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Original article

Evaluation of electrocardiograms recorded in cynomolgus monkeys with short- and long-term intracardiac lead implantations

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ABSTRACT

Introduction: minimally invasive placement of intracardiac (IC) ECG leads in monkeys has greatly improved signal quality and the ability to interpret these ECGs. However, information on characteristics of the ECGs recorded using the IC lead is not available in the literature. There are concerns about the potential impact of IC lead placement on the ECG waveform and cardiac function as a result of potential irritation or trauma resulting from the placement and/or long term residence of the IC lead. The purposes of this study were to characterize IC ECG morphology, to obtain information on the recovery processes after IC ECG lead implantation, and to evaluate the IC ECG model application to safety pharmacology studies. **Methods:** the telemetry transmitter, arterial blood pressure catheter and IC ECG lead were implanted in 40 cynomolgus monkeys, two of which were also implanted with subcutaneous (SC) ECG leads. The data of IC ECG, heart rate (HR) and mean arterial blood pressure (MABP) were collected telemetrically for a period of 1–12 months after implantation, and measured using computer softwares. **Results:** the IC ECG waveforms varied greatly from those of SC ECG. There was no clearly identifiable S–T segment, and T waves were biphasic in the majority of IC ECGs. The morphology of IC ECG was diversified among animals, progressively changed in the first 2 weeks post-surgery and stabilized approximately 3 weeks post-surgery. MABP and HR were elevated after implant surgery, but recovered to the levels comparable to those of SC in approximately 1 and 4 weeks, respectively. The IC ECG values obtained during week 8 to 10 (HR = 134 ± 25 bpm, PR interval = 87 ± 13 ms, QRS interval = 40 ± 7 ms, and QT interval = 246 ± 30 ms, QTcF = 318 ± 28 ms) were comparable to those from SC ECG. **Discussion:** the IC ECG provides a clear ECG signal with values comparable to, and waveforms different from, SC recordings. The complicated surgical procedure with long substantial recovery time, high incidence of IC lead malfunction, and high costs for IC leads may limit application of the IC ECG model in safety pharmacology studies.

1. Introduction

The telemetered non-human primate (NHP) model has been commonly used to acquire electrocardiogram (ECG) from conscious, freely moving animals in cardiovascular safety pharmacology and toxicology studies (Ando et al., 2005; Authier, Tanguay, Gauvin, Fruscia, & Troncy, 2007; Chaves et al., 2006; Haushalter et al., 2008; Yamamoto, Hombo, Hashimoto, Kasai, & Omata, 2005). The ECG waveforms from non-human primates were usually small in amplitude and perturbed with muscle noise and movement artifacts with the traditional subcutaneous or intramuscular ECG lead placement (Holzgrefe et al., 2007). As a result, measurement and evaluation of electrocardiograms, particularly by automated computer systems that depend on clear, consistent waveforms, is often difficult. To improve ECG signal quality, an integrated intracardiac (IC) ECG lead was introduced, which can be connected to the telemetry transmitter and allows recording ECG signals from the inside of the heart. The results from the limited publications (Arrigoni et al., 2008; Singer, Stonerook, Vinci, Hassler, & Vadnais, 2006) demonstrated that IC ECG yielded relatively noise-free waveforms with minimal movement artifact, and the percentage of measurable waveforms for automated ECG analysis software was significantly greater relative to the subcutaneous ECG. However, information on the characteristics of IC ECG in non-human primates is not available in the literature. There are also concerns regarding the potential impact of IC lead placement and surgical procedures on the ECG morphology, cardiac function and general conditions of animals due to possible irritation or trauma.

The purposes of this study were to characterize IC ECG morphology and to obtain information on the post-surgery recovery processes after IC ECG lead implantation. The data collected from 40 cynomolgus monkeys implanted with IC ECG lead showed that IC ECG signals from monkeys had high amplitude and high signal-noise ratio. It was found that the morphology of most IC ECGs was different from those of lead II subcutaneous ECGs although their parameter values were comparable. The waveform pattern progressively changed after surgery and

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stabilized in approximately 3 weeks. The implantation of IC lead caused elevations in the blood pressure and heart rate, which recovered in approximately 3 and 30 days after surgery, respectively.

The current study focused on the methodology of applying the novel IC lead technology to acquiring clear ECG data from monkeys, including evaluation of monkey IC ECG and post-implant recovery process. To fully support the application of IC ECG model in safety pharmacology studies, further studies are necessary for evaluation of this model under challenge of pharmacological agents.

2. Methods

2.1. Animals

Forty adult Cynomolgus monkeys (male and female, 3–5 years old) were used for telemetry device, IC and/or subcutaneous lead implantation and data collection in this study. All aspects of animal use were in accordance with Animal Welfare Act (Title 9, USC) and USDA guidelines, and were approved by the Wyeth Institutional Animal Care and Use Committee. The animals were housed individually in the animal rooms with alternating 12 h periods of lights-on and lights-off.

2.2. Surgical procedures

All surgical procedures were performed under aseptic conditions. Anesthesia was induced by intramuscular injection of 10 mg/kg ketamine hydrochloride. A surgical plane of anesthesia was maintained by 0.5–3% isoflurane (mixed with medical grade oxygen) through endotrachea intubation. A telemetry transmitter (TL11M2-D70-PCT) manufactured by Data Sciences International (DSI, St. Paul, MN) was implanted onto the anterior wall of the peritoneal cavity through a ventral midline laparotomy incision. The blood pressure catheter was tunneled subcutaneously to the left medial thigh and advanced into the abdominal aorta via the left femoral artery. An integrated intracardiac (IC) ECG lead was tunneled subcutaneously to the right lateral cervical area and advanced through the jugular vein and right atrium to the right ventricle. The distance between the two electrodes of the integrated IC lead is either 40 mm (45-IC lead-4P, DSI) or 50 mm (45-IC lead-5P, DSI). At the distal end of the IC lead there are small silicon tines designed to anchor the tip of the lead in the trabeculae carnae in the right ventricle. During surgery, the telemetry signal captured by the IC lead was continuously monitored after transmitter implantation. Entrance of the IC lead into the right ventricle was indicated by an ECG signal with a large amplitude R wave, which usually merged with a highly elevated ST–T wave complex (ST elevated as much as 6–10 mV). Under fluoroscopic surveillance with a Siremobil Compact-L C-arm Machine (Siemens AG, Munichen, Germany), the tip of IC lead was further advanced and anchored to the trabeculae of the right ventricle, close to the apex (see Fig. 1). The proximate terminal of the IC lead was coupled to the ECG wires from the telemetry transmitter via an IC lead adaptor, which was further anchored to the musculature underneath subcutaneous tissue in the lateral abdomen. To allow direct comparison of the IC ECG with subcutaneous ECG, the dual ECG leads (i.e., IC lead and subcutaneous leads) were implanted in 2 animals. The subcutaneous leads were placed in the superficial musculature at the lower left thorax close to the apex (positive lead) and at the upper right thorax close the lateral end of the clavicle. The incisions were closed with monofilament sutures. Before being returned to their home rooms the animals were placed in an intensive care unit and closely monitored until anesthetic recovery. All animals received antibiotics and analgesics pre- and postoperatively.

2.3. Data acquisition and analysis

Data transmitted from the implanted telemetry device were received by the RMC-1 receiver, and recorded and initially processed by the Dataquest Acquisition system (DSI) with a low-pass filter setting at 1000 Hz. Telemetry data (blood pressure and ECG waveforms) were collected continuously for 72 h after IC lead implantation, and then collected in an intermittent pattern (60 s every 5 min) for a period of 24 h on the post-surgery monitoring days. The 24 h period data collection was performed approximately once weekly, biweekly, or monthly depending on the time elapsed after IC lead implantation. Thoracic fluoroscopy examinations were performed immediately and once a week for three weeks after implant surgery, to monitor any potential displacement of the IC lead.

The systolic, diastolic and mean arterial blood pressure and heart rate were automatically measured or computed with Dataquest ART (Version 3.1, DSI) software. ECG waveforms were inspected visually for rhythm and configuration abnormalities. ECG parameters (PR, QRS, QT and QTc intervals) were generated using the ECG-auto software (EMKA technologies, Falls Church, VA). An example of IC-ECG with computer markings is demonstrated in Fig. 1. Fridericia's formula ($QTcF = QT/^3Ö(60/HR)$ was used correct on the QT interval for changes in HR (see Discussion for rational and limitations of using this method).

To exclude the potential influence of lighting status and disturbances to animals on the cardiovascular parameters, only data collected during lights-on time and without investigator's presence in the animal room for at least 2 h were analyzed. Statistical data analysis and linear regressions were carried out using Excel 2000 (Microsoft, Redmond, WA) and GraphPad Prism (V3.02, GraphPad Software, San Diego, CA). Summary data are presented as mean ± SD (standard deviation). Results from different groups were compared using Student's *t*-test or one-way ANOVA followed by Dunnett's comparison test. *F*-test was used to determine deviations of the slope factor from zero in linear regressions. Statistical significance was considered when $p<0.05$.

3. Results

3.1. Stabilization of IC ECG after IC lead implantation

All animals appeared to tolerate the IC lead implantation, and no obvious behavioral and physical changes were observed. The morphology of IC ECG demonstrated variability during the immediate post-surgical period and gradually stabilized 2 to 3 weeks after implant surgery in most of the animals. As shown in Fig. 2 the ST–T wave complex of IC ECG as well as the J wave (Brunson, Abbud, Osman, Skelton, & Markov, 2005; Yan & Antzelevitch, 1996) migrated from the positive to equivalent potential (which was determined as the potential level at the start of Q or R wave) in the first three days after surgery. The pattern of T wave appeared as biphasic immediately post-surgery, dominantly inverted on day 1, and upward on day 3 after surgery. The ST–T wave complex showed elevation again on day 6. Subsequently, the IC ECG morphology became more uniform on Day 20, 30 and 70 with a biphasic T wave, indicating a stabilization of ECG waveforms around 3 weeks after IC lead implantation. In some animals the post-surgery recovery was more rapid and the secondary ST–T wave complex elevation was not observed around 1 week such that the ECG waveform stabilized in about 2 weeks. Regardless of IC ECG waveform changes post-surgically, the chest fluoroscopy examination usually did not reveal any signs of IC lead dislodgement.

3.2. Characteristics of IC ECG

IC ECG waveform morphology was different from those of the modified lead II ECG obtained from subcutaneous lead placement in monkeys. In the IC ECGs collected from the majority of animals no clear S–T segment could be identified, and ST segment and T wave were usually merged to form a ST–T wave complex (see Fig. 3), or ST segment merged with a J-wave, which is followed by a T wave (as ECGs shown in Fig. 2). The IC ECG morphology exhibited a series of changes after lead implantation, which were probably caused by slight