The Holter bin approach and beyond





Outlines

- Background of quantitative digital ECG
- The rate RR bin approach in depth
- Results of RR bin from different trials
- Rate-bin versus Time-bin
- Coping with Hysteresis phenomenon

What is a "bin" ?

Just a box, a digital box in which one does store some items

a Gold Standard in Digital ectrocardiography



« bin » : a box used for storage

Digital cardiac waveform stored in « bin »

Quantitative Digital Electrocardiography Objectives



Wave measurement, all leads Matrix of measurements Diagnosis

	PA	PPA	QA	QD	RA	RD	SA	SD	RPA	RPD	SPA	STJ	STM	STE	ТА	ТРА
V1	53	-73	0	0	234	29	839	59	0	0	0	-49	43	58	63	0
V2	53	-29	0	0	332	37	1035	51	0	0	0	-54	58	112	263	0
V3	68	0	0	0	341	41	605	47	0	0	0	-25	39	78	219	0
V4	68	0	0	0	410	46	253	42	0	0	0	0	24	48	190	0
V5	73	0	0	0	668	88	0	0	0	0	0	39	24	34	170	0
V6	63	0	53	20	708	68	0	0	0	0	0	58	19	24	131	0
I	68	0	87	22	766	66	0	0	0	0	0	19	4	9	112	0
aVL	-14	48	78	22	522	37	136	29	0	0	0	-20	-10	5	43	0
II	102	0	14	19	517	69	0	0	0	0	0	83	29	29	146	0
aVF	73	0	0	0	29	24	34	9	356	55	0	73	29	24	92	0
Ш	53	-29	0	0	73	23	278	30	312	35	0	63	24	19	0	0
aVR	-83	0	0	0	48	21	629	67	0	0	0	-54	-20	-20	-131	0

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Quantitative Digital Electrocardiography 3 strategies for analysis

- « best complex » for analysis, the one with the least noise and baseline wander
- Analysis of every complex and subsequently averaging of measurements
- Averaging of all complexes morphologically of the same type, « binning » or « representative beat formation »

Representative Beat Formation



10-second digital ECG recording

Representative Beat Formation Other rules

- By rate
- By autonomics (circadian periods)
- By physical activity (exercise, recovery)
- By rate x autonomics
- By rate x physical activity



Representative Beat Formation, by rate



RR 900 bin

After S Reddy et al

Circadian Periods x Rate



Results o	n CH1	ID: 0001	ID: 0001				
Per. 1 (n=1022) 10:00:00-14:00:00	buglu401	QTm = 309 QTo = 383	QRS = 94 PR = 133				
Per. 2 (n=113) 00:00:00-04:00:00	buglu401	QTm = 324 QTo = 398	QRS = 94 PR = 133				

15 msec QT lengthening



Day bin, RR 800





Night bin, RR 800

Physical Activity x Rate



After Krahn Am Heart J 2002

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Overview of the Holter Bin Method

- Patient specific, rate-independent approach of time matched ECGs
- Wide range of RR interval explored for each subject allowing: direct comparison of QT at the same HR between placebo and drug, development of QT/RR regression model
- Control rather than correct for HR

Holter Bin Method: a 3-step process

- 1. Sinus complexes detected and edited from Holter data of each subject are:
 - 1-Sorted by calculated RR intervals
 - 2-Arranged in successive RR categories (bins) of 10 msec
 - With or without control for hysteresis
- 2. For each RR bin, signal averaged waveforms are derived
- 3. QT interval (or other parameters) measured for each bin

1. RR interval measurement



2. Classification of ECG complexes into 10ms groups (« Bins »)



On-screen calipers analysis



Different bin techniques

Average the waveforms WinAtrec Average the intervals Compass

- Only 1 PQRST per RR
 n PQRST per RR bin bin.
- Audit trail of individual beats statistics (e.g. noise, QT, ...).
- Reasonable editing.

- Beat-to-beat QT variability is a direct output.
- Beat-to-beat editing.

Heart Rate Changes with Alfuzosin

	Alfuzosin 10 mg	Alfuzosin 40 mg	Moxifloxacin 400 mg
∆HR (bpm) Mean*	1.5	3.7	1.5
Subjects with ∆HR >15 bpm	7%	33%	9%

*HR differences vs. placebo – Study 5105

sanofi~synthelabo

QT Changes at Various RR Intervals

📃 Alfuzosin 10 mg 🛛 🔲 Alfuzosin 40 mg

Moxifloxacin



sanofi~synthelabo

Binning vs regular ECG samples

		Mean	95			
	Change from baseline	vs placebo (ms)	Lower bound	Upper bound	P-value	
	QT ₁₀₀₀ (ms)	+ 10.26	+ 3.38	+ 17.14	0.0039	
Holter bin method	QT at largest sample size RR bin (ms)	+ 9.33	+ 3.93	+ 14.73	0.0009	
	Average QT change of all RR bin (ms)	+ 8.75	+ 3.30	+ 14.19	0.0019	
	QTcNi (ms)	+ 8.91	+ 3.33	+ 14.32	0.0019	
42 lood ECCo	QTcF (ms)	+ 10.10	+ 4.63	+ 15.56	0.0004	
12-leau ECOS	QT (ms)	+ 6.12	- 2.20	+ 14.44	0.1476	
	HR (bpm)	+ 2.14	- 1.28	+ 5.55	0.2169	

Holter Bin Method Negative Thorough QT Study

QT change at 1000 ms RR bin (ms)



Holter Bin Method Positive Thorough QT Study

QT change at 1000 ms RR bin (ms)



Clinical Trials with RR bin

• Flecainide

Coumel P, Maison-Blanche P, Tarral E, Perier A, Milliez P, Leenhardt A. Pharmacodynamic equivalence of two flecainide acetate formulations in patients with paroxysmal atrial fibrillation by QRS analysis of ambulatory electrocardiogram. *J Cardiovasc Pharmacol.* 2003 May;41(5):771-9.

Amiodarone

Milliez P, Leenhardt A, MaisonBlanche, P, Vicaut E, Badilini F, Siliste C, Benchetrit C, Coumel P. Usefulness of Ventricular Repolarization Dynamicity in Predicting Arrhythmic Deaths in Patients with Ischemic Cardiomyopathy (From the European Myocardial Infarct Amiodarone Trial), **Am J Cardiol**, **2005**; **95:821-826**.

Alfusozin (moxi-validated)

Extramiana F, Maison-Blanche P, Cabanis MJ, Ortemann-Renon C, Beaufils P, Leenhardt A. Clinical assessment of drug-induced QT prolongation when associated with heart rate changes. **Clin Pharmacol Ther. 2005;77:247-58.**

Three other compounds (all moxi-validated)

using both conventional 3 leads and 12 leads Holter recordings, using both rate and time bins

Criticisms to the Holter bin



- Within the Period, the time reference is lost.
- Averaging waveforms in Holter can be a problem.
- Does not account for hysteresis

Not True!

From rate-bins to time-bins





Time bins, 1 minute

OFF drug Bins ON drug Bins

Proper Beat Averaging

Trigger jitter correction



With 20 msec bin resolution, the same QRS could have been assigned 4 bins to the left!!!!

Hysteresis during Holter



real QRS complexes with same RR intervals taken from the same subject in a 3 hour time frame

Hysteresis two simple examples

RR-1 = RR-2 = $RR_{MIN-1} \pm th$ Where *th* is a threshold set by user Subperiods of RR_{MIN-1}

Determines the RR bin

 $RR_{P1} = RR_{P2} = RR_{P3} \pm th$ Where P1 = P2 = P3

F. Badilini, Med Biol Eng Comput 1999; 37: 71

Moxifloxacin effects on QT interval Control for heart rate stability

	RR-1	R30	R60	
ΔQT700	4.3±3.9	7.0±4.7	4.3±5.1	
ΔQT800	2.7±3.9	4.4±3.2	3.7±3.2	
ΔQT900	4.2±7.2	7.3±6.7	7.5±6.4*	
ΔQT1000	8.2±11.2	10.7±9.4*	11.1±10.6*	
ΔQT1100	10.5±13.0	12.6±13.0	13.8±9.5	
ΔQT1200	15.0±21.2	15.0±11.3	13.0±14.1 28	

2D binning: Rate and Time

RATE BINS

- Few templates to edit
- Loose time track

- TIME BINS
- Many templates to edit
- Track time

- No need HR correction
- Need QTci

 Good for slow response drugs



Good for fast response
 drugs

Thank You !