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Original Research

Novel Technique for Retroperitoneal Implantation of Telemetry Transmitters for Physiologic Monitoring in Göttingen Minipigs (*Sus scrofa domesticus*)

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Telemetric monitoring of physiologic parameters in animal models is a critical component of chemical and biologic agent studies. The long-term collection of neurobehavioral and other physiologic data can require larger telemetry devices. Furthermore, such devices must be implanted in a location that is safe, well-tolerated, and functional. Göttingen minipigs (*Sus scrofa domesticus*) present an ideal large animal model for chemical agent studies due to their relatively small size, characterized health status, and ease of training and handling. We report an effective approach to implanting a novel device to measure transthoracic impedance to approximate respiratory tidal volume and rate in Suidae. We tested the approach using 24 male Göttingen minipigs. A ventral midline abdominal incision extending from the umbilicus to the prepuce was followed by a paramedian incision of the parietal peritoneum and dorsal blunt dissection to create a retroperitoneal pocket. The device was anchored inside the pocket to the internal abdominal musculature with 3-0 nonabsorbable suture, biopotential leads were routed through the abdominal musculature, and the pocket was closed with 3-0 absorbable suture. Paired biopotential leads were anchored intermuscularly at the level of the seventh rib midway between spine and sternum bilaterally to provide surrogate data for respiratory function. Postoperative recovery and gross pathology findings at necropsy were used to assess safety and refine the surgical procedure. Results demonstrated that this procedure permitted effective monitoring of complex physiologic data, including transthoracic impedance, without negatively affecting the health and behavior of the animals.

Telemetric monitoring of physiologic parameters in animal models is a critical component of chemical[9] and biologic agent studies.[32,36] The attenuation of the adverse effects of these agents by using medical countermeasures can be assessed also.[21,25,28,35] The long-term collection of neurobehavioral and other physiologic data can require large telemetry devices. Furthermore, such devices must be implanted in a location that is safe, well-tolerated, and functional. Potential complications of inserting telemetry devices include infection,[29] dehiscence,[7] neoplasia,[33] and extrusion.[20]

Göttingen minipigs (*Sus scrofa domesticus*) present an ideal large animal model for chemical agent studies due to their relatively small size, characterized health status, and ease of training and handling, including for physiologic studies.[12,15,16,30] The lightly pigmented skin, sparse haircoat, fine intersecting lines of epidermal sulci, lipid biophysical properties, and epidermal turnover kinetics of Göttingen minipigs are similar to those in humans.[22,34] Swine in general are a particularly relevant animal model for assessing percutaneous absorption exposure to chemical agents.[8,11] Percutaneous application of agent represents the most likely real-world threat scenario for persistent chemical agents.[8,11] Extensive in vivo and in vitro studies have characterized percutaneous absorption,[10,13,31] protection,[5] and decontamination[23] in swine models.

Previously, respiratory impedance has been measured by using implantable telemetry devices in nonhuman primates,[2] and respiratory parameters have been determined by using external impedance-based technology in minipigs[1] and dogs.[24] We report an effective approach to implanting a device for measuring transthoracic impedance to approximate respiratory tidal volume and rate in minipigs.

Materials and Methods

The experimental protocol was approved by the Animal Care and Use Committee at the United States Army Medical Research Institute of Chemical Defense, and all procedures were conducted in accordance with the principles stated in the *Guide for the Care and Use of Laboratory Animals* and the Animal Welfare Act of 1966 (PL 89-544), as amended.

Preoperative care. We tested our approach by using 24 sexually mature male Göttingen minipigs (Marshall BioResources, North Rose, NY) housed in pairs in swine runs. Runs were hosed down twice daily and thoroughly sanitized every 2 wk. Animals

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were given water ad libitum and fed a commercial swine diet (Harlan Laboratories, Indianapolis, IN) twice daily immediately after runs were cleaned. Enrichment consisted of a mixture of fruits and vegetables 3 times weekly, rubber toys, chains, and scratch boards. Ambient temperature was maintained between 16 and 27 °C and humidity between 30% and 70%, with a 12h:12-h light:dark cycle. Although most animals tested positive for porcine rotavirus on immunofluorescent antibody tests by the supplier, they did not exhibit any clinical signs and were otherwise SPF for an exhaustive list of viral, bacterial, fungal, and parasitic pathogens.

Minipigs were fasted for at least 12 h prior to surgery. Each animal received amoxicillin–clavulanic acid (13.75 to 20 mg/kg PO; Clavamox, Zoetis, Florham Park, NJ) 1 d prior to surgery. Each animal was sedated with tiletamine–zolazepam (3 mg/kg IM; Telazol, Zoetis) and xylazine (1.5 mg/kg IM; Rompun, Bayer Animal Health, Shawnee, KS). Minipigs were clipped and scrubbed at all required sites, prepped in dorsal recumbency, and draped. Tracheal intubation enabled maintenance of anesthesia with isoflurane (1% to 3% in O_2). In addition, cefazolin (25 mg/kg IV; West-Ward, Eatontown, NJ) and buprenorphine (0.01 mg/kg IV; Reckitt Benckiser, North Chesterfield, VA) were administered before the first incision was made. The telemetry device was soaked in sterile saline for at least 20 min prior to surgery.

Intraoperative care. Normal saline was administered intravenously via right auricular vein, body temperature was maintained by using a Bair Hugger (3M, St Paul, MN), and physiologic parameters were monitored via a pulse oximeter, blood pressure cuff, external ECG, and rectal temperature probe. Preemptive and polymodal analgesia was obtained by concomitant administration of tiletamine, xylazine, and buprenorphine, with local lidocaine or epinephrine for EEG-lead incisions, and postoperative ketoprofen.

Retroperitoneal implantation of telemetry device. All minipigs were 4 to 5 mo old and weighed 7 to 13 kg at the time of surgery. A 10-cm ventral midline abdominal incision extending from the umbilicus to the prepuce was made in the skin, followed by incisions through the subcutaneous tissue and linea alba. A 7-cm paramedian incision was made in the left parietal peritoneum, and dorsal blunt dissection from the internal abdominal musculature was used to create a retroperitoneal pocket (Figure 1 A). The 49-g, 33-mL circular device (D70-PCTR, Data Sciences International, St Paul, MN) was anchored inside the pocket to the internal abdominal musculature by using 3-0 nonabsorbable suture (Figure 1 B), biopotential leads were routed through the abdominal musculature via trocar (Figure 1 C), and the pocket was closed with 3-0 absorbable suture in a simple continuous pattern (Figure 1 D). The abdomen was closed in a cruciate pattern of 2-0 nonabsorbable suture through the external sheath of the rectus abdominus muscles. The ground wire (green) was shortened and tunneled subcutaneously dorsally to the right of the abdominal incision.

Arterial pressure cannula. The right femoral pulse was palpated in the medial femoral region slightly distal to the femoral triangle. A 5-cm incision was made through the skin and subcutaneous tissues, followed by gentle blunt dissection between gracilis and sartorius muscles and retractor placement to isolate the femoral artery. The artery was moistened with lidocaine to prevent vasospasm during this procedure, and as much of the thick adventitia was removed as possible. The clear blood-pressure cannula was routed subcutaneously via trocar from the abdominal incision area to the femoral incision. Hemostasis was preemptively managed by stay ligatures of 3-0 silk to manipulate the isolated femoral artery. The distal ligature was accomplished before a 20-gauge needle (bent to a right angle) was used to perform an arteriotomy. The tip of the pressure cannula was introduced to the arteriotomy using a vein pick. Cannulation forceps were used to further advance the transducer cranially into the artery and feed it to its proper estimated position in the abdominal aorta, sufficiently caudal to the left renal artery and leaving a curve of slack for leg movement. Telemetric pressure readings were compared with those of the external pressure cuff. The proximal ligature was affixed around the cannula within the femoral artery, and the distal ligature was also tied around the cannula to prevent movement within the artery. Two to 3 other 3-0 nonabsorbable stay sutures were used to anchor the curve of the pressure lead to the muscular sheath. The gracilis and sartorius muscle sheaths were apposed with a simple continuous pattern of 3-0 absorbable suture, followed by skin closure with subcutaneous and subcuticular patterns.

ECG. The following describes the procedure for the 8 minipigs fitted for ECG in a lead II configuration. The alternate procedure for the remaining 16 animals fitted for EEG is described later in the EEG section.

A loop of stripped positive ECG lead (red) tied with 3-0 silk was buried intermuscularly just left of the midline at the xiphoid. The right jugular furrow was incised, and the negative ECG lead (clear, solid-tip) routed from the abdominal incision area via trocar. Then the right external jugular vein was palpated, isolated with blunt dissection, and the adventitia stripped in comparable fashion to the femoral artery. Three 3-0 silk stay sutures were placed to manipulate the vein. The cranial suture was ligated, a bent 20-gauge needle opened the venotomy site, and the vein pick held the vein open for introduction of the solid-tipped probe. The probe was advanced to the level of the cranial vena cava, just outside the right atrium, until the ECG computer readout was optimal quality. The best signal was ascertained by moving the minipig to different positions and fixing the bullet-tip at the length for the optimal signal. In addition, the signal was visually correlated with that of the external ECG monitor. A plastic sleeve was placed around the wire at the level of the venotomy site, and the middle and caudal stay sutures were used to ligate the vessel and wire, which rested in grooves in the sleeve. Similar to the femoral artery, a curve of slack in the wire (allotted to accommodate movement) was anchored to muscle with 2 or 3 additional 3-0 nonabsorbable stay sutures. The jugular furrow incision was closed in a simple continuous pattern of 3-0 absorbable suture, followed by a subcuticular pattern.

Transthoracic impedance leads. Paired biopotential leads were anchored intermuscularly at the level of the seventh rib midway between the spine and sternum bilaterally to provide surrogate data for respiratory function. Longitudinal incisions approximately 5 cm in length were made through skin and subcutaneous tissue to expose the external thoracic musculature (Figure 2 A). The respiratory impedance wires, 2 leads to each side of the thorax, then were passed to these thoracic incisions via trochar. Positive (solid turquoise and violet) leads were routed to the left lateral incision, whereas negative (white-striped turquoise and violet) leads were routed to the right lateral incision. In minipigs fitted for EEG, the EEG wires were passed to the left side and maintained temporarily in a subcutaneous pocket dorsal to the

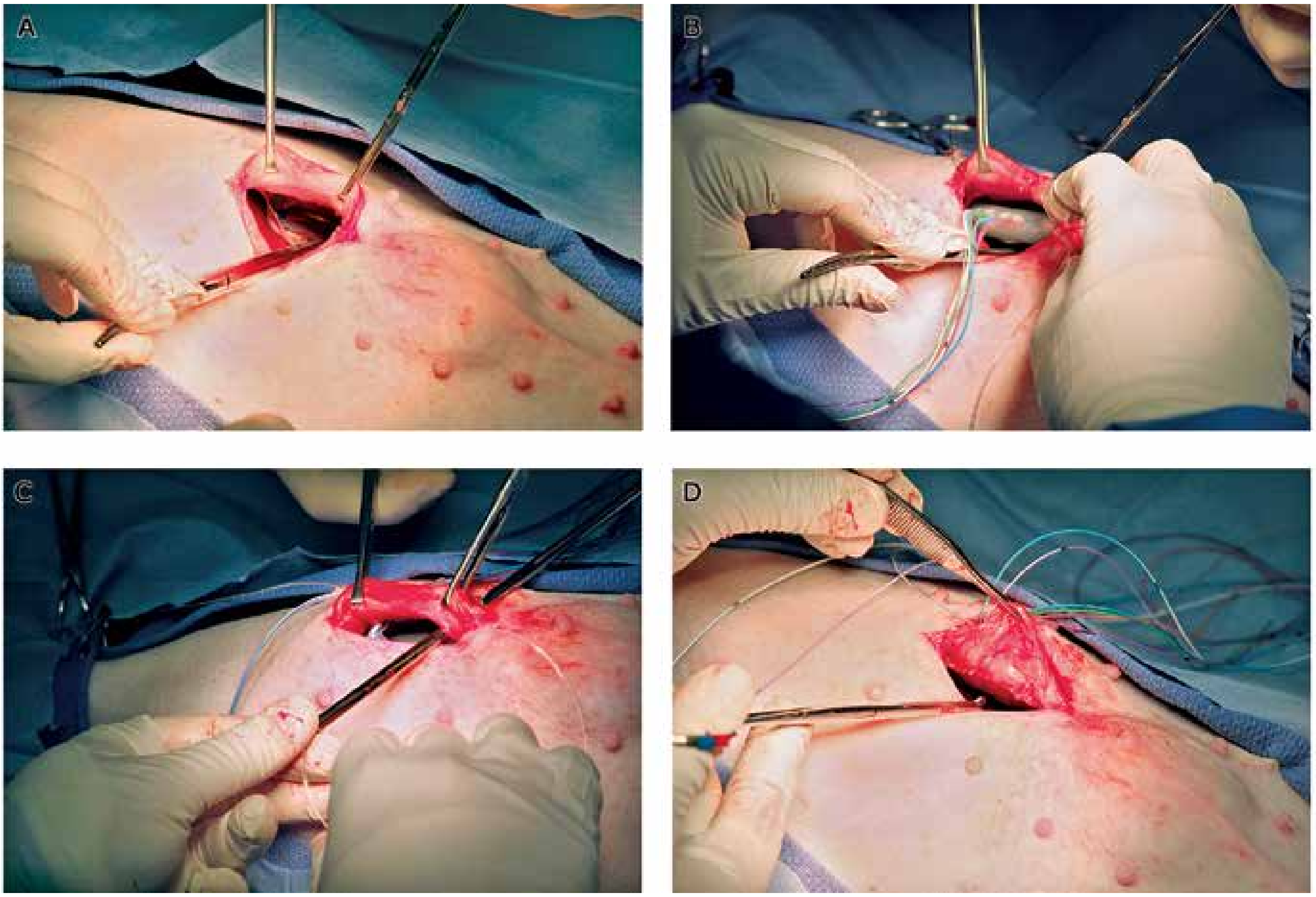

Figure 1. Retroperitoneal implantation of the telemetry device is accomplished by (A) paramedian incision into the parietal peritoneum and blunt dissection of a pocket, (B) anchoring the device to the internal abdominal musculature, (C) routing leads through the abdominal wall via trochar, and (D) closure of the pocket.

incision. The remaining layers of the initial abdominal incision then were closed to prevent interference from the impedance leads. The subcutaneous layer, tacked down to the external sheath of the linea alba to reduce dead space, was closed with 3-0 nonabsorbable suture in a simple continuous subcutaneous pattern, followed by a subcuticular pattern. Impedance leads contained gel between solid nodes, which are marked with an annular black stripe. Leads were stripped of coating distal to the first full node interval beyond the lateral incisions, and loops of exposed wire were tied with 3-0 silk just distal to the nodes (Figure 2 B). The 2 loops on each side were advanced by blunt force into the musculature and positioned approximately 2.5 cm apart. Violet leads were advanced cranially (Figure 2 C), whereas turquoise leads were advanced caudally (Figure 2 D). Respiratory impedance was verified intraoperatively to ensure that positioning was appropriate. The manufacturer's recommendations were a baseline of 60 ± 10 ohms and a difference of more than 2 ohms between inspiration and expiration. Once correctly positioned, the leads were anchored with 3-0 nonabsorbable suture to the muscle, followed by subcuticular closure with 3-0 absorbable suture. For minipigs fitted for EEG, the left lateral incision was apposed temporarily by using towel clamps, for later retrieval of the EEG leads.

EEG. Each of these 16 minipigs was undraped and rotated to sternal recumbency, the dorsal skull scrubbed and draped, and a dilute lidocaine and epinephrine linear injection was administered along the dorsal midline of the skull. EEG wires were retrieved from the temporary closure of the left lateral thoracic incision. Due to the distance from this location to the skull, as well as the presence of dense dorsal neck fat and connective tissue, the EEG wires were routed via trochar to a midway stab incision dorsal to the left scapula. The skin over the calvarium was incised, and the EEG wires were passed via trochar to the caudal end of this incision. The periosteum of the calvarium was stripped with periosteal elevators. Frontal bone electrode sites were selected approximately 2.5 cm apart, equidistant from the sagittal suture, and approximately 0.5 cm rostral to the coronal suture. Holes (depth approximately 5 to 6 mm) were predrilled by using a 1-mm hand chuck to determine the distance required to penetrate the dura overlying the frontal lobes. Larger holes (diameter, approximately 2 mm) were drilled through the predrilled holes by using a sterile rotary tool and bit (Dremel, Racine, WI). Anchor screws (length, 5 to 6 mm) were placed in the prethreaded holes, the exposed ends of the EEG leads were wrapped around the screws 2 or 3 times (red lead on the left, clear solid-tip lead on the right), and the screws were hand-tightened. The wire ends were trimmed, and the screws were secured to the skull by using dental acrylic (Integrity Temporary Crown and Bridge Material, Dentsply Caulk, Milford, DE). The head, dorsal neck, and lateral thoracic skin incisions were closed 3-0 nonabsorbable suture in a subcuticular pattern.

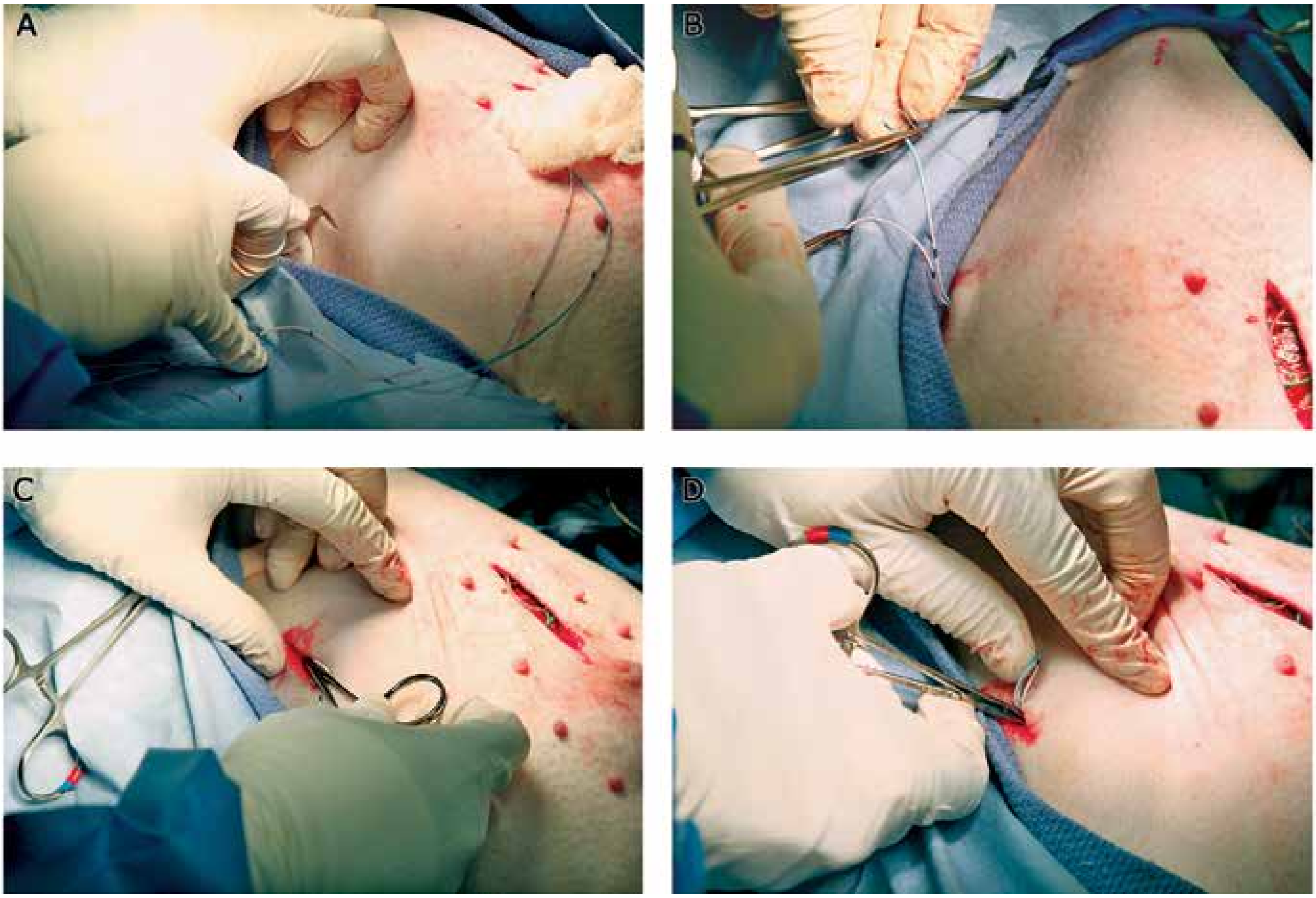

Figure 2. (A) Transthoracic impedance leads were routed subcutaneously from the abdominal incision to lateral thoracic incisions. (B) Loops of exposed wire one node distal to the incisions were created; negative (striped) leads are seen on the left side. (C) Violet (positive) leads were buried and anchored intermuscularly cranially, (D) whereas turquoise (positive) leads were routed caudally.

Postoperative care. Clavamox (13.75 to 20 mg/kg PO) was continued twice daily, along with 1 tablet of probiotics (Children's Acidophilus, Vitabase, Monroe, GA), for 10 d postoperatively Minipigs were given buprenorphine (0.01 mg/kg IM twice daily) immediately postoperatively and on the day after surgery. Ketoprofen (3 mg/kg IM) was given postoperatively, and meloxicam (0.1 mg/kg in feed) was given daily for the next 3 d. Minipigs were given at least 2 wk of recovery time and behavioral reinforcement before exposure to chemical agents. Minipigs previously had been trained to rest in a sling, thus facilitating the synchronization of raw respiratory telemetry data with nose-cone pneumotachometer data. Arterial pressure, ECG, EEG, and temperature data were analyzed by using Ponemah Analysis Modules (Data Science International).

Results

Telemetry data. Intraoperative, postoperative, and preexposure telemetry data were obtained to establish individual and species-typical baselines. Figure 3 demonstrates representative real-time traces of postoperative blood pressure, respiratory impedance, and EEG.

Surgical refinements. In similar surgical procedures involving nonhuman primates in our lab, we used polymethyl methacrylate to secure the EEG leads to the skull. Switching to dental acrylic in the current study dramatically reduced the polymerization time and increased the precision of application compared with those of our nonhuman primate procedures and eliminated the noxious and potentially carcinogenic fumes of polymethyl methacrylate.[19]

Anatomic variability occasionally required intraoperative modifications to the procedure. For example, one minipig with extensive vascular branching of both external and internal jugular veins bilaterally could not be fitted with the indwelling jugular lead. The negative ECG lead instead was placed subcutaneously on the left ventral thorax approximating, the sinoatrial node. The signal did not appear different from those with indwelling jugular leads, and this minipig recovered more rapidly than did others in its cohort.

Recovery. All minipigs had resumed their normal diet on the day of surgery or the next day. Animals with EEG instrumentation ($n = 8$) returned to normal activity, behavior, and study-related training on day 1 postoperatively, whereas most of those fitted for ECG (total $n = 16$) showed signs of discomfort and lethargic until day 2. One EEG animal with profound nuchal fat displayed bruising in that area. No noteworthy surgical complications, such as infection or dehiscence, occurred.

Postmortem findings. All swine underwent complete postmortem examination upon reaching the study endpoint. Endpoints varied depending on study requirements. All 8 of the ECG-implanted minipigs and 8 of the 16 EEG-instrumented animals succumbed to chemical agent exposure, recovered from exposure

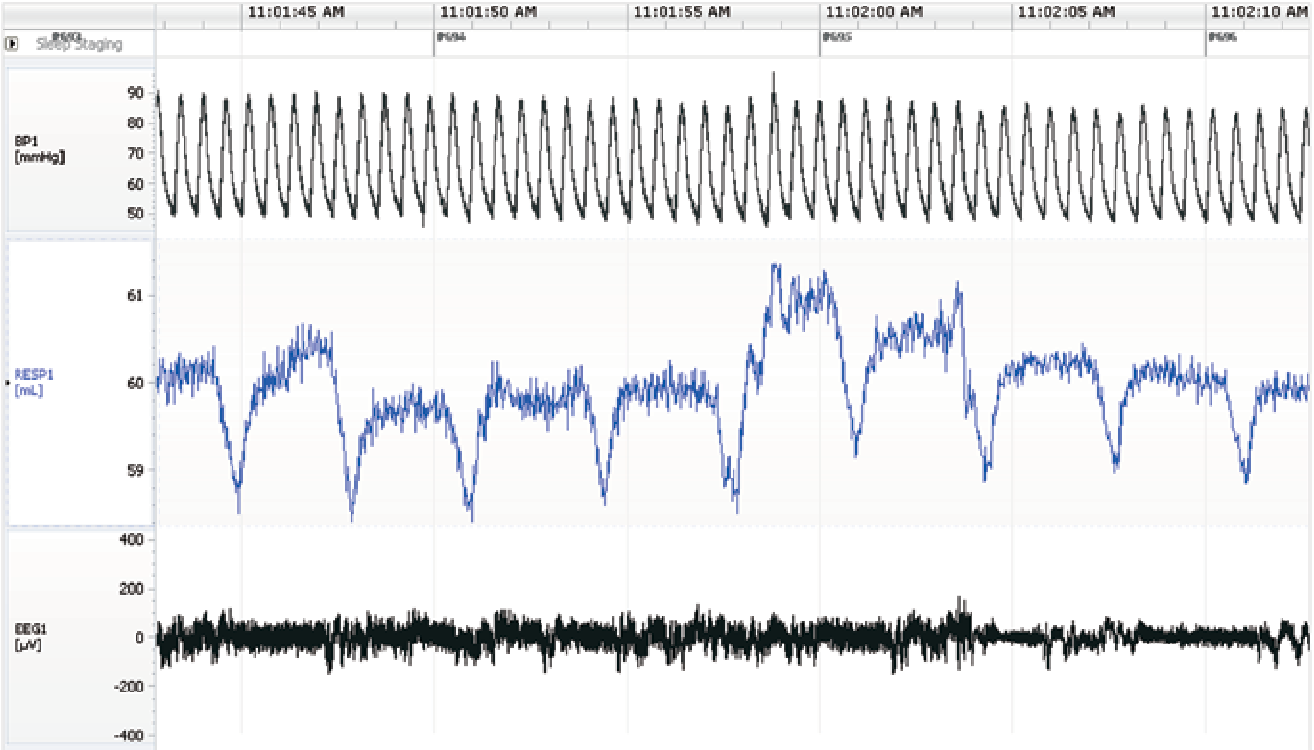

Figure 3. Representative real-time traces of postoperative blood pressure, respiratory impedance, and EEG.

after 24 h and subsequently were euthanized, or were euthanized after being recumbent for 3 h. The remaining 8 EEG-implanted minipigs were maintained for long-term (approximately 4 m) behavioral analysis after exposure to agent. At necropsy, 2 of these animals had moderate fibrous adhesions of the retroperitoneal pocket incision to the liver, spleen, or spiral colon. The remaining 6 swine had no gross or histologic evidence of infection, inflammation, adhesions, dehiscence, or other adverse tissue reaction associated with the telemetry device and leads. Furthermore, all surgical sites appeared normal at the time of necropsy. In one minipig, one of the EEG lead wires was kinked, resulting in loss of the outer covering with exposed wire. In this animal, the compromised EEG lead appeared to be recording the electrical activity in the heart, displaying an ECG reading instead of an EEG, thus defaulting to the stronger biopotential. The femoral pressure cannulae were all positioned appropriately within the aorta, and no thrombi were found. Furthermore, the distances approximated for indwelling jugular leads were precise and positioned as expected without the need for confirmatory intraoperative radiographs. Postoperative recovery and gross pathology findings at necropsy were used to assess safety and refine the surgical procedures.

Discussion

Our current results show that retroperitoneal implantation of the telemetry device permitted effective monitoring of complex physiologic data, including transthoracic impedance, without negatively affecting the health and normal behavior of Göttingen minipigs. Communication with the manufacturer (Data Science International) suggested that, to reduce the risk of adhesions, dehiscence, and extrusion, retroperitoneal implantation was preferable to paramedian implantation between the external and internal abdominal musculature, as typically is performed in our African green monkeys (*Chlorocebus aethiops sabaeus*), or intraabdominal implantation. In addition, minipigs are generally considered to be a more appropriate model than are nonhuman primates for studies of percutaneous chemical penetration given the similarity between swine and human skin.[18,26,27] To reduce surgical time, we recommend that 2 skilled surgeons, each with predetermined designated responsibilities, perform the procedure together.

The prolonged times for recovery and return to normal behavior in ECG minipigs (2 d, compared with 1 d for ECG swine) may reflect the traumatic manipulation of the jugular furrow in ECG animals and the local anesthesia that they received. The negative leads were implanted in the right jugular per recommendation from the manufacturer, as well as previous studies indicating that indwelling jugular leads reduced signal noise, increased P-QRS-T amplitudes, and abated circadian rhythm-related interference in minipigs relative to those associated with subcutaneous placement in other species.[3,17] Positive leads attached to the diaphragm are not recommended for minipigs and would have been even more invasive. Subsequent surgeries have demonstrated that subcutaneous placement of both ECG leads is as effective as the indwelling jugular procedure with significantly less surgical time and postoperative discomfort. Simple transposition of the ECG and respiratory impedance techniques across species should not be assumed since cardiac anatomic and electrical axes and thoracic conformation can vary across species.

Another measure to reduce surgical time and trauma that we incorporated here was to obtain the optimal initial measurement possible with the transthoracic impedance leads and then leave them alone. This technique was most effective when a baseline was 50 ohms and a difference of at least 1.5 ohms between expiration and inspiration was achieved. Excessive manipulation was not likely to improve results markedly relative to the additional time invested. To prevent disruption of the impedance signal, we recommend temporary apposition of lateral thoracic incisions by using towel clamps after impedance lead placement and confirmation that all other leads are unexposed. The single instance of an ECG signal due to the kinked EEG wire underscores the need to completely cover all exposed parts of the wires and screws with dental acrylic or similar polymer.

Test exposures to chemical agents often require that physiologic and neurobehavioral parameters are monitored with minimal interference while the animals are in the fume hood. In addition, telemetric monitoring similarly can provide valuable insight into the adaptation to and accommodation of environmental challenges in both free-ranging[6,14] and captive wildlife.[4] Our current results suggest that the technique we describe is appropriate for studies of the physiologic responses of other members of the family Suidae, such as red river hogs (*Potamochoerus porcus*) and warthogs (*Phacochoerus africanus*), to environmental conditions.

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