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Original article

Intravenous solid tip lead placement in telemetry implanted dogs. Part 1: Surgical methods, signal quality, and pathological endpoints

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ABSTRACT

Introduction: Electrocardiogram (ECG) signals in safety pharmacology studies are generally collected via subcutaneous or epicardial leads. Subcutaneous placement is an easier procedure, but signals often contain artifacts. Epicardial leads offer improved quality but require additional surgical expertise. Signal quality and tolerability of intravenous (IV)/diaphragmatic ECG leads were investigated as a less invasive alternative to the epicardial ECG lead approach for cardiovascular assessment in dogs. **Methods:** Twenty-eight beagle dogs were implanted with PCT ($n = 14$) or PCTP ($n = 14$) transmitters with IV (negative)/diaphragmatic (positive) ECG leads arranged in approximate Lead II configuration. Surgical time for previous epicardial and current IV lead placement approaches was compared. The ECG signals were assessed for up to 32 weeks post-surgery. Signal quality was assessed based on good wave/total wave (GW/TW) ratios calculated using ECG PRO (Ponemah Physiology Platform, Version 4.8) and variability in ECG parameter measurements for each surgical model. Clinical pathology was assessed on all animals before surgery and approximately 2 and 12 weeks post-surgery. A specialized necropsy was conducted on four animals (two PCT and two PCTP) to assess the tolerability of telemetry equipment; selected tissues were examined microscopically. **Results:** Surgical time using the IV lead method was approximately 18% shorter than the epicardial lead method. The GW/TW ratio for IV lead-implanted dogs indicated good durability of signal that was similar to epicardial leads. Intra- and inter-animal variability in ECG parameter measurements was similar between IV lead-implanted and epicardial lead-implanted dogs. Clinical pathology revealed no noteworthy findings, and the IV/diaphragmatic surgical approach had minimal consequences on local vasculature and associated implantation sites. **Discussion:** Advantages of the IV/diaphragmatic lead model include a less invasive and shorter surgical procedure; high tissue tolerance, ECG signal quality, and durability; and data processing procedures similar to that of epicardial leads. Therefore, the IV/diaphragmatic lead configuration is a viable alternative to more invasive surgical approaches for telemetry device implantation in dogs.

1. Introduction

In human beings, relatively small increases in systolic and diastolic arterial pressure or delayed ventricular repolarization (QT interval prolongation) poses a risk for development of potentially fatal vascular events or arrhythmias (Fermini & Fossa, 2003; Kannankeril, Roden, & Darbar, 2010; Lewington, Clarke, Qizilbash, Peto, & Collins, 2002). The International Conference on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use Guidelines ICH-S7A and S7B describes the conduct of nonclinical safety pharmacology studies intended to evaluate the potential risk of pharmaceuticals on the cardiovascular system prior to Phase I first-in-human testing (ICH, 2001, 2005). Although there is a movement towards combining safety pharmacology end points in toxicology studies (Luft & Bode, 2002; Pugsley, Authier, & Curtis, 2008; Sarazan et al., 2011), particularly for biologics (Vargas, Amouzadeh, & Engwall, 2013; Vargas et al., 2008), the current standard for cardiovascular assessment remains the use of chronically implanted radiotelemetry devices in large animals, such as dogs, nonhuman primates, and pigs (Gauvin, Tilley, Smith, & Baird, 2006a, 2006b; Guth, 2007; Stubhan et al., 2008). In these species, assessment of heart rate, blood pressure, and electrocardiograms (ECGs) in freely moving animals provides the highest sensitivity for detection of drug-induced effects (Chaves et al., 2006, 2007; Stubhan et al., 2008). Intrinsic to the concept of sensitivity is that high-quality blood pressure and ECG signals are essential for the detection of small yet potentially important changes in hemodynamic and ECG parameters.

Compared with subcutaneous lead placement, telemetry signal quality and sensitivity to detect drug-induced changes were improved with the development of the epicardial ECG lead surgical method (Holzgrefe, Cavero, Buchanan, Gill, & Durham, 2007; Henriques et al., 2010).

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However, epicardial lead placement requires a more complex and invasive thoracotomy surgical technique to gain access to the pleural cavity (Henriques et al., 2010). Consistent with procedure refinement, one of the guiding principles of the 3Rs (replacement, refinement, and reduction), a method should be employed that reduces the possible stress or discomfort to research animals whenever possible (Russell & Burch, 1959). In addition to animal welfare considerations, the need for high-quality telemetry data must be balanced with technical requirements and expense of the surgical technique, as well as any potential impact of telemetry hardware implantation on animal physiology and response to the compound tested.

The current study evaluated a novel surgical approach for ECG electrode placement using implantable telemetry transmitters and intravenous (IV)/diaphragmatic ECG leads in beagle dogs and evaluated ECG signal quality and tissue tolerance to device placement.

2. Methods

2.1. Regulatory guidelines

This study was performed in compliance with the Guide for Care and Use of Laboratory Animals published by the United States National Institutes of Health (National Institute of Health Publication No. 85-23, revised 1996) and was performed in accordance with the guidelines set by the Covance Laboratories Animal Care and Use Committee. The study was also conducted at an Association for Assessment and Accreditation of Laboratory Animal Care International accredited site.

2.2. Animals

Male and female purebred beagle dogs were obtained from Covance Research Products Inc. (Kalamazoo, Michigan). At study initiation, male and female dogs were 7 to 15 months of age, and body weights ranged from 8.8 to 15.3 kg for males and 10.2 to 10.4 kg for females. Dogs were housed in stainless steel cages and offered Certified Canine Diet (PMI 5007C) ad libitum for at least 6 h each day. Water was provided ad libitum. Environmental controls for the animal room were set to maintain 18 to 26 °C, a relative humidity of 30 to 70%, a minimum of 10 room air changes/h, and a 12-hour light/12-hour dark cycle. All dogs were given additional dietary supplements as a form of environmental enrichment and various cage-enrichment devices. Animals had the opportunity to exercise in double-wide cages during the course of this study, except during telemetry data collection. Animals were checked twice daily (a.m. and p.m.) for mortality, abnormalities, and signs of pain or distress.

2.3. Surgical procedures

An eight lead-ECG digital recording was conducted for 60 s on all unanesthetized, manually restrained animals once prior to surgery and used to confirm the absence of ECG abnormalities. Surgical implantation of telemetry devices in dogs was completed according to Covance standard operating procedures. Surgical procedures were performed using aseptic techniques under general anesthesia. Antibiotics, analgesics, and nonsteroidal antiinflammatory drugs (NSAID) were administered postoperatively as needed. On the day prior to surgery, animals were given meloxicam [NSAID; 0.2 mg/kg, subcutaneous injection (SQ)] and Naxcel (antibiotic; 2.2 mg/kg, SQ). Approximately 20 min prior to surgery, animals were given oxymorphone [analgesic; 0.1 mg/kg, intramuscular injection (IM)], midazolam (sedative; 0.2 mg/kg, IM), and glycopyrrolate (preanesthetic anticholinergic; 0.01 mg/kg, SQ). Dexmedetomidine (0.01 to 0.02 mg/kg, IV) was used for induction, and dogs were intubated and placed under sevoflurane for general anesthesia. Approximately 20 min prior to the end of surgery, midazolam was administered. Dogs were also given meloxicam and Naxcel on the day of surgery. Immediately postoperatively, a fentanyl patch was applied, and oxymorphone (0.025 to 0.1 mg/kg, IM) was given in the afternoon on the day of surgery. During recovery, dogs were given oxymorphone (0.05 mg/kg, IM) one to two times daily as needed, meloxicam (0.1 mg/kg, SQ) once a day for 3 days, and Naxcel once a day for 3 days. For implantation of the left ventricular catheter, 10% bupivacaine (intercostal nerve block; 1.0 mL, IM) and 2% lidocaine (antiarrhythmic, 0.25 mL, IV) were administered just prior to initiating catheter implantation procedures. Additional dietary supplementation (e.g., canned food) was offered to facilitate post-surgical recovery.

For single-pressure transmitter and IV/diaphragmatic ECG lead placement, an ECG, pressure and temperature transmitter [Data Sciences International (DSI); Model No. TL11M2-D70-PCT (PCT)] was implanted into the abdomen and sutured to the peritoneum on the right side of the peritoneal cavity at the level of the umbilicus. The ECG leads of the transmitter were arranged in an approximate Lead II configuration. The negative ECG lead was placed into the right external jugular vein and advanced towards the heart; the positive lead was sutured to the abdominal side of the diaphragm close to the apex of the heart. The blood pressure catheter was tunneled from the transmitter body to the inguinal muscle pocket located under the sartorius muscle of the left leg, and the full length of the catheter was inserted into the femoral artery; the location of the catheter tip in the aorta varied from slightly below to slightly above the renal arteries depending on the size of the animal. For dual-pressure transmitters [Data Sciences International (DSI); Model No. TL11M3-D70-PCTP (PCTP)], a second pressure catheter was inserted from the abdominal side through an incision in the diaphragm into the left ventricle at the apex of the heart.

For diaphragmatic ECG lead placement, the positive ECG lead was cut to appropriate length, the terminal end was formed into an uninsulated loop, and the loop was sutured to the abdominal side of the diaphragm near the apex of the heart. The suture location was determined by visualization and palpation of the left apex of the heart through the diaphragm.

For IV ECG lead (IV lead) placement, the negative lead was tunneled to the neck of the animal by first making an incision at the caudal margin of the right jugular furrow. The closer proximity to the thoracic inlet was used to reduce the potential influence of head and neck movement on the ECG lead tip. The right external jugular vein was selected for implantation due to a slightly more direct approach to the right atrium in order to achieve a configuration that best approximates Lead II.

The external jugular vein was prepared for insertion by isolating approximately 2 cm of the vein via sharp and blunt dissection and passing three pieces of 3-0 non-absorbable suture underneath the isolated vein section. One suture was cranial and two sutures were caudal to the proposed insertion site. The cranial suture was used to ligate the jugular vein prior to insertion of the lead and then fix the IV lead to the catheter after insertion. A venostomy was performed, and the IV lead was introduced into the jugular vein using a catheter introducer while simultaneously applying gentle tension to the caudal piece of suture. The caudal sutures were used to encircle the vein and lead to prevent backflow of blood through the insertion site and to fix the IV lead in place.

The solid tip of the IV lead was advanced to a position where the ECG waveform had a high-amplitude P wave with clear QRS and T morphologies. A sterile marker was used to mark the lead insertion depth. The lead was advanced further until the ECG waveform changed dramatically in amplitude and morphology and another sterile mark was created. The lead was retracted to a location between those marks, acceptable waveform morphology was confirmed, and the lead was sutured into position at three sites around the catheter and vessel to prevent catheter migration. A stress loop was created and sutured in an adjacent subcutaneous pocket to provide for head and neck movement. The incision was closed using appropriate suture and technique.