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Intravenous Recording of Intracranial, Broadband EEG

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Abstract

The most direct evaluation of human brain activity has been obtained from intracranial electrodes placed either on the surface of the brain or inserted into the brain to record from deep brain structures. Currently, the placement of intracranial electrodes implies transcranial surgery, either through a burr hole or a craniotomy, but the high degree of invasiveness and potential for morbidity of such major surgical procedures limits the applicability of intracranial recording. The vascular system provides a natural avenue to reach many brain regions that currently are reached by transcranial approaches, along with deep brain structures that cannot be reached via a transcranial approach without significant risk. To determine the applicability of intravascular approaches to high-frequency intracranial monitoring, a catheter containing multiple macro- and micro-electrodes was placed into the superior sagittal sinus of anesthetized pigs in parallel with clinical, subdural electrode grids to record epileptiform activity induced by direct, cortical injection of penicillin and to record responses to electrical stimulation. Intravascular electrodes recorded epileptiform spikes with similar magnitudes and waveshapes to those obtained by surface electrodes, both for macroelectrodes and microelectrodes, including the spatiotemporal evolution of epileptiform activity, suggesting that intravascular electrodes might provide localizing information regarding seizure foci. Sinusoidal electrical stimulation showed that intravascular electrodes provide sufficient broadband fidelity to record high-frequency, physiological events that may also prove useful in localizing seizure onset zones. As intravascular techniques have

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transformed cardiology, so intravascular neurophysiology may transform intracranial monitoring, in general, and the treatment of epilepsy, in particular.

1. Introduction

The success of endovascular technology in cardiology has prompted attempts across several decades to obtain intracranial electrophysiological recordings. Acute, intracranial recordings in patients have been obtained from the carotid artery (Penn et al., 1973), the middle cerebral artery (Boniface and Antoun, 1997) and veins in the temporal lobe (García-Asensio et al., 1999), while chronic recordings have been obtained from the Cavernous Sinus (Kunieda et al., 2000). These studies showed the practicality of both venous and arterial recordings, particularly in regards to epilepsy monitoring, for both acute and chronic recordings in patients at relatively low frequencies (normally, less than 100 Hz), but did not explore the frequency range of physiological signals that might be recorded or whether microelectrode recordings from blood vessels was feasible. Recent developments in intracranial monitoring, particularly with regards to epilepsy, have shown the utility of recording at higher frequencies (Bragin et al., 1999) and on smaller spatial scales (Stead et al., 2010), but it is unclear whether high-frequency recordings (> 100 Hz) or recordings from microelectrodes within a blood vessel would be degraded by endothelial walls or by the surrounding, moving blood cells.

Epilepsy surgery relies on invasive techniques of intracranial subdural EEG recording for localization of seizure foci (Engel et al., 2007). This is associated with significant risk, discomfort, morbidity, and cost, due to highly invasive surgical procedures to penetrate the skull and prolonged monitoring, often without a bone flap in place. Often, this increased risk results in under-utilization of this procedure for chronic epilepsy, which in many cases is surgically curable (Van Gompel et al., 2008). Intravascular approaches would allow less invasive access to seizure foci and greater flexibility to reach different brain structures than subdural grid implantation, which is limited by surface vascular and bony structures. Currently, neurosurgical use of endovascular techniques is limited to non-electrophysiological therapies, such as occlusive treatment of vascular malformations and tumor vascular supply, maintenance of vascular patency through stenting, and delivery of pharmacotherapeutics (Jeon and Kwon, 2008). Nanotechnology opens the possibility of allowing high-fidelity, long-term, vascular access with reduced morbidity associated with larger catheters that would also be capable of reaching a much broader range of intracranial blood vessels that might be accessible with current intravascular catheter technologies (Llinas et al., 2005; Watanabe et al., 2009). To determine whether endovascular approaches might be applicable to electrophysiological recording for the treatment of epilepsy, we recorded induced epileptiform foci and responses to electrical stimulation of the cortical surface simultaneously from standard electrode grids and electrodes on intravenous electrodes in the superior sagittal sinus in anesthetized pigs. To establish the temporal, spectral and spatial relationship between recordings from subdural and intravenous electrodes, we recorded penicillin-induced epileptiform spikes and responses to electrical stimulation of the cortex simultaneously from macro- and micro-electrodes on subdural grid on the surface of the brain and a depth electrode within the superior sagittal sinus.

2. Methods

2.1 Surgery

All studies were performed with the approval of the Mayo Clinic Institutional Animal Care and Use Committee. Data were collected from castrated, male swine (30-35 kg, Large-white/Landrace/Duroc cross) according to a surgical protocol described previously (Van

Gompel et al., 2011). Briefly, pigs were induced with Telazol (tiletamine and zolazepam) (5–6 mg/kg, IM) and Xylazine (2 mg/kg, IM) and maintained on isoflurane (1–4%). Pigs were placed in the prone position, a craniectomy (5 × 6 cm over the midline) opened and the dura removed from the exposed hemispheres, but not across the superior sagittal sinus. Epileptiform activity was induced by subcortical injection of 2–3 μ l Benzyl-penicillin solved in 1X PBS (PCN, 1100 Units/ μ l, Penna-G, Sigma, St. Louis MO) 2–3 mm below the cortical surface and 5–6 mm lateral to the midline, 1–2 hours after induction of anesthesia (Figure 1A). Penicillin induces large-amplitude (>1 mV), periodic (2–5 Hz), epileptiform spikes that can be recorded by electrode grids (Goldensohn et al., 1977), although the mechanism that generates these field potentials (“spikes”) is not completely understood. To place the intravascular electrode, a small incision was made into the superior sagittal sinus under the dura and the catheter electrode inserted. The subdural grid was then placed on the brain surface and the edges tacked down with sutures to the surrounding dural edge. Pigs were euthanized with pentobarbital overdose at the end of these acute experiments.

2.2 Electrophysiology

Subdural data were collected from a hybrid, subdural grid (PMT Corp., Chanhassen, MN) containing microelectrodes (40 μ m diam. separated by 1 mm in 4×4 arrays) between standard, clinical contacts (2 mm diam., 5 mm separation in a 5×6 array). Intravascular data were collected from a standard, clinical depth electrode (4 contact, 1 mm length each, separated by 5 mm) containing 16 microelectrodes (40 μ m diam. separated by 0.5 mm) distributed between the macro contacts (Figure 1B). Each channel was recorded at 32 kHz and filtered between 0.1 Hz - 9 kHz (i.e., “wideband” recordings) using a Digital Lynx and Cheetah recording system (Neuralynx, Inc., Bozeman, MT). Data were stored to disk in the MEF format (Brinkmann et al., 2009). For the stimulation portion of each recording session, macroelectrode contacts at diagonal corners were connected to a stimulus isolation unit (World Precision, Sarasota, FL) controlled by a special-purpose, real-time experimental control program (Neuralynx, Inc., Bozeman, MT) that wrote stimulus on-off timestamps to an event file.

2.3 Data Analysis

Epileptiform spikes were detected by bandpass filtering (1–80 Hz) and thresholding data collected from the macroelectrode closest to the penicillin injection site. These detection times were used for centering all data from a given recording session. Spectrograms were computed using multi-taper prolate spheroids (“pmtm”, Matlab, Mathworks, Natuck, MA).

3. Results

Epileptiform spikes recorded intravascularly had roughly the same amplitude as those obtained from subdural grids (Figure 1.C-E). On some occasions, intravenous recordings recorded high-frequency signals that were observed on microelectrodes contained in the subdural grid and the intravascular electrode, but that were missed by surrounding, standard, clinical macroelectrodes (Figure 1C “b”). These “microspikes” presumably arose from small, spatially-restricted neural populations, much like “microseizures” that can be observed on microwires in human patients, but which are missed by clinical macroelectrodes (Stead et al., 2010). Importantly, these microspikes were observed on subdural electrodes and not only on intravascular microelectrodes, making it unlikely that they represented vascular artifact. Observation of such low-amplitude, high-frequency events also suggested that intravascular recording may provide sufficient spatio-temporal resolution to record a broad range of neurophysiological signals.

To quantify the filtering produced by recording across blood vessel walls, low-amplitude, sinusoidal currents were passed between macroelectrodes at opposing corners of the subdural grid located on the surface of the brain, while simultaneously recording from intravascular and non-stimulated, subdural electrodes (Figure 2.A). Root Mean Square (RMS) values were larger for intravascular recordings at low frequencies and smaller at higher frequencies (Figure 2.B). Though relative frequency response curves of intravascular recordings were reduced by 11.0% at 30 Hz and 24.2% at 100 Hz, recording fidelity remained sufficient to observe epileptiform activity on the intravascular electrode (Figure 2.C). Surprisingly, relative responses did not continue to decrease with higher frequencies, but were reduced by only 7.5% at 1,000 Hz, suggesting that intravascular recordings may be capable of acquiring signals reliably across a broad range of frequencies, including “high-frequency oscillations” (HFOs) that may be associated with epileptogenic brain regions (Bragin et al., 1999).

4. Discussion

These studies have shown that there are no significant electrophysiological limitations to recording intracranial neuronal fields potentials (EEG) across a broad, physiologically relevant frequency spectrum from the interior of blood vessels. Intravascular electrodes reliably recorded epileptiform EEG spikes that were time-locked to those recorded on a clinical, subdural grid. In addition, intravascular electrodes recorded epileptiform EEG microspikes that were recorded by subdural microelectrodes, but were missed by macroelectrodes. These results suggest that intravascular electrodes display recording sensitivities similar to those of standard, subdural clinical grids, both in regards to macro- and micro-electrodes, and also provide the advantage of laying deeper in the brain and possibly closer to the tissue generating epileptiform activity. During sinusoidal stimulation, intravascular electrodes retained recording fidelity up to 1 kHz, suggesting that intravascular electrodes are sensitive to a broad range of frequencies, such as HFOs, which could make intravascular recording particularly valuable for use in the clinical localization of seizure foci. All recordings in the study were obtained from veins, but arterial recordings could prove equally feasible.

Intracranial, endovascular catheters certainly pose problems for practical therapies, including blockage, clot formation and punctures of vessel walls, but catheter design currently has not been optimized for neurophysiological applications (e.g., nanoscale technologies offer advantages for chronic intravascular recording that have not yet been fully explored (Watanabe et al., 2009)). Compared to depth electrodes, real-time placement of intravascular electrodes confers multiple advantages with less risk. First, the endovascular placement of an electrode would be similar in procedure to a diagnostic cerebral angiogram. As such, the overall time of this procedure would be shorter than a surgical procedure. In addition, patients would not necessarily require general anesthesia, but could most often have intravascular electrode placement done under local anesthesia only. This reduces risk associated with general anesthesia. An intravascular approach is considered less invasive than transcranial approaches, in that a large cranial surgery and exposure of the brain is avoided, and endovascular treatment for intracranial vascular disease have been shown to have lower rates of complication than traditional open surgery (Health Quality Ontario, 2006). Risks specific to endovascular procedures would include bleeding at the groin catheterization site, as well thromboembolic stroke or vessel perforation. The risk of groin hematoma is approximately 4.2%. The risk of the latter two is exceedingly low. The risks associated with open craniotomy surgery, however, include infection, subdural or epidural hemorrhage, temporary or permanent neurologic damage, or stroke, with higher risks than those observed for endovascular procedures.

The largest risk for chronic placement of an intravascular electrode would be that of thromboembolism due to the catheter, for which there is precedent both for intravenous and intra-arterial catheter placement. In the case of superior sagittal sinus thrombosis, chronic catheters left in place for several days for continuous administration of a thrombolytic agent pose little risk of venous thrombosis, if appropriate prophylactic heparinization is used (<1%) (Phillips et al., 1999). Likewise, chronic placement of arterial intravascular catheters has been used for continuous infusion of nimodipine for the treatment of vasospasm following subarachnoid hemorrhage also pose little risk of thromboembolism, if appropriate prophylactic heparinization is employed (1%) (Doukas et al., 2011). Chronic implantation of intravenous electrodes in animal models of neuropathology could reduce infection risks associated with chronic electrode implants, reduce parenchymal tissue damage associated with depth electrodes, and provide a novel perspective, particularly for vasculature-associated neuropathologies. In addition, the relatively consistent spatial relationships between large blood vessels and various brain structures could provide increased spatial repeatability across animals, which is sometimes difficult to achieve in some animal models of neuropathology (e.g., the large anatomical shifts associated with brain atrophy in animal models of epilepsy).

These results suggest that epileptiform foci can be recorded with intravascular electrodes with the sufficient fidelity to localize (and possibly ablate) the source of epileptiform activity (Henz et al., 2008). Intravascular electrodes could also be moved relatively easily within a given blood vessel or to different blood vessels to get closer to a region of interest. This approach may prove useful for EEG localization of epileptogenic foci that are currently only accessible via penetrating depth electrodes (e.g., cingulate gyrus, hippocampus and insular cortex). Stereotactic placement of depth electrodes can be used for recording from a wide range of potentially epileptogenic brain regions, including deep structures (Cardinale et al., 2012). It should be noted, however, parenchymal depth electrodes are fundamentally more invasive, because they must directly penetrate brain tissue to reach their target.

While these studies have focused on the use of intravascular recording techniques for use in the treatment of epilepsy, the same techniques could prove useful in other conditions currently treatable via intracranial recording (e.g., deep brain stimulation, intractable facial pain), as well as opening up new possibilities for intracranial monitoring in conditions that currently do not warrant invasive craniotomies. In a sense, these techniques suggest that intracranial monitoring could follow a path similar to that of cardiothoracic surgery, which used to rely on the invasive techniques of open-heart surgery, but which now has been replaced in many cases with less-invasive, catheter-based techniques.

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Figure 1.

Intravenous (IV) recordings detect epileptiform spikes with similar fidelity to subdural grid electrodes. **A**) Schematic of experimental setup. Following intracortical penicillin injection (green), intracranial recordings were obtained from standard, subdural grids and IV catheter electrodes. **B**) Schematic drawings of the (left) IV and (right) subdural grid electrode arrays containing both macroelectrodes (colored regions) and microelectrodes (black dots). **C**) Macroelectrodes (thick lines) and microelectrodes (thin lines) on both the IV catheter (magenta) and standard clinical grid (cyan) recorded large epileptiform spikes ("a"). Smaller epileptiform spikes ("b"), missed by macroelectrodes, were recorded by microelectrodes on both electrode arrays, suggesting that IV microelectrode wideband recording fidelity is

similar to grid microelectrodes. D) Expanded view from dotted box in C showing different recorded waveforms for the same event. E) average responses (600 sec window, N=479 spikes) for IV electrodes (top row) and grid electrodes (bottom row) with one standard deviation shown in gray. Three, neighboring macroelectrodes are shown on the left side and a single, representative microelectrode is shown at right. (*) All waveforms were centered on the peak of the field potential on this macroelectrode.

Figure 2.

Intravenous electrodes record similar signals compared to those recorded by grid electrodes.

A) Schematic showing the sinusoidal stimulation of grid macroelectrodes from opposing corners and simultaneous recording from intervening grid macroelectrodes (blue) and intravenous (red) electrodes. B) Spectral power of background activity prior to injection of penicillin on macro (thick lines) and micro (thin lines) electrodes. C) Relative spectral power at stimulation frequencies of recordings obtained from intravenous and grid macroelectrodes reveals a slight low-pass filtering effect, while high frequencies are only slightly degraded. D) Physiologically relevant signals (such as the emergence of a train of rhythmic spikes reminiscent of a seizure) are recorded from the intravenous electrode with

temporal progression of the seizure down the length of the sinus, suggesting intravenous recording could provide spatially localizing information.