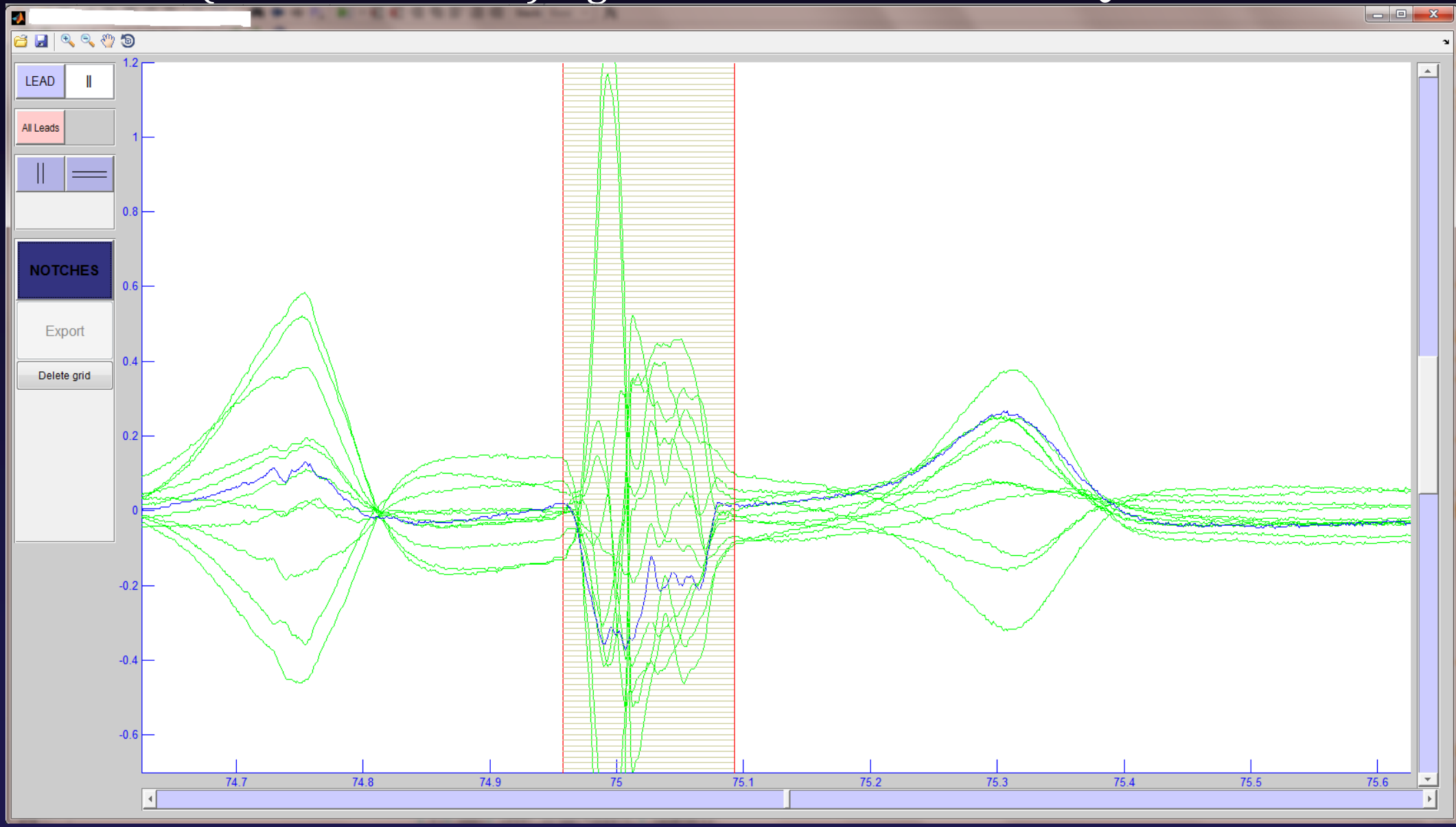


Spontaneous type 1 Brugada pattern in a 53-year old man with aborted cardiac arrest, implanted ICD and subsequently multiple appropriate shocks of the device. No considerable fractionation of the QRS complex is visible.

Fractionated QRS complex in a 25-year-old asymptomatic male patient with BrS (ajmaline-induced type 1 Brugada ECG pattern).

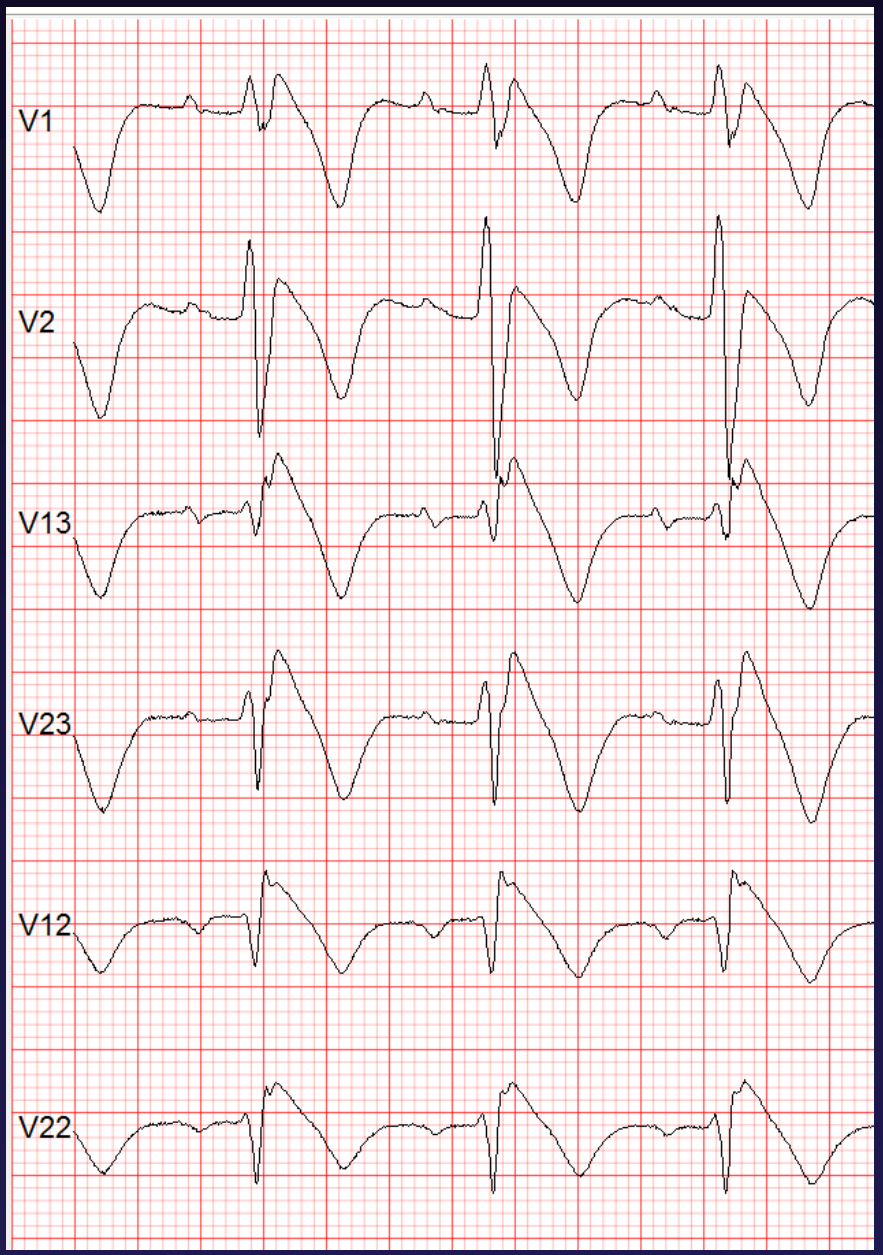


A novel (“common sense”) algorithm for assessment of QRS fractionation



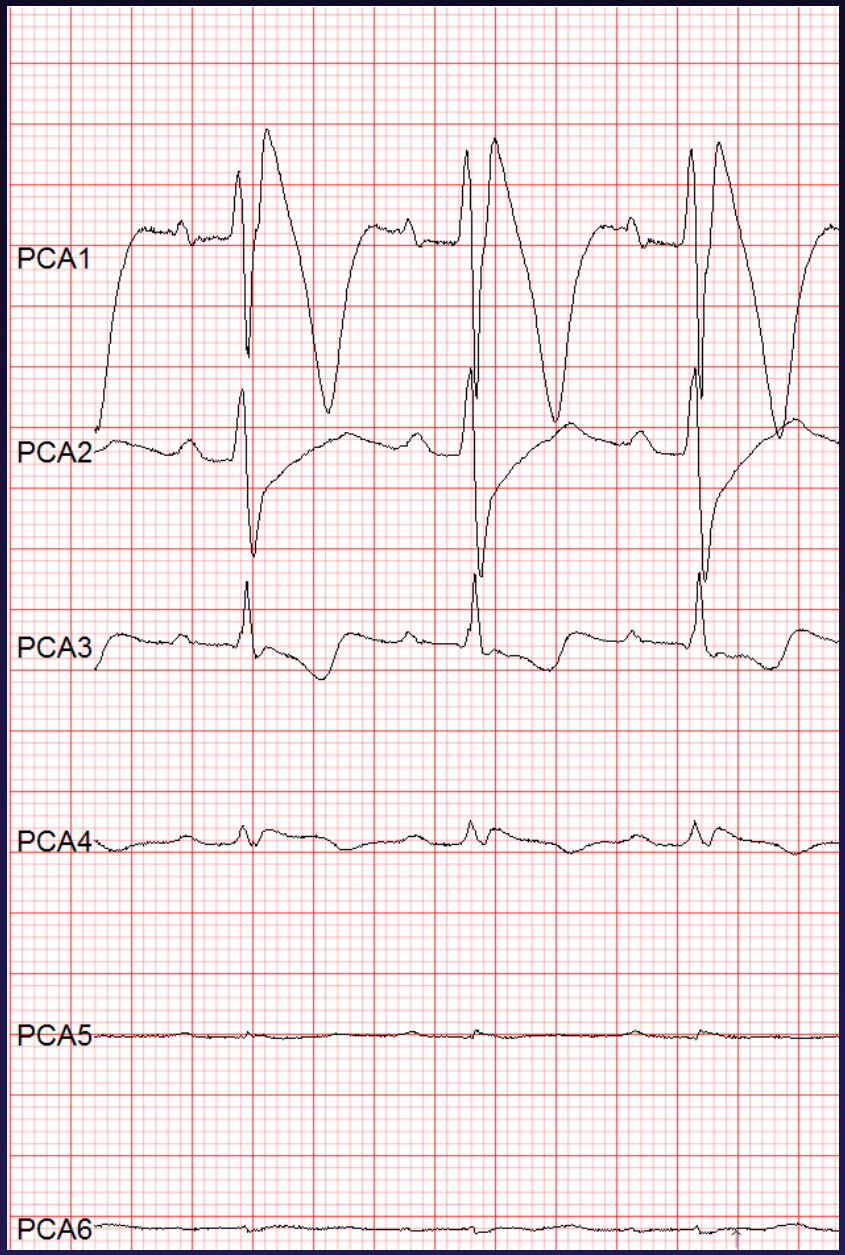
The 12 leads are superimposed; the beginning and end of the QRS are detected (manually or automatically); the program draws horisontal line at 30 μV (arbitrary value) from the top to the bottom of the QRS (in any lead). The number of crossings of each line with the QRS curve is an indicator of how fractionated the QRS is.

Principal Component Analysis (PCA) of the ECG – The Concept



Original ECG

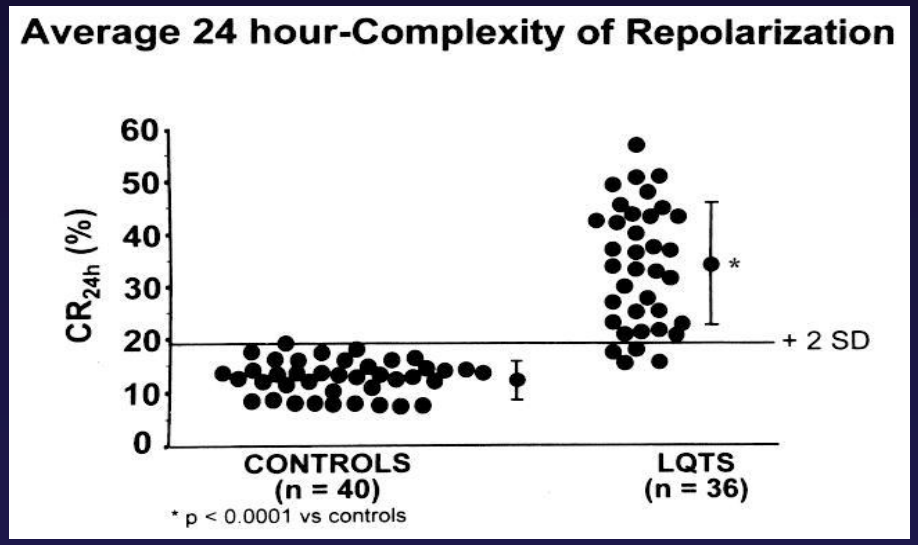
Reconstructed ECG which contains no redundant information

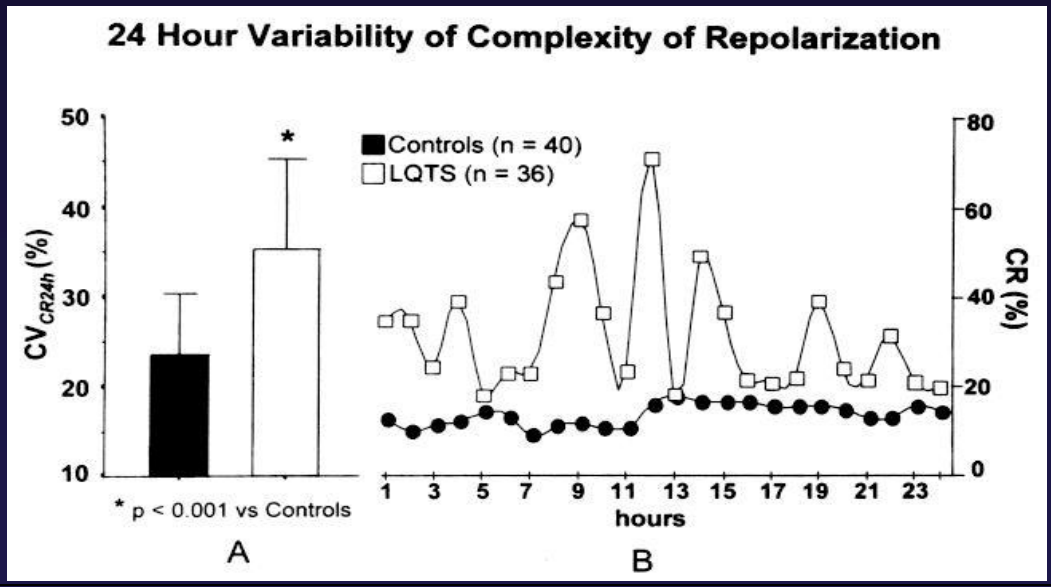


Principal Component Analysis (PCA) of the T Wave in LQTS

PCA gives a general numerical measure of the complexity of the T wave

24-h Holter recordings of 40 healthy subjects and 36 LQTS patients with diagnostic score > 4, i.e. "definite LQTS". 4-second long ECGs analysed at hourly intervals.





CR = Complexity Ratio (ratio between the 2nd and 1st eigenvalues)

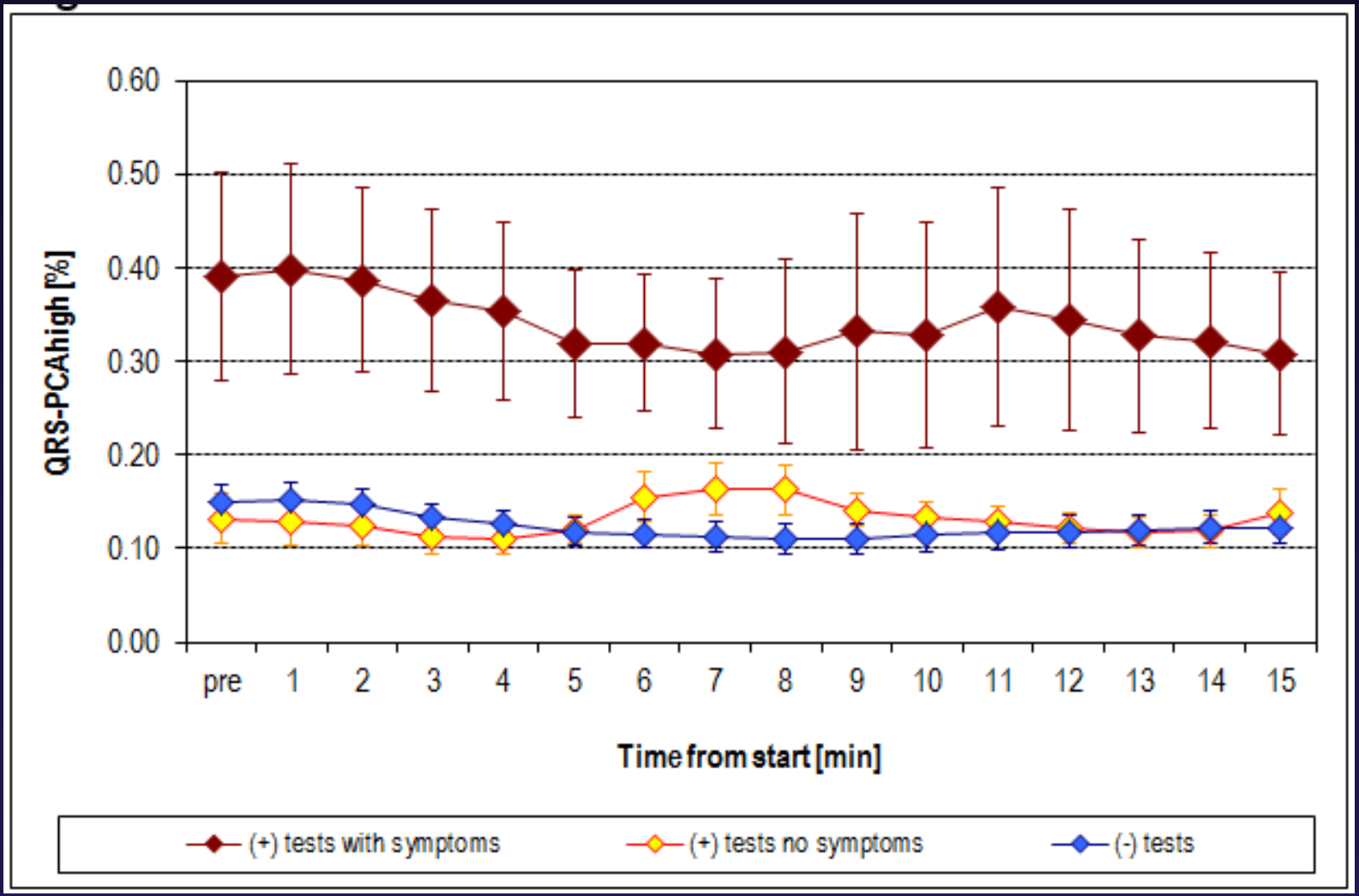
P<0.0001

Increased hourly variability of complexity of repolarisation in LQTS patients compared to controls.

Left: Coefficient of variability = SD of complexity / mean complexity × 100

Priori et al. Circulation 1997; 96:3006-3012

Prognostic value of Principal Component Analysis (PCA) of the QRS of leads V1-V3 in 3rd i.c. space during ajmaline test



Increased conduction (QRS) abnormalities in patients with history of arrhythmia related symptoms and positive ajmaline test compared to asymptomatic patients with positive test and patients with negative tests

Data are mean±SE

Batchvarov VN, …Behr ER. Computers in Cardiology 2010;37:501

Future

RASE Consortium
Steering group
Encourage centres to join and work together
Leverage numbers – demonstrate effectiveness
Additional project ideas
Apply for prolonged funding
Leverage relationships with industry for support
Leverage 100KG data