UTILITY OF NOVEL ELECTROCARDIOGRAM-LEAD SYSTEM FROM CARDIAC SURFACE USING TELEMETRY SYSTEMS IN FREE-MOVING DOG

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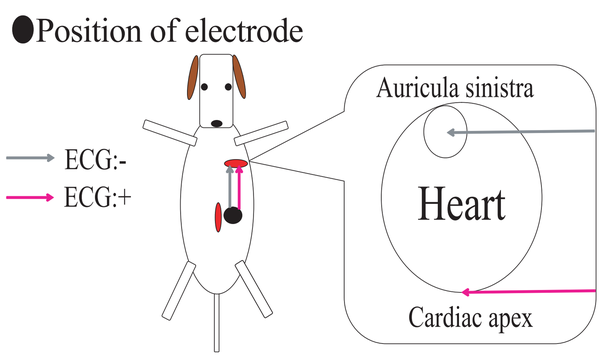
Introduction

Safety pharmacology core battery studies verifying new chemical entities' effects on the central nervous, cardiovascular, and respiratory systems are essential before they are dosed to humans. Among the safety pharmacology core battery, verifying abnormality in the electrocardiogram (ECG), namely QT-interval prolongation, for the cardiovascular system is one of the most important items. For this purpose, ECGs are currently recorded in the same method as that for humans, that is from the body surface (BS) using telemetry systems, Holter monitor, etc. However, precise assessment of abnormality in the BS-recorded ECGs is sometimes interrupted by various factors such as commingling of noise (electromyogram etc.) resulting from an animal's movement and the deviation of the axis of the heart, irregularly undulating base line, and waveform change due to an animal's posture. Thus an additional assessment using anesthetized animals and/or the AV-block-model is sometimes required. Now we report the precise ECG-assessment technique which combines the analysis method using the QT/RR plot and ECG recording, directly from the unanesthetized free-moving dogs' cardiac surface (CS), that almost completely avoids the undesirable factors such as commingling of noise (electromyogram etc.) and deviation of the axis of the heart and that minimizes irregularly undulating base line and waveform change.

Methods & Results

Male beagle dogs, to which 2 telemetry transmitters (TL11M2-D70-PCT) each were implanted, were used. One transmitter was for the bipolar apex-base lead ECG from the BS, which is widely employed in telemetric assessments. The other was for the CS ECG with the electrodes directly fixed to the CS.



【*Experiment 1*】
BS and CS ECGs of undosed dogs were recorded and compared in terms of various factors such as commingling of noise (electromyogram etc.) resulting from an animal's movement and deviation of the axis of the heart, irregularly undulating base line, and waveform change due to an animal's posture.

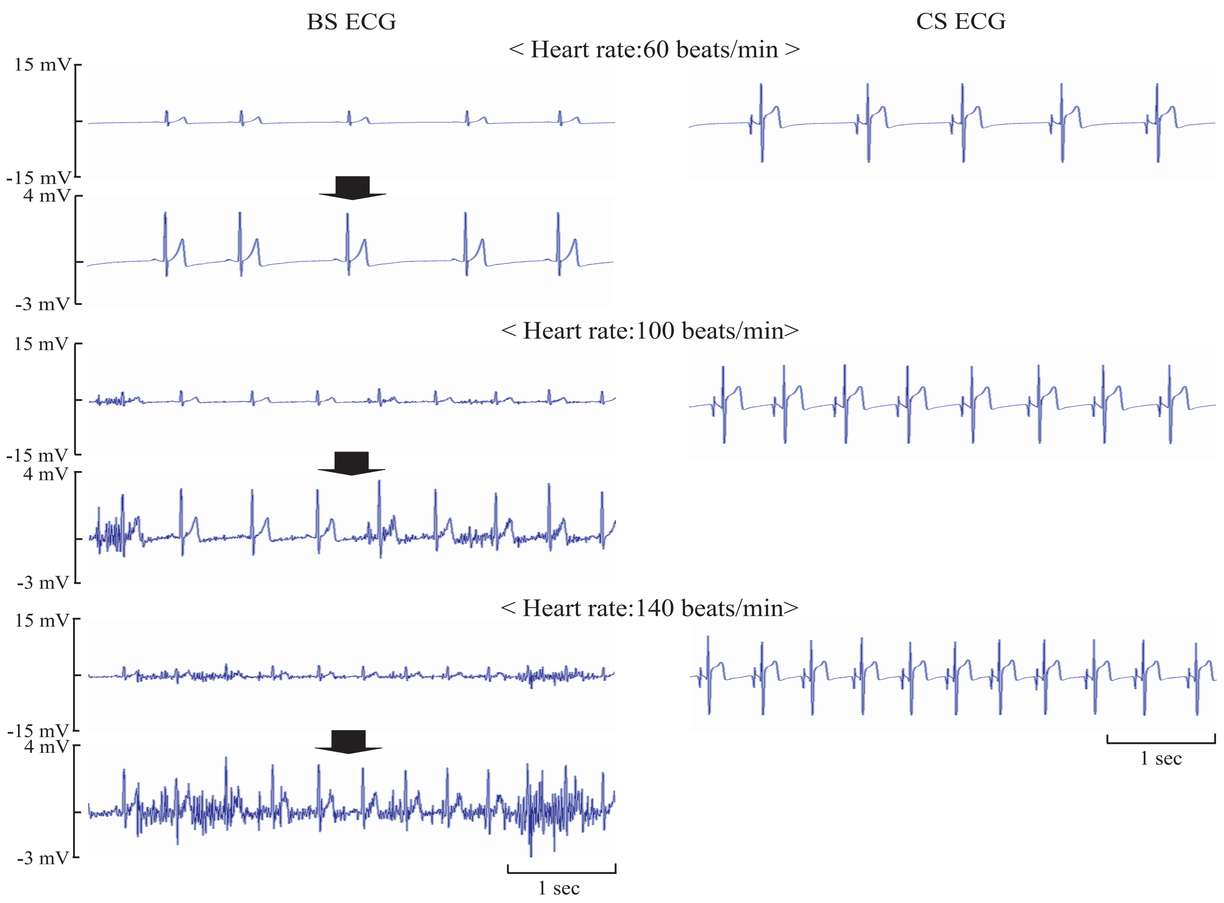


Fig. 1. Typical ECG waveforms form recorded from body and cardiac surfaces.

Fig. 2. Potential variation of BS and CS ECGs for 24 hours.

BS ECG Table1. Potential of P-, Q-, R-, S-, and T-waves recorded from body and cardiac surfaces.

Wave	Potential (mV) Body surface (B)	Cardiac surface (C)	C/B rate
P	0.06 ± 0.03 (50)	2.07 ± 0.31 (15)	35
Q	-0.09 ± 0.03 (33)	-0.86 ± -0.26 (30)	10
R	2.99 ± 0.31 (10)	9.74 ± 0.35 (4)	3
S	-1.14 ± 0.14 (12)	-10.54 ± 0.11 (1)	9
T	0.86 ± 0.29 (34)	4.72 ± 0.51 (11)	5

Each value represents the mean ± S.D.
Values in parentheses represent the percent ratio of standard deviation against the mean value.

【*Result 1*】
In the BS ECG, commingling of noise (electromyogram etc.) resulting from an animal's movement, irregularly undulating base line, and waveform change were noted. In contrast, the CS ECG was hardly affected by such factors.
As for potential, remarkable variation of potential was noted in the BS ECG. In the CS ECG, the waveform change and potential variation due to an animal's posture were much smaller than those of the BS ECG, and the variance was small.

【*Experiment 2*】
Influences of the surgical procedure for fixing electrodes to the CS were investigated by assessing the ECG.

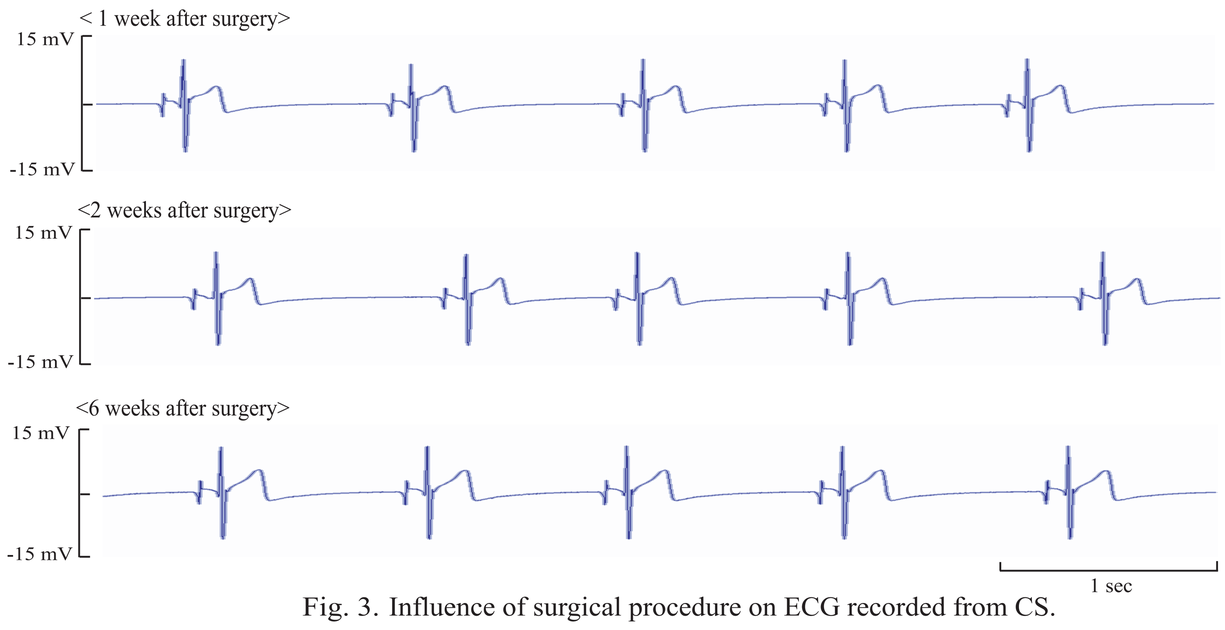


Fig. 3. Influence of surgical procedure on ECG recorded from CS.

【*Result 2*】
No influence of the surgical procedure for fixing electrodes to the CS was noted.

【*Experiment 3*】
QT-prolongation effect of oral *dl*-sotalol (10 mg/kg) was examined by BS and CS ECGs.

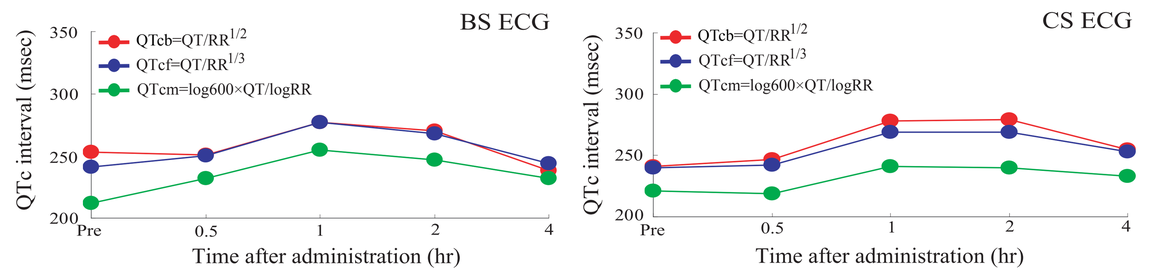


Fig. 4. Effect of *dl*-sotalol on ECG recorded from body and cardiac surfaces.

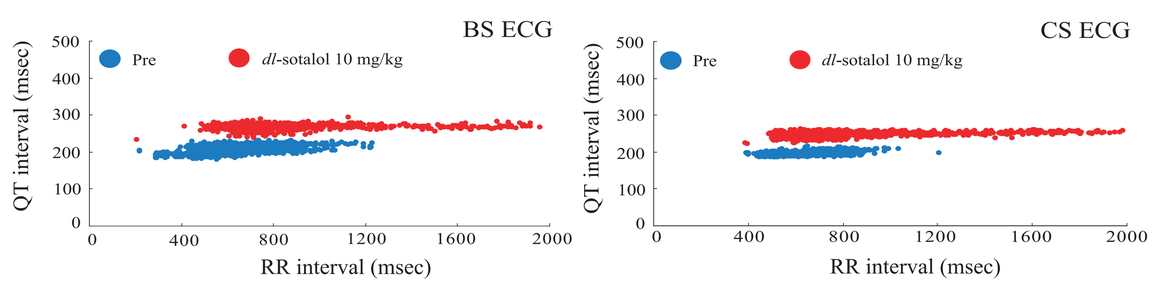


Fig. 5. Beat-to-beat QT/RR relationship 1 hr after administration of *dl*-sotalol.

【*Result 3*】
QT prolongation induced by *dl*-sotalol was noted in the CS ECG as well as BS ECG. In addition, the QT/RR plot 1 hr after administration, at which point the prolongation degree was high, was minutely examined; the plot of the CS ECG was more precise than that of the BS ECG.

【*Experiment 4*】
Effects of oral quinidine (50 mg/kg) on the ECG were examined using the CS lead.

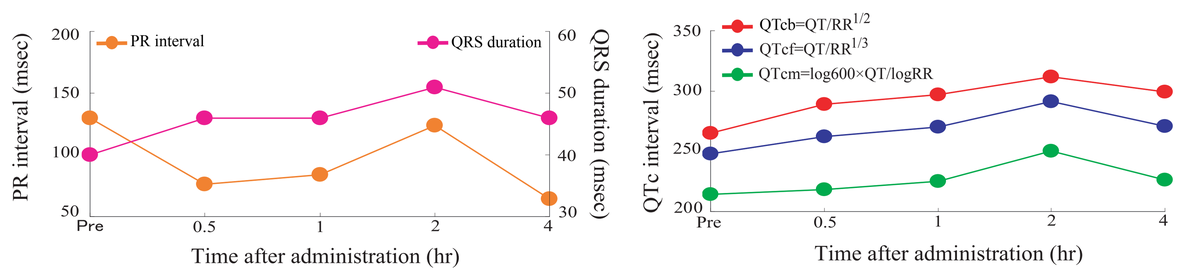


Fig. 6. Effect of quinidine on ECG recorded from cardiac surface.

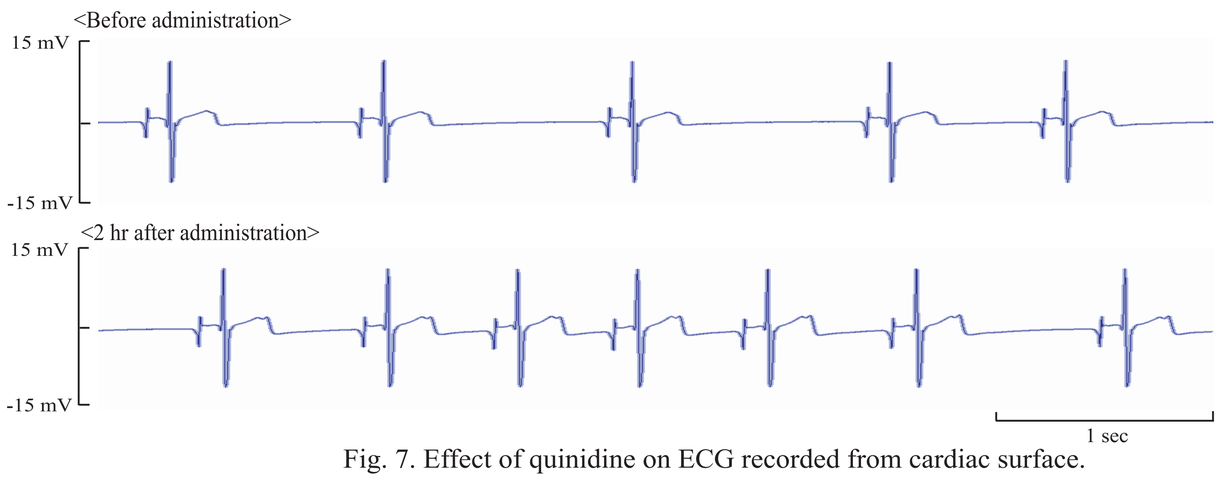


Fig. 7. Effect of quinidine on ECG recorded from cardiac surface.

【*Result 4*】
After dosing of quinidine, prolongation of PR interval, QRS duration, and QTc interval accompanied with an increase in the heart rate was confirmed in the CS ECG.

Conclusion

The present result demonstrated that the CS lead enables the stable ECG recording almost without being affected by the animal's movement or posture, ie, commingling of noise (electromyogram etc.), deviation of the axis of the heart, or irregularly undulating base line. The effects of *dl*-sotalol and quinidine on the ECG were appropriately confirmed using the CS lead. It was also suggested that the CS ECG is useful for assessment employing the QT/RR plot.
In conclusion, the CS ECG is considered to be beneficial for assessing adverse effects of new chemical entities on ECGs in the safety pharmacology core battery.