

Analysis of Intracardiac Electrogram Changes

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Abstract

The main purpose of this study is to investigate if sinus conducted beats in patients with a conventional ICD have changing intracardiac electrograms (EGM) and if any association with ventricular tachycardia or ventricular fibrillation (VT/VF) exists.

Thirty-two patients with ICD implants were included. Sinus conducted EGM complexes were investigated. For each beat similarity measures were calculated in relation to all other beats. All beats satisfying the beat similarity criterion were allocated to the same morphology group. Normal beats were defined according to the beat morphology group similarity between visits. If the similarity between these normal beat clusters did not satisfy the similarity criterion, this was defined as EGM change. The number of EGM morphology groups were also observed.

During the observation period EGM changed in 7 (20%) of the patients while 14 (44%) had > 5 EGM morphology groups. No association with VT/VF was observed, but the number of morphology groups increased significantly by age.

1. Introduction

In heart with sinus rhythm, the activation wavefront enters the A-V node from the atria and is distributed from the Bundle of His through myocardial cells. These cells depolarize and the QRS complex of the intracardiac electrogram (EGM) is formed. Following the cellular refractory period, the cells repolarize in time for the next activation wavefront. The conductive wavefront may change over time, and if the EGM produced by the modern ICD is able to record these changes, the EGM is a potential tool for detection of small differences in sinus conducted beats. It is the purpose of this pilot study to report if there are EGM morphology changes during different observation periods in patients with a conventional ICD.

2. Material and methods

Except for one patient, the study was performed in patients with first time ICD implantation. All patients received the same device (Vitality 2 DR[®], model T165 and T167, Guidant Corp.). The atrial and ventricular signals were derived with bipolar sensing. The lengths of the right ventricular and atrial leads were 64 and 52 cm respectively. Only EGM recorded between the shock canal and superior vena cava + can was used for morphological analysis. The filter characteristics of the EGM channel was 20-140 Hz. The study was approved by the Regional Ethics Committee, and informed consent was obtained from all patients.

The patients were seen during follow-up at week 1, 4, 12, 24. Three minutes of EGM with a sampling rate of 200 Hz were recorded during rest and in supine position. Measurement of the pacing impedance of the atrial-, ventricular- and shock leads were done in all patients in addition to the amplitude (mV) of the atrial- and ventricular leads and their pacing thresholds (V) with a fixed pulse width of 0,5 ms. With both atrial- and ventricular leads, it was possible to distinguish between atrial and ventricular arrhythmias. In order to detect ventricular tachycardia, the initial detection interval at the start of the study was set low and adjusted upwards if sinus tachycardia, frequent episodes of high rate atrial fibrillation or frequent episodes of nonsustained ventricular tachycardia occurred. For 29 patients the lowest monitoring zone had a cycle length (CL) of 428 ms, and 3 patients had a cycle length between 500 and 480 ms. Ventricular tachycardia (VT) or ventricular fibrillation (VF) was classified as VT/VF when 8 of 10 CL were \leq the detection limit and with duration of > 2.5 s. At follow-up visits it was possible to determine the first VT/VF in number of days after ICD implantation.

With MATLAB, a semi-automated method was used to detect the fiducial points as the highest deflection of the QRS complexes in the ventricular channel. The P wave was detected in the atrial channel in a similar way (Figure 1). All QRS complexes in the EGM channel were paired with the closest preceding P waves. The QRS complexes without preceding P waves were not included for further

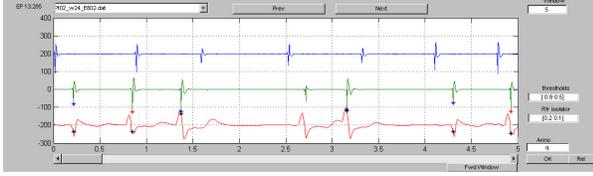


Figure 1. The graphical user interface developed for detection of P and QRS waves. Cardiac activity measured by the ICD from top to bottom: atrial channel (A), ventricular channel (R), and EGM channel (S).

analysis. The RR interval before and after the QRS complex had to deviate by less than 10 % of the median of 5 RR intervals before the QRS complex. Also the ratio between the RR interval before and after the QRS had to be 0.8-1.2. The analysis epoch for the beat was from 150 ms before and 450 ms after the fiducial point.

In each episode all delineated normal beat candidates are analysed to automatically cluster all beats according to similarities in shape[1]. The delineated beats are denoted by $b_i(n)$, $i = 1, \dots, N$, $n = 1, \dots, M$ where b_i , n , N and M correspond to beat number i , sample number, number of beats and number of samples, respectively. As an example, 13 candidate beats with varying beat shapes are shown in figure 2.

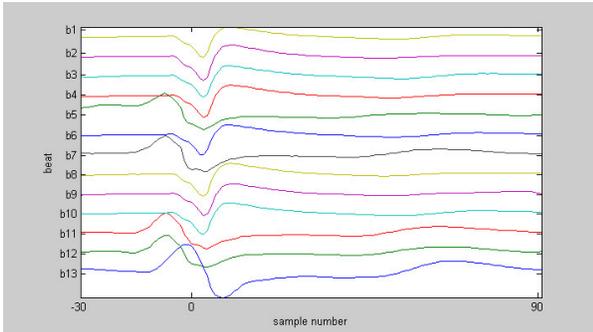


Figure 2. 13 delineated example beats from episode shown in figure 1.

For each beat, b_i , the correlation coefficient, r_{ij} , and root mean square deviation, rms_{ij} , are calculated to express the similarity between beat b_i and b_j . Thus b_i can be compared to all other beats, b_j , $j = 1, \dots, N$, $j \neq i$, and for episode number l , all beats, b_j , satisfying the similarity criteria, $r_{ij} \geq 0.95$ and $rms_{ij} < 0.3$, arbitrary chosen, are defined as belonging to the same beat cluster, $\omega_{k,l}$, as b_i ($\omega_{k,l}$ is cluster number k in measurement series number l for a given patient).

The same procedure is continued for the next beat, b_m , not yet classified into any group. If b_m satisfies the similarity criteria for any beat already classified, b_m is classified into that cluster. Looking at the beats in figure 2, the algo-

rithm would start checking the similarity between b_1 and all the other beats. If the similarity criteria are satisfied by $b_2, b_3, b_4, b_6, b_8, b_9, b_{10}$, these beats would be classified as belonging to the same cluster, $\omega_{1,1}$, as b_1 . Furthermore b_7, b_{11}, b_{12} would be classified as belonging to the same cluster $\omega_{2,1}$, as b_5 while b_{13} would define its own cluster $\omega_{3,1}$.

One cluster in each episode should be identified as representative for the patient's normal beats, and only clusters containing 20 or more beats are considered. For a candidate cluster sequence, the sum of the average value of all interbeat correlations between the neighbour clusters in the sequence are computed, and the normal beat sequence is defined as the sequence among all possible sequences yielding the highest value. Figure 3 A and B illustrates the result of identifying the sequence of normal beat clusters in two patients shown in the top row of the subplots in the two figures.

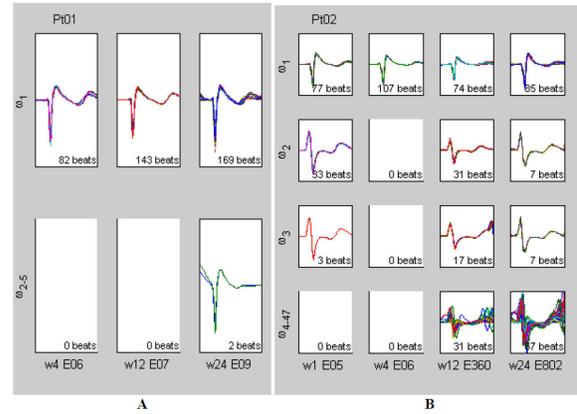


Figure 3. Examples of identifying the sequence of normal beat clusters ω_1 shown in top row with few clusters in (A) and many in (B).

For each episode, the intercluster correlations are calculated to express the EGM changes from the normal beats in the initial episode to the normal beats in a later episode. The numbers of beat clusters in each episode are also calculated.

Fishers exact test was used when comparing categorical variables and Mann Whitney U test for continuous variables. Spearman rank correlation was used for calculation of correlation between EGM changes and standard deviation of the RR interval. The formula used for calculation of beat shape diversity is explained under that heading. Linear mixed effects models[2] with random intercepts and EGM-correlation or numbers of clusters as responses and weeks after the first measurements as explanatory variables, were fitted to test whether there were systematic changes over time in the mean of these measures.

3. Results

We studied 32 patients, 27 males and 5 females, mean age 64 ± 8 years. Thirty patients had coronary heart disease (CHD) with postinfarction scars and 2 had dilated cardiomyopathy (DCM). In the latter two patients, one probably had postviral- and the other cytostatic induced DCM. Left ventricular ejection fraction (LVEF) was 31 ± 10 %. All patients had first time ICD implantation, except for one patient with device replacement. The indications for ICD implantation were secondary prevention in 18 patients, 9 with sustained VT and 9 survivors of sudden cardiac death. Fourteen patients had primary prevention as indication for ICD implantation and these patients had nonsustained ventricular tachycardia (NSVT) and LVEF < 30 %. The follow-up time was 24 weeks for 27 patients and 12 weeks for 5 patients. No patient had any acute coronary syndrome during the follow-up period.

A total of 118 electrograms recorded from the 32 patients were analysed. The mean RR interval of all beats recorded were $903 \text{ ms} \pm \text{SD } 189 \text{ ms}$. No significant differences between the RR interval recorded at each follow-up were observed ($p > .1$). Only sinus beats were included in the study and their median number was 94 % (minimum 11 % and maximum 99%) of all beats. No relationship between the standard deviation (SD) of the RR interval of all included sinus beats and EGM-correlations were found ($p = .725$). All correlations of the EGM at week 4, 12 and 24 have recordings at week 1 as reference, except for 3 patients with the reference at week 4, but the changes from week 12 to week 24 were also calculated. During the observation period EGM changes as classified by $r_{ij} < 0.95$ and $rms_{ij} > 0.3$, were observed in 7 (20%) patients. Patients with more than 5 EGM clusters in any of the episodes recorded at follow-up, were observed in 14 (44%) patients.

There was a significant decrease in EGM correlations over time ($p = .002$) with an estimated change per week of -0.001 . The EGM morphology changes from week 12 to 24 had a borderline significance of $p = .08$. For clusters there were no significant changes during the complete observation period ($p = .38$).

Fourteen of the 32 patients had VT/VF with a median RR interval of 335 ms (428 ms 260 ms) at VT/VF detection, corresponding to a median pulse rate of 179 (140-230). By crosstabulation of VT/VF with EGM correlation < 0.95 or ≥ 0.95 and cluster ≤ 5 or > 5 , no significant differences were observed. When the number of clusters recorded during a 3 minutes period at week 1, 4, 12 and 24 (12 weeks for 5 patients), were summed up, no significant differences ($p = .62$) between the group with or without VT/VF were observed. The amplitude, impedance and threshold values and the changes of these values during the observation period were not different between the group with different EGM correlation or numbers of clus-

ters. The value of LVEF, ProBNP and IMA were not significantly different between the groups with EGM correlation < 0.95 or ≥ 0.95 and cluster ≤ 5 or > 5 . There was significantly ($p = .037$) more clusters in the high age group.

4. Discussion

If a correlation of < 0.95 is accepted as change of EGM, 7 of 32 patients had changes. The mean EGM-correlations decreased significantly during the relative short observation period from week 1 to week 24. During a period of about 12 weeks after lead implantation, a healing process with local inflammation, edema and fibrosis occurs. If the healing process was the cause of EGM changes, one would not expect the EGM changes to increase during the whole observation period of 24 weeks. There were no significant differences in the impedance of the ventricular and shock canal or amplitude of the ventricular lead and the ventricular threshold values between week 1 and 24. These findings support the assumption that the EGM changes are not caused by post implantation inflammation. At follow-up, all recordings are from the supine position and at rest with no significant change of the recording RR interval. It is therefore very unlikely that the EGM changes are due to changes in body position or rate-dependent aberrancy. Moreover the medication during the study period was not altered. To exclude changes of EGM caused by respiration, comparison of the variation of the RR interval and the corresponding EGM correlations were calculated and no association was found. However, the average age of the population was 64 ± 8 years, and respiratory sinus arrhythmia expressed as variation of the RR interval due to breathing, declines steadily from age 9 to near zero at age 62[3] Therefore changes in the EGM and respiration cannot be excluded[4]. The far-field EGM is a registration between right distal ventricular shock coil and superior vena cava shock coil + can located in the left pectoral region, and migration of the can electrode can not be excluded as a cause for EGM changes. Generally the EGM changes are small, except for two patients, but we are unable to determine if this was related to lead migration or change of the myocardial substrate. Subtle morphologic EGM changes during the first 3-months after ICD implantation are also documented in other studies[5-7].

Our study was not addressed to answer this question, but we have explored the possibility of any connection with coronary circulation and myocardial damage. The two patients with cardiomyopathy, had no EGM-changes. Our measurements of coronary circulation are only surrogates and have to be interpreted with great caution. In CHD patients with visible retrograde coronary flow, we were unable to demonstrate any association between EGM-changes, clusters and retrograde coronary flow. IMA is a marker of myocardial ischemia, and high IMA at rest

and after exercise has been observed in patients with myocardial ischemia during perfusion scintigraphy[8], but we were unable to demonstrate any differences in IMA between the two groups in our study. With age, many physiological changes occur and some may be related to poorer circulation and more tissue heterogeneity. This assumption is supported by the finding of significantly more clusters in the highest age group. However, due to the multiple testing done, there is also a chance that this is a false positive finding. LVEF is widely used as a measure of cardiac damage, but we could not demonstrate any association with EGM-changes or clusters. Pro-B-type natriuretic peptide is a measure of heart failure, but we could not demonstrate any association of this peptide with EGM-changes and clusters.

During the relative short observation period, we were unable to demonstrate any association between the incidence of ventricular arrhythmias and EGM-changes. If the EGM changes during the 24 weeks of observation are caused by changes of the myocardium, the used lead configuration will only reflect EGM changes in the right ventricular apex and the interventricular septum. Furthermore, loss of myocardium is in most cases not associated with arrhythmias, rendering it difficult to detect all association between EGM-changes and arrhythmias, especially with a short observation period. Our results only confirm the need for automatic template updating.

The frequency of ventricular ectopic activity has for a long time been recognised as a risk factor for serious ventricular arrhythmias[9]. We examined every sinus beat with a window of 150 ms before and 450 ms after the fiducial point. Patients with the “R/T” phenomena will therefore occasionally have an EGM recorded and classified as a cluster (Figure 3). During this relatively short observation period of 24 weeks, we were unable to find any association of clusters with VT/VF.

In this study we have used a leader-follower clustering algorithm combined with the crosscorrelation coefficient as a measure of pattern similarity[1]. Use of other algorithms or limits for significances may have given different results. Modern ICDs use morphology discrimination criteria as a tool to discriminate supra- and ventricular-arrhythmias, but they are not designed for the purpose of quantifying EGM changes. The ICD will always represent a limitation due to many features such as software, electrode configuration, sampling frequencies and storage capacity. The 8-bit A/D conversion we used may decrease the sensitivity to find subtle changes, and are a potential limitation. The small number of patients, limited number of episodes, short recording times for each episode and lack of correlation of EGM changes and respiration sensors is a limitation in this study. Furthermore, the EGM is not recorded from all parts of the heart, and the beat simi-

larity criteria values were also determined arbitrarily.

5. Conclusion

Patients with ICD have EGM morphology changes over time, but the reasons for these changes have not been clarified. Analysis of normal sinus mediated beats reveal classes or clusters of different EGM complexes. No association of VT/VF and EGM changes, clusters, retrograde coronary circulation, LVEF, ProBNP or IMA was observed, but the numbers of clusters increased significantly with age.

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