ラット心電図における陽性T波の成因

誌名	動物の循環器 = Advances in animal cardiology
ISSN	09106537
巻/号	261
掲載ページ	p. 24-32
発行年月	1993年

動物の循環器 第 26 号, (1) 24-32 (1993)
Adv. Anim. Cardiol. No. 26(1). 24-32 (1993)

原著

Studies on the positive T Wave on ECG in the Rat - Based on the Analysis for Direct Cardiac Electrograms in the Ventricle

Jun SUZUKI, Hirokazu TSUBONE[1] and Shigeru SUGANO[1]

Development Research Laboratories, Banyu Pharmaceutical Co., Ltd., 810 Nishijo, Menuma-machi, Saitama 360-02, and 1) *Department of Comparative Pathophysiology, Faculy of Agriculture, The University of Tokyo, 1-1-1 Yayoi, Bunkyo-ku, Tokyo 113, Japon*

(Received 27 January 1993/Accepted 25 September 1993)

Abstract. In order to obtain direct evidence of the genesis of "positive" T wave on the standard limb lead II electrocardiogram (ECG) in the rat, ventricular activation and its recovery patterns were investigated by recording direct cardiac electrograms. Multiple unipolar electrograms were recorded from 7 sites in the left ventricle including the septum, subendocardium and subepicardium under the constant sinus rhythms in 12rats. The unipolar electrograms and their differentiated waves were analyzed for local QT intervals and local activation times, respectively. In addition, the direct bipolar electrograms between the subendocardium and the subepicardium of the left ventricle were also recorded in 6 rats. The proceeding times from the septum (initial) to the subepicardium (terminal) were very short as less than 10 msec. Nevertheless, the activation sequence in the left ventricle was clearly shownin accordance to the following order ; the septum, subendocardium and subepicardium. The local QT intervals in the subepicardial sites were significantly shorter than those in the corresponding subendocardial sites ($p<0.05$). These activation sequences and local QT intervals in the rat ventricle suggest a presence of transmural gradient of depolarization and repolarization, with an earlier depolarization at the endocardium and with an earlier repolarization at the epicardium. Such a transmural gradient might produce an electrical dipole which would contribute to the configuration of positive T wave on the rat ECG. In fact, the positive waves recorded by the direct bipolar electrograms between the subendocardia and the subepicardia can account for the formation of an electrical dipole having a positive charge at the subepicardia against the subendocardia.

Key Words: ECG, electrogram, rat, T wave, ventricular activation

INTRODUCTION

On the limb lead II electrocardiogram (ECG) in the rat, T wave has a positive polarity as does the QRS complex, similar to T wave in the normal human ECG, although there are several noticeable characteristics such as an extremely short QT interval and a lack of ST segment in the rat as compared with the human ECG[1-4]. In the case of human ECG, T wave concordance has been explained by the fact that the repolarization wave travels in an opposite direction to the depolarization wave in the ventricular wall[5-9]. It has been also explained by the cellular event that myocardial cells with an earlier activation at the endocardial site have longer action

potential durations than those with a later activation at the epicardial site[5,7,9]. The same mechanism is speculated to be applied to the rat heart, but any line of evidence to prove this is still not available. The rat is one of useful experimental animals for the assessment of the drug effects on cardiac functions, and various changes in T wave or QT intervals were found with regard to some drug effects[3,10]. Therefore, it is of importance to establish the mechanism of T wave formation associated with a whole ventricular activity.

Spach[9] and Millar[11] reported in a canine model that locally recorded electrograms could be used to estimate the time of excitability on the ventricle. In a previous study[12], we reported the activation and its recovery pattern on the rat ventricular surface, and showed that the multiple simultaneous recordings of regional ventricular activity are adequate for exploring electrical phenomena in the rat heart.

On the basis of multiple local electrograms, in this study, we investigated the whole excitation and the recovery sequence in the left ventricle (septum, subendocardium and subepicardium), and the results are considered to be reasonable for accounting for the occurrence of the positive T wave on the rat ECG.

MATERIALS AND METHODS

Animals and surgical procedure: Twelve male Wistar rats aging 12 to 16 weeks were used in this study. All rats were anesthetized with pentobarbital sodium (40 mg/kg, i. p.) and restrained in supine position on an operating table warmed 37°C during experiments. Artificial ventilation was maintained through an endotracheal tube by a positive pressure respirator at a frequency of 70 rpm. The chest was surgically opened at the ventral side so that the heart was disclosed. In all experiments, spontaneous sinus rhythms were normally maintained.

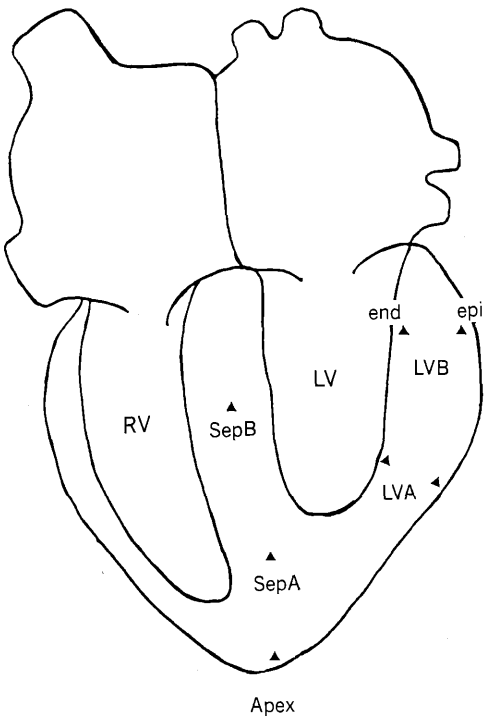

Fig. 1. Recording sites (closed triangle) of unipolar electrograms in the ventricle.

RV : right ventricle, LV : left ventricle, LVB : basal site in left ventricular free wall, LVA : apical site in left ventricular free wall, SepB : basal site in ventricular septum, SepA : apical site in ventricular septum, epi : subepicardium, end : subendocardium.

Recordings of multiple unipolar electrograms from ventricular sites: In order to record the multiple unipolar electrograms in the ventricle, unipolar electrodes with enamel coated copper wire (0.06 mm in diameter) were attached onto 7 sites restricted to the basal and apical regions of the septum, subendocardium and subepicardium of the left ventricular free wall in 12 rats (**Fig. 1**). Standard limb lead II electrocardiogram (ECG) was also recorded simultaneously for referring to the records obtained from the unipolar electrograms mentioned above. After recording electrical signals from the unipolar electrograms, local QT intervals (duration of

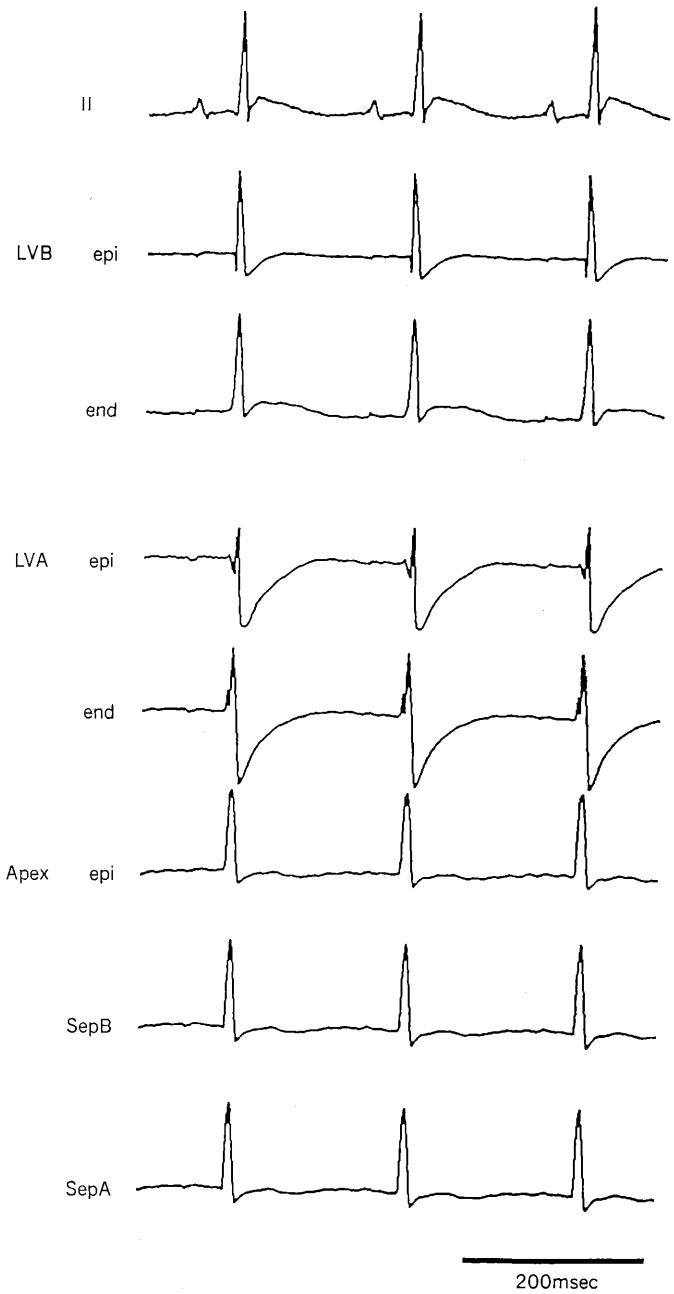

Fig. 2. Representative recordings of unipolar electrograms in the various sites in the ventricle.

II : Limb lead II ECG. The other abbreviations are the same as those in Fig. 1.

local activation) on unipolar electrogram at various ventricular sites were measured according to the method previously reported[12]. In addition, the signals from unipolar electrograms were differentiated to obtain dv/dt. The time point of absolute maximum of dv/dt was defined as the local peak activity just at the position of the electrode attachment. The activation time through all seven recording sites was measured by referring to the time of a given local peak activity for its delay from the time of the earliest peak activity. The definition of the local peak activity and the methods for their measurements were essentially the same as those reported previously by Spear[3], Suzuki *et al.*[12], Iwa *et al.*[13] and Josephson *et al.*[14].

Recordings of direct bipolar electrograms between the suben docardium and corresponding subepicardium sites: In 6 of 12 rats direct bipolar electrograms were led between the subendocardia and their corresponding subepicardia in basal and apical regions in the left ventricular free wall. Limb lead II ECG and two unipolar electrograms were simultaneously recorded. "T waves" obtained from such direct bipolar electrograms were evaluated in comparison with those on ECG recorded.

In all experiments electrical signals were amplified by biophysical amplifiers (San-ei Sokki: 1205C), using a time constant of 1.5 sec for unipolar electrograms and ECG. All these signals were stored on a personal-computer system (Epson: 286 US) equipped with an analog-digital converter (Softron: SAR-8) using a sampling time of 0.5 msec. The differentiation (dv/dt) of electrical signals was conducted by the special progrom (Softron: SBP-2). The onset of local excitation and the local QT interval were accurately measured by the ECG-analysis program (Softron: SP-2). These electrical signals were printed out on a laser printer (Ricoh: LP-1060-SP 3).

Data analysis: Statistical analyses of data were made with Student's paired t-test. A p value less than 0.05 was considered significant statistically.

RESULTS

Local QT intervals in the ventricle: Representative recordings of the unipolar electrograms from the seven ventricular regions, together with limb lead ECG, are shown in **Fig. 2.** The appearance of these local activities was well corresponded to QRS-T complex on ECG.

Figure. 3. shows average local QT intervals at the seven ventricular sites. The QT intervals in the two subepicardial regions (75.8 and 76.4 msec in average) were significantly shorter than those in the corresponding subendocardial (99.4 and 90.2 msec in average) and septal regions 90.8 and 91.3 msec in average) in the ventricles ($P<0.05$). There were no significant differences in the local QT intervals between the two septal regions, and between the two subendocardial regions,

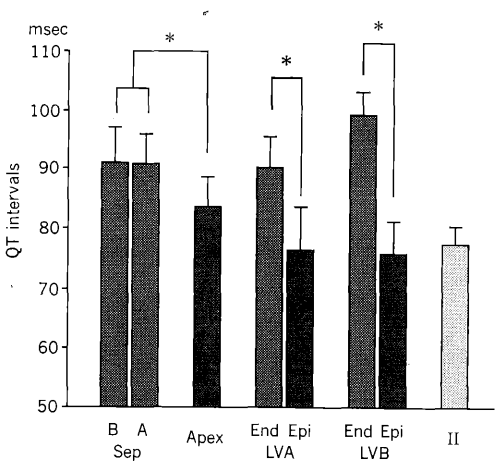

Fig. 3. Local QT intervals recorded from the various sites in the ventricle.

Each vertical bar shows mean value and SE, *: Significantly different ($p<0.05$, paired t-test). The abbreviations are the same as those in Figs. 1 and 2.

and among the three subepicardial regions including the apex. The intervals in the subendocardial regions were significantly longer than the QT intervals on ECG (77.3 msec in average), while the intervals in the subepicardial regions matched with those on the ECG.

Conduction sequences in the ventricle: Average times of arrival of activation on the seven sites in the ventricle are shown in **Fig. 4**. The septum was first activated, followed by the activation of the apical subepicardim, ventricular subendocardium and subepicardium. There were no significant differences in times between the two sites in intraseptum, between the two sites in subendocardia, and also between the two sites in subepicardia. The time conducted from the septum (initial) to the subepicardium (terminal) in each experiment was 6 to 10 msec.

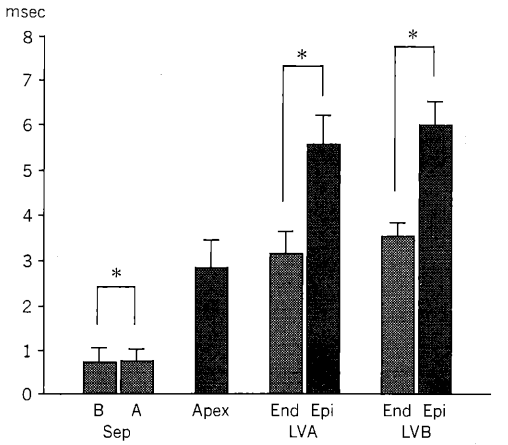

Fig. 4. Activation times at the various sites in the ventricle.

Each vertical bar shows mean value and SE, *: Significantly different ($p<0.05$, paired t-test). The abbreviations are the same as those in Fig. 1.

"T waves" on direct bipolar electrograms between the subendocardium and the subepicardium in the ventricular free wall: Representative direct bipolar electrograms recorded between the subendocardium and

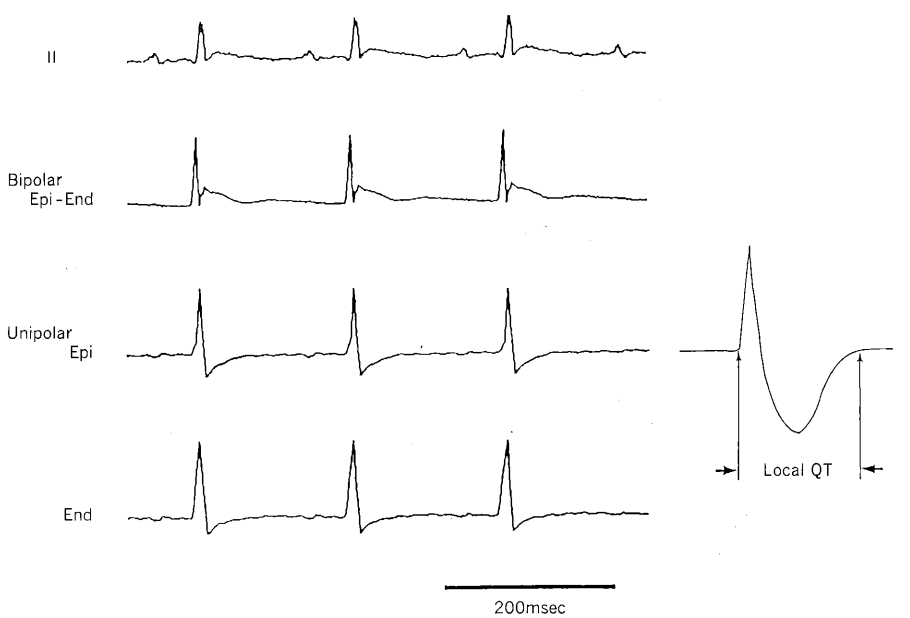

Fig. 5. Representative recordings of bipolar electrograms between the subendocardium and subepicardium with respect to the unipolar and limb lead II ECG.

Bipolar: bipolar electrogram, Unipolar: unipolar electrogram, II: Limb lead ECG

the subepicardium together with ECG and unipolar electrograms are shown in **Fig. 5.** In the bipolar electrogram in **Fig. 5** the positive "R wave" and positive "T wave" were apparent which were clearly corresponded to QRS complex and T wave on limb lead II ECG. In the basal sites of the left ventricular free wall, the presence of positive T wave was confirmed in all of the six rats, and in the apical sites positive T waves were also recorded in five out of the six rats. In all the unipolar electrograms, the polarity of the wave following "R wave" was simply negative, while the bipolar electrograms showed a positive phase ("Twave") following a small negative phase ("S wave"). This reflected that, during ventricular repolarization, the negative phase was deeper and the recovery to the baseline was earlier at the subepicardial site than those at the subendocardial site.

DISUSSION

In order to elucidate the genesis of positive T wave on rat ECGs, we attempted to find the nature of the local QT interval and the ventricular activation sequence in various ventricular regions. In general, the hypothesis accounting for the T wave concordance of the normal human ECG is that the repolarization wave proceeds in an opposite direction to the depolarization wave, and therefore that some areas activated earlier have a longer activation duration than those activated later[6-9,11]. In this investigation, we analyzed regional activities recorded simultaneousy from the septum, subepicardium and subendocardium in the rat. Such an investigation would be required for the accurate comparison on time difference among several regions in the ventricle. The present study demonstrated that in the rat ventricle the activation occurred in the septum, subendocardium, and subepicardium in this order, although the proceeding time from the septum to the subepicardium was very short(6 to 10 msec). A theoretical correlation among electrical factors regarding the formation of T wave on ECG is illustrated in **Fig. 6**. Based on the analysis for the local QT intervals, the QT intervals on the septal and subendocardial regions were significantly longer than those on the corresponding subepicardial regions. Namely, more rapid repolarization with a shorter duration occurred in the subepicardial myocytes (later depolarization site) than in the subendocardial myocytes (earlier depolarization site) (**Fig. 6-A**). Because the local unipolar electrogram is substantially represented by dv/dt of action potential on myocytes just at the electrode (**Fig. 6-B**)[15], negative waves following "R wave" on unipolar subepicardial electrograms tended to be deeper (lower electric potential) with a shorter duration than those from subendocardial regions (**Fig. 6-C**). Therefore, the difference of electric potential between the unipolar subendocardial and subepicardial electrograms in the repolarization phase would produce the positive "T wave" in the bipolar electrogram between them (**Fig. 6-D**), resulting in the formation of an electrical dipole with positive charge at subepicardial site. Furthermore, the electrical current derived from such ventricular depolarization and repolarization should be more predominant in the left ventricle than in the right ventricle, resulting in the net electrical dipole toward the left (**Fig. 6-E**). Although there has been no direct evidence of transmural gradient in the human heart[7], such a mechanism might be essentially common in both the human and the rat, as indicated by a similar tendency of ventricular activation sequence and repolarization duration between them[5-7,16]. In conclusion, it was elucidated that the endocardial electrical activity with a duration longer than that in the epicardial activity might largely contribute to the formation of positive T wave in the rat ECG.

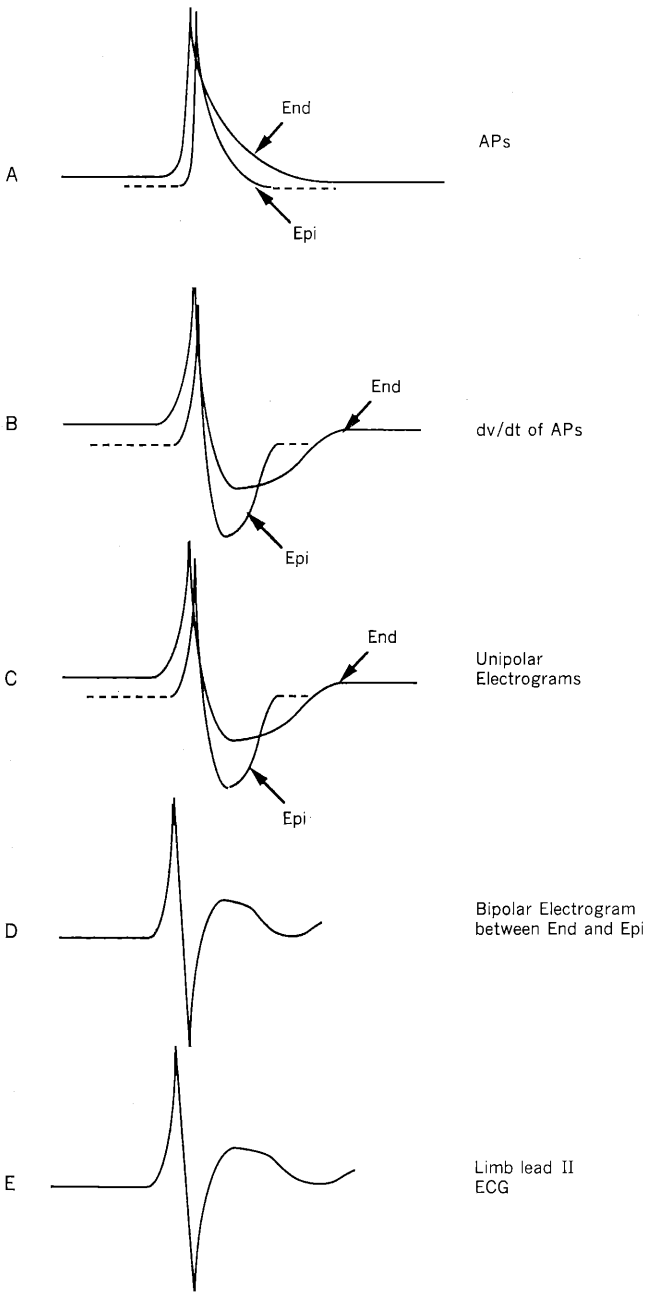

Fig. 6. A possible, theoretical correlation of myocardial action potentials (APs), differentiation (dv/dt) of APs, unipolar and bipolar electrograms, and limb lead II ECG in order to explain the formation of positive T wave.

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要　約

ラット心電図における陽性T波の成因—心臓直接誘導電位図による検討

鈴木　順，局　博一[1)]，菅野　茂[1)]

萬有製薬㈱開発研究所

1)　東京大学農学部比較病態生理学教室

ラット標準第Ⅱ肢誘導心電図（心電図）における陽性T波の成因を，心臓直接誘導電位図の記録による心室の興奮伝播および再分極に関する知見から明らかにした。開胸，人工呼吸下のラットにおいて心室中隔，心内膜下および心外膜下の7カ所の部位から単極誘導電位図を同時記録した。得られた単極誘導電位図およびその微分波を用いて，それぞれ local QT interval（局所興奮持続時間）および局所興奮到達時間に関する解析を行った。さらに，左心室心内膜下と心外膜下を結線した双極誘導電位図を記録し，その電位図で記録されたT波の形状に関しても検討した。

心室中隔（イニシャル）から心外膜下（ターミナル）までの興奮伝播時間は10 msec 以内と非常に

短時間であったが，左心側の興奮伝播過程を明らかにすることができた。即ち，興奮は始めに心室中隔に起こり，ついで心内膜下に，最後に遊離壁心外膜下に伝播した。心外膜下の local QT interval はそれに対応する部位の心膜下の local QT interval に比べ，有意に短く（$P<0.05$），心外膜側は心内膜側に比べてより早期に再分極が起こることが示唆された。また，心内膜下と心外膜下を結線した双極誘導電位図において陽性T波が記録された。これら興奮伝播および local QT interval に関する成績は脱分極と再分極の transmural gradient を示唆しており，ラットにおける心電図上の陽性T波の成因を理解する上で有益と思われた。