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Automated JTpeak analysis by BRAVO

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Abstract Using BRAVO algorithm (AMPS-LLC, NY, v4.4.0), 5223 ECGs from a publicly available annotated dataset from a randomized clinical trial on four different compounds and placebo were analyzed. ECGs were automatically processed and JTp interval was computed on: 12 standard ECG leads, Vector Magnitude (VM), and root mean square (RMS) leads. On VM and RMS, JTp intervals were nearly identical (228 ± 29 vs. 227 ± 30 ms respectively, with correlation of 0.99, $p < 0.0001$). On lead II, JTp interval was about 10 ms longer, but highly correlated with that measured on VM (0.94, $p < 0.0001$). Similarly, on lead V5, JTp was about 8 ms longer than on VM, with a correlation of 0.95, $p < 0.0001$. When compared to the public available annotations, JTp by BRAVO generated longer (about 8 ms) measurement and evidenced outliers conducible to both the T-wave peak (in few ECGs presenting notched shapes) and, to a lesser degree, to the J point, due to variability of the two algorithms. Differences on the drug-induced effect from the four compounds were negligible.

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Introduction

Measurements of time intervals and voltage amplitudes are critical to clinical diagnoses made by automated ECG diagnostic algorithms. Several ECG measurement fiducial points, such as the end of the T-wave, the T-wave peak and the end of the QRS complex (J point), have no precise medical and mathematical definition; consequently different algorithms, from both manufacturer industry and research community, have evolved different engineering and algorithmic solutions.

This study has been conducted under the premises of the "JTPeak initiative for the ISCE 2017 meeting" and because of that the methodology applied followed the guidelines and directions recommended by the organizers of the initiative. The data consisted of the ECG from a randomized placebo controlled five-way single dose crossover clinical trial, the ECGRDVQ database [1,2], which was made publicly available through the PhysioNet platform [3].

The ECGRDVQ database consists of multi-channel ECG recordings from 22 healthy subjects partaking from a randomized, double-blind, 5-period crossover clinical trial aimed at comparing the effects of four known QT prolonging drugs (placebo, ranolazine, dofetilide, verapamil and quinidine). ECG data was originally acquired from 12-lead Holter recordings (H12+, Mortara Instrument) and later processed to obtain 10-seconds triplicate ECGs extractions at 16 predefined time-points using Antares software (AMPS-LLC, NY) [4]. Out of the overall 5232 extracted ECGs, 5223 also included the representative median beats and the vector magnitude (VM) lead based on the vectorcardiogram (as obtained from the Mason–Likar 12-lead ECG by applying the Guldenring transformation matrix [5]). Finally, the database provides semi-automated annotations based on the VM lead, which contains marker positions for the P wave onset, the QRS onset, the J point, the T-wave peak (and secondary T-wave peak, when present) and the T-wave offset. Of note, reference Physionet annotations for J-point, Tpeak and Tend were first automatically obtained with ECGLib (an automated algorithm that reproduces these human Tpeak and Tend annotations which has been recently released as open source [6,7]), and then semi-automatically reviewed by human ECG readers [1].

Methods

ECG data from the ECGRDVQ database was automatically processed with BRAVO algorithm (AMPS-LLC, NY, v4.4.0). This algorithm provides comprehensive, protocol-dependent and user configurable ECG

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measurements on both individual beats from rhythm (10-second) data and on representative (mathematically derived) leads. For the purpose of this study, the analysis focused on the J-to-T-wave peak (JTp) interval measured on the 12 standard representative leads and on the associated Vector Magnitude (VM) lead available from the ECGRDVQ source data. In addition, the root mean square (RMS) lead, which (as the VM) is another "global" lead commonly used in commercial algorithms, was also computed and the JTp interval measured.

In BRAVO, the detection of the J point is based on the analysis of a time window centered in the QRS complex, whereas the T-wave peak is determined on the low-pass filtered repolarization segment with combined analysis of the filtered and first-derivative signals.

The detection of J point slightly differs when performed on standard versus global leads. On standard leads, the QRS complex is first normalized and filtered (using a variable-length moving average), and the first derivative is computed. The J point is defined as the first inversion point of the first derivative after the R-wave peak; in case an inversion point is not detected, the J point is defined as the left edge of a 15 ms minimal variability buffer of the normalized/filtered wave. On global leads, the QRS complex is first processed with an high-pass numerical filter; the J point is then searched on the filtered QRS with an adaptive threshold approach, applying a 100 ms window starting 40 ms after the R-wave peak. The J point is assigned when four consecutive samples of the filtered signal reach an amplitude lower than a prefixed threshold (J point being the first of the four samples); when this condition is not met, the threshold is iteratively increased until the J point is identified.

Independently of the type of processed lead (standard or global), the detection of the T-wave is obtained on the low-pass filtered first derivative (using a bidirectional 4th order Butterworth), and by characterization of first-derivative zero crossings within a heart-rate dependent window. A single zero crossing identifies the T-wave peak associated with a monophasic T-wave, whereas more zero-crossings are associated with more complex repolarization morphologies and the T-wave peak is either the first or the third crossing, whichever closer to the T-wave absolute maximum. A user selectable minimum T-wave amplitude threshold, which for this study was set to 100 μV, is finally applied.

Qualitative and quantitative comparisons between all the JTp intervals were performed; in addition, Bland-Altman analyses were conducted to compare the JTp measurements on the VM lead as automatically provided by BRAVO versus the reference annotations in ECGRDVQ [6,7], and on the BRAVO measurements comparing first VM and RMS leads and then RMS and standard lead V5.

The drug effect produced by the different compounds was assessed by quantification of baseline and placebo corrected variations of the JTp interval (double-delta JTp, or ΔΔJTp) computed on each of the timepoints over the four arms of the study. The double-delta analysis was also repeated on the heart-rate corrected JTp interval (JTpc) which was computed using a power-law model with a coefficient of 0.58, as previously proposed in the literature [8].

Results

Summary results of the JTp interval measurements by BRAVO algorithm and by the reference annotations in ECGRDVQ on VM are reported on Table 1. On the VM lead, the JTp interval was measured on almost all ECGs, both by ECGLib-based approach and by BRAVO algorithm. BRAVO successfully measured JTp interval also on the RMS lead and on lead II, aVR, V2-V6 (with an incidence >98%). Conversely, and mainly due to the low T-wave amplitude, on lead V1 and aVL the JTp interval was measured only on <50% of the ECGs.

The shortest JTp intervals were measured on lead V2 and V1 (210 ± 28 and 215 ± 4 ms, respectively), whereas the longest measurements were observed on lead III (242 ± 27 ms) and lead II (239 ± 27 ms). On the VM lead, the JTp measured by BRAVO was significantly longer than the one measured in ECGRDVQ (228 ± 29 vs 221 ± 29 ms, $p < 0.0001$).

Bland-Altman analyses (i.e. comparison of the differences versus the averages of different pairs of JTp intervals) are shown in Fig. 1. Panel A refers to the differences of the JTp intervals on the same lead VM between the two methods (same lead, different approach) whereas Panel B shows the differences in JTp as measured by BRAVO on the VM and RMS leads (same algorithm, different global leads). Panel C shows the differences in JTp as measured by BRAVO on V5 and RMS leads (same algorithm, standard lead versus global lead).

The algorithm comparisons on VM lead (Panel A) indicate a significant bias of 7.9 ms (JTp longer with BRAVO) with 44 ms 95% limits of agreement, but the absence of a significant trend slope effect. About 30 outliers (almost all from the quinidine group), were observed and were all linked to ECGs with T-wave notches, which will be commented in the Discussion section. Conversely, BRAVO comparisons between VM and RMS enhanced small biases (<1 ms) and narrower 95% limits of agreement (19 ms). Finally, BRAVO comparisons between V5 and RMS leads indicated a significant negative slope of 0.056, with an averaged bias of 9.3 ms (JTp longer on V5 lead) and a 95% limits of agreement of 41 ms.

The drug effects as per ΔΔJTp/ΔΔJTpc analysis for the dofetilide study arm are reported in Fig. 2. ΔΔJTp assessed by BRAVO algorithm on the two global leads were nearly identical, reaching a maximum of 40.0 ± 5.5 (mean ± SE) and 40.3 ± 5.8 mecs at the 2.5 h timepoint, on VM and RMS leads respectively. At the same timepoint, ΔΔJTp of VM lead in ECGRDVQ was about 1.5 ms lower, with comparable SE. ΔΔJTp on lead V5 was 7 ms longer (with SE of 3.9 ms) than that on VM lead (measured by BRAVO).

Very similar results (but somehow less interesting, due to the lack of a significant JTp effect) were observed with verapamil and ranolazine, with nearly identical ΔΔ curves on the lead VM by the two methods. On the quinidine study

Table 1
Summary results of JTp intervals on different leads computed by BRAVO algorithm and by all available leads and on the VM lead reference annotations from ECGRDVQ.

	ECGRVDQ	BRAVO algorithm												
	VM	VM	RMS	I	II	III	aVR	aVL	aVF	V1	V2	V3	V4	V5	V6
Detection (%)	99.96	99.96	99.92	90.25	99.18	84.32	98.33	39.27	95.39	24.56	98.81	98.54	99.22	99.43	99.02
Mean (ms)	221	228	227	228	239	242	236	224	241	215	210	225	234	237	238
SD (ms)	29	29	30	27	27	27	27	33	27	44	28	30	31	28	27
Min (ms)	132	141	139	157	162	135	163	150	163	138	143	137	153	159	164
Max (ms)	360	360	365	347	373	363	358	338	382	333	371	399	384	374	367

arm, a peak effect of about 20 ms (confirming what reported in the literature) was shown on all curves, but with a few noticeable differences, which were however linked to the same outliers of Fig. 1A (ECGs with T-wave notches). After removal of these outliers the quinidine ΔΔ curves on the lead VM by the two approaches were again nearly the same.

Discussion

This study has been conducted under the premises of the "JTPeak initiative for the ISCE 2017 meeting", which required analysis of JTp intervals as applied to ECG data from a previously published crossover trial involving four QT prolonging drugs (ranolazine, dofetilide, verapamil and quinidine) [1]. The ECG source data, publicly available from PhysioNet [3], consisted of both the 10 seconds 12-lead rhythm (extracted from continuous Holter recordings), and the computed representative (median) beats inclusive of the derived orthogonal leads Vx, Vy and Vz and the Vector Magnitude VM.

Our analysis of JTp was performed on the 12 median beats and on (two) globally derived leads: the vector magnitude lead VM, and the root mean square lead RMS. This choice's rational is simply based on previous literature, but also on most common commercial systems, which are based on median beats.

All results based on Bravo are fully automated, i.e. no editing or data exclusion has been applied on the outputs produced by the measuring algorithm (other than the automated exclusion of leads in which T-wave was found to be smaller than 100 μV). For some of the reported comparisons (and more specifically for the comparisons with the ECGLib-based analysis in ECGRDVQ, which on the contrary is based on a semi-automated analysis) this may be misleading. On this regard, we want to stress that the by-algorithm comparison was not done with the intent to

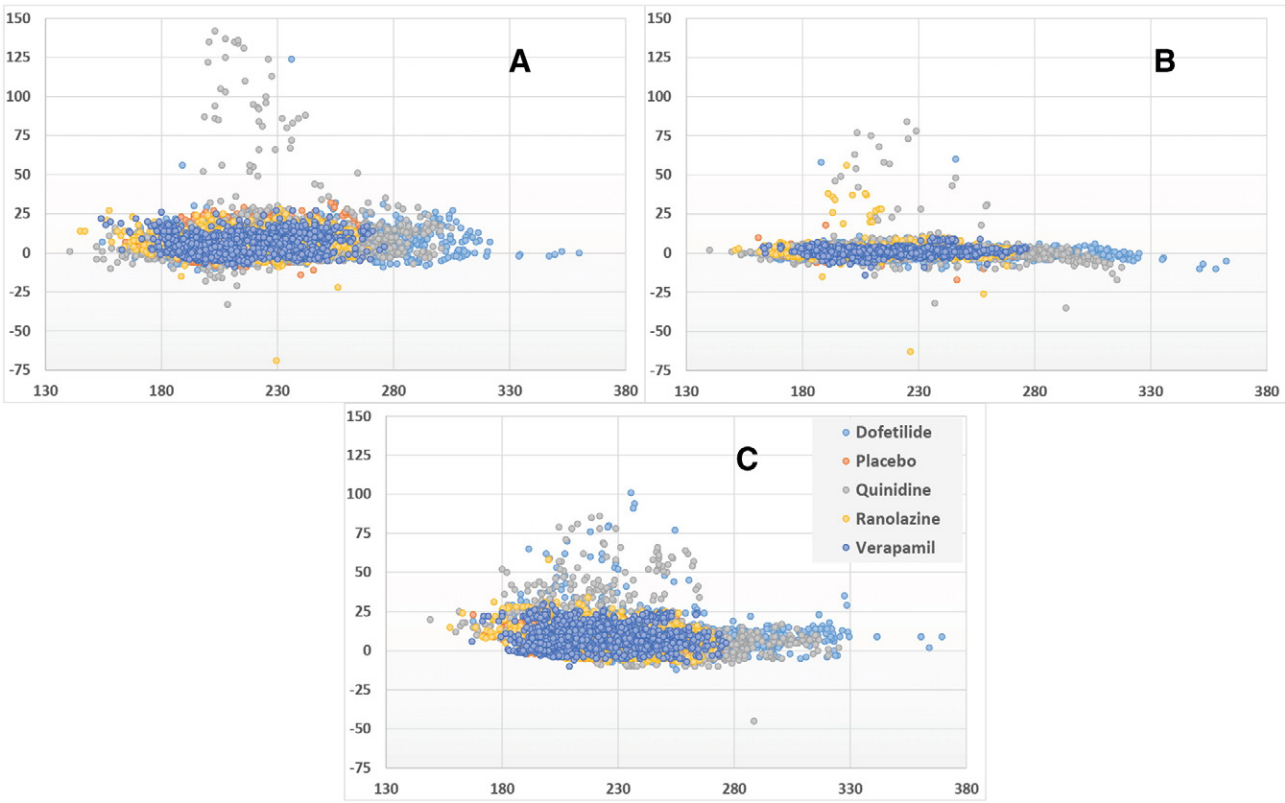

Fig. 1. Bland-Altman plots of JTp intervals: JTp measured on lead VM by BRAVO vs. ECGRDV (A), JTp measured on VM and RMS leads by BRAVO (B) and JTp measured on V5 and RMS leads by BRAVO (C).

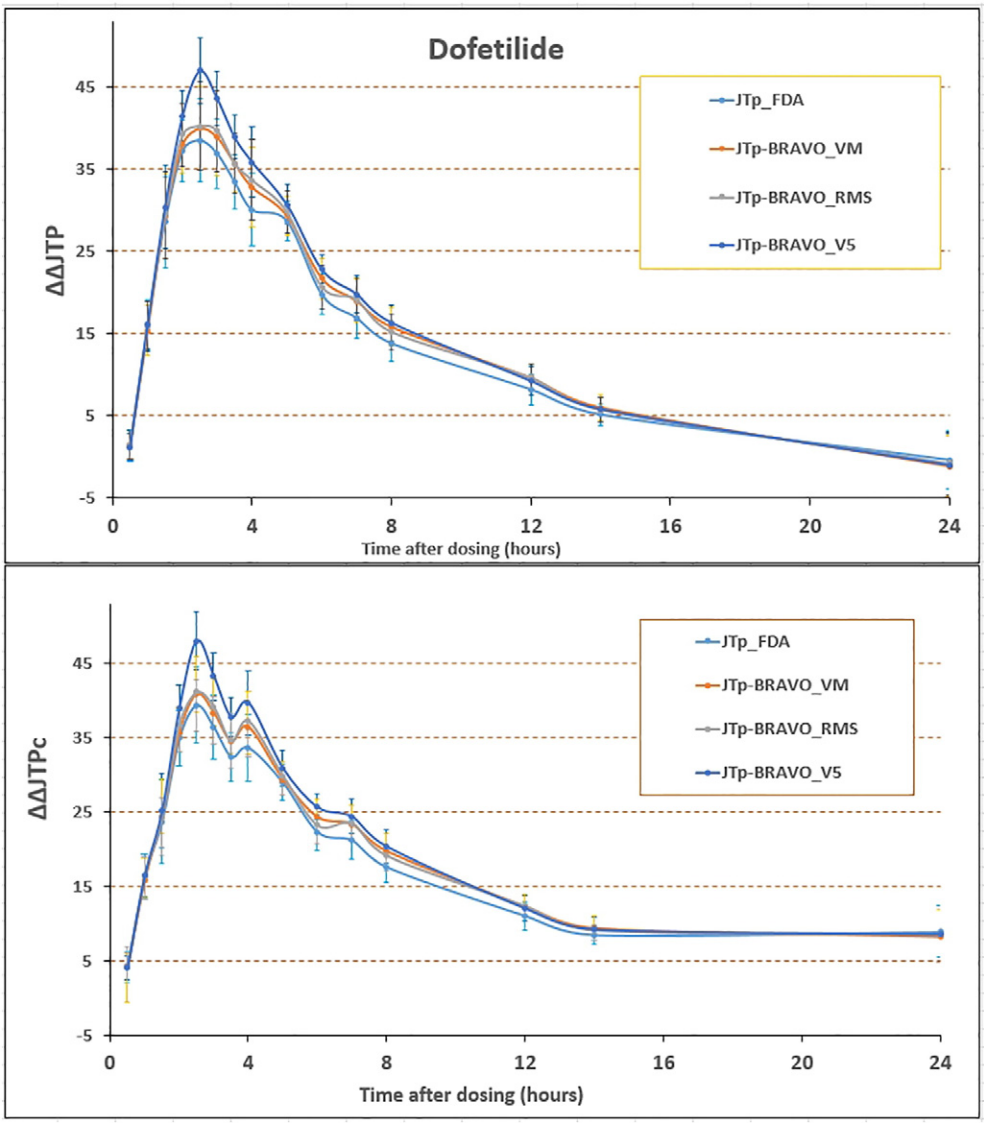

Fig. 2. ΔΔJTp/ΔΔJTpc of four different JTp intervals from the dofetilide study arm.

establish a gold standard, but simply with the goal to gain insight on potential differences arising by different methods when dealing with the JTp interval.

As expected, leads presenting a more pronounced T-wave were measured with higher incidence of success (e.g. VM, lead II and lead V5, which were measured on >99.9% of the ECGs, as reported in Table 1). Somehow expectedly, significant between-leads differences were observed (e.g. lead II and V5 when compared to the global leads); but perhaps more surprisingly, significant differences (about 8 ms) were also observed in the by-algorithm comparison.

Going into more details, and focusing on the data shown in Fig. 1, it is however apparent that both method-dependent (Panel A) and lead-related variabilities (Panels B and C) can be observed. The dispersion and variability between the two methods can be linked to two separate effects. The first is related to alterations on the morphology of repolarization leading to notch-like shapes, which in this study was particularly evident in the quinidine branch (although limited to some subjects and only observed at the highest concentration levels of the drug), but visible also on few ECGs of the dofetilide arm. In these cases, and in absence of a clear rule, different algorithms can select different T-wave peak points (depending for the internal rules applied) [9], leading to a disagreement that can reach the magnitude of several decades of milliseconds. Fig. 3A (left hand side), selected from one of the big JTp outliers from the dofetilide study arm, is a representative example of this effect: the green color lead is the VM over which the two algorithms choose different peaks.

The second effect, of smaller magnitude but systematically present, (and somehow less expected), is the between-method variability in the detection of the QRS offset marker (J point) which apart for the few outliers is causing the large scatter of Fig. 1A. Indeed, even after the removal of the ECGs with double T-wave peak morphologies, the 95% limit of agreement remains in the 30 ms range. Fig. 3B (right hand side), selected from the center of the scatter plot, is a representative example of this effect: on this ECG, pooled from placebo arm, the difference in JTp interval (26 ms) was solely linked to the difference of the J point.

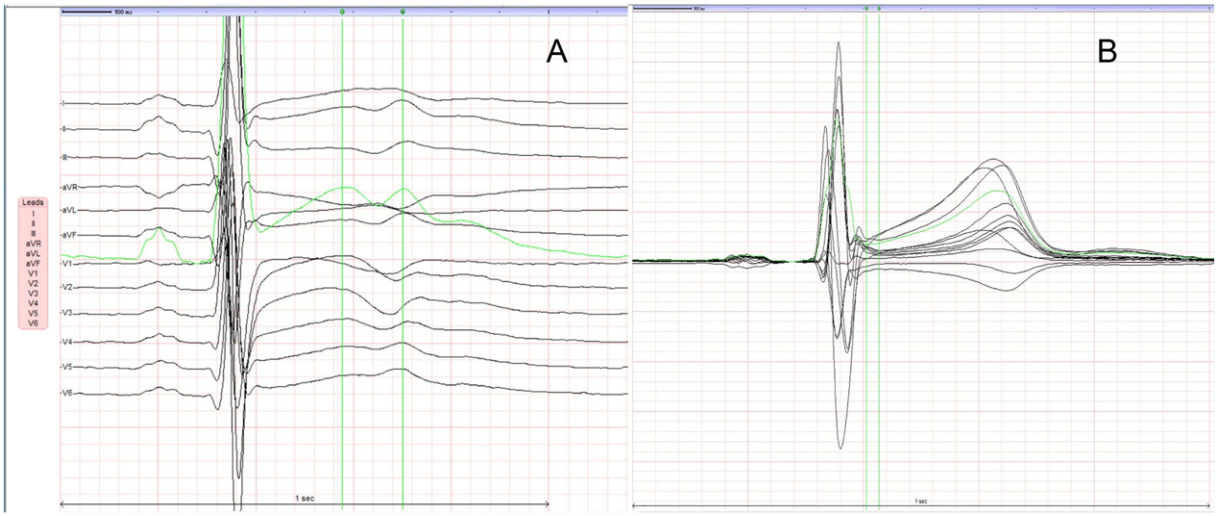

Fig. 3. JTp interval differences on VM lead between the two compared methods, due to difference placement of T-wave peak (A) and J point (B) annotations. A and B are ECGs from dofetilide and placebo study arms, respectively.

But even using the same algorithm/method, differences can be observed. Fig. 2B, which shows JTp difference as measured by BRAVO on VM and RMS leads, has a very narrow spread (and null bias) but still enhance a few outliers. One representative example is given in Fig. 4, with the blue trace being the VM lead and the green the RMS. Once again, this is a problematic ECG with a broad shape (although without a clear notch) related to the high drug concentration; the different in shapes of the VM and RMS leads is remarkable and warns us that even "global" leads should be taken and used with some caution.

Despite the reported by-algorithm comparison differences, the overall drug-effect results are remarkingly close to those previously published (Fig. 2). At least for the four compounds of the dataset, BRAVO algorithm can thus properly track drug effects with a fully automated approach.

In conclusion, automated analysis of JTp by BRAVO has been demonstrated feasible and reliable, although some caution has to be taken, particularly with respect to the correct definition of J point which may turn out to be more critical than the T-wave peak.

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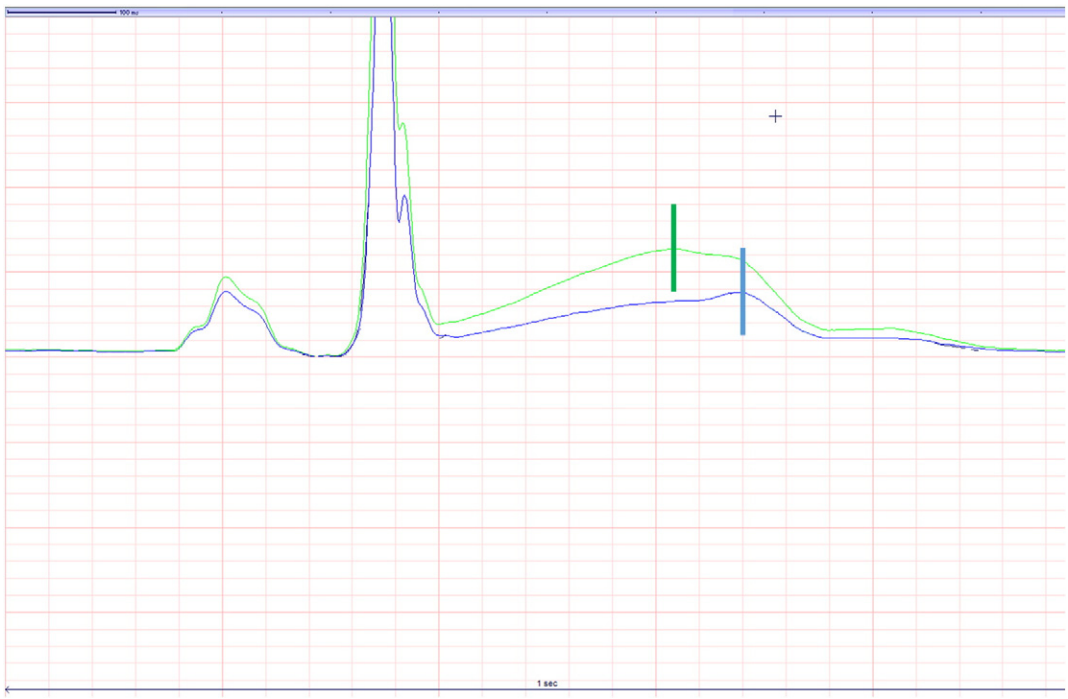

Fig. 4. Different T-wave morphology on the two global leads VM (in blue) and BRAVO-generated RMS (in green), causing very different T-wave peak detection.

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