Endovascular brain intervention and mapping in a dog experimental model using magnetically-guided micro-catheter technology

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Aim. Despite the substantial progress that has been achieved in interventional cardiology and cardiac electrophysiology, endovascular intervention for the diagnosis and treatment of central nervous system (CNS) disorders such as stroke, epilepsy and CNS malignancy is still limited, particularly due to highly tortuous nature of the cerebral arterial and venous system. Existing interventional devices and techniques enable only limited and complicated access especially into intra-cerebral vessels. The aim of this study was to develop a micro-catheter magnetically-guided technology specifically designed for endovascular intervention and mapping in deep CNS vascular structures.

Methods. Mapping of electrical brain activity was performed via the venous system on an animal dog model with the support of the NIOBE II system.

Results. A novel micro-catheter specially designed for endovascular interventions in the CNS, with the support of the NIOBE II technology, was able to reach safely deep intra-cerebral venous structures and map the electrical activity there. Such structures are not currently accessible using standard catheters.

Conclusion. This is the first study demonstrating successful use of a new micro-catheter in combination with NIOBE II technology for endovascular intervention in the brain.

Key words: central nervous system, magnetically-guided endovascular interventions, mapping, NIOBE

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INTRODUCTION

Within the last twenty years, significant progress in the diagnostics and treatment of major cardiovascular diseases has been achieved particularly due to tremendous progress in interventional cardiology and cardiac electrophysiology. Introduction of direct percutaneous coronary interventions has completely changed the management and treatment of acute coronary syndromes and ST-segment elevation myocardial infarction in particular, demonstrating clear benefit in comparison with thrombolytic therapy\textsuperscript{1,2}. Similar progress has been achieved in invasive cardiac electrophysiology. Development of novel methods and techniques for electrical and magnetic mapping, hybrid imaging, and ablations introduced the novel concept of non-pharmacological treatment of both supraventricular and ventricular cardiac arrhythmias, providing clear benefit for many indications in comparison to standard pharmacological therapy\textsuperscript{3,4}.

Furthermore, progress in interventional cardiology and electrophysiology has provided new opportunities for the treatment of structural heart diseases, such as aortic stenosis, mitral regurgitation, patent foramen ovale, hypertrophic cardiomyopathy, and many others. Combining interventional cardiology and electrophysiological techniques provides the necessary basis for the treatment of pharmaco-resistant hypertension using renal sympathetic denervation\textsuperscript{5,6}. Similarly, novel bio- and nanotechnologies for the treatment of cardiovascular disease will begin a new era of cardiovascular regenerative medicine\textsuperscript{7,8}.

Novel technologies are being developed to make both coronary and non-coronary cardiac interventions and methods for cardiac electrophysiology and pacing even safer and more effective. One such example is technology for magnetically-guided endovascular and intra-cardiac procedures. Remote magnetic navigation systems, such as the NIOBE II technology, allow for very precise three-dimensional navigation of interventional devices (catheter, guidewire) (ref.\textsuperscript{11,12}). The precise positioning of the tip of the interventional device is achieved with two permanent magnets which directly control the tip of a remotely directed interventional device. Thus, movement of specially designed catheters can be very precisely controlled by the physician. Changing the vector of the magnetic field allows rapid and safe navigation of the catheters into positions that are challenging to achieve by traditional manual or even robotic control\textsuperscript{11,14}.
So far, magnetically-guided coronary and intracardiac procedures have only been used for the treatment of cardiovascular diseases and substantial progress in interventional cardiology and cardiac electrophysiology has been made. However, the use of endovascular intervention for the diagnosis and treatment of CNS disorders, such as stroke, epilepsy and CNS malignancy, is still limited. One reason for this is that the cerebral arterial and venous system is highly circuitous. Existing interventional devices and techniques enable only limited and complicated access, especially into intra-cerebral vessels.

On the other hand, magnetically-guided interventions may represent new hope for interventions within the CNS, as they have the ability to safely navigate catheters even into extremely complex vascular structures. However, the catheters used for cardiovascular interventions are too large and too rigid to be used for interventions in the CNS.

To the best of our knowledge, there is no catheter technology yet available that is designed for specifically magnetically-guided interventions within the CNS.

The aim of our study was to develop a micro-catheter magnetically-guided technology that would be specifically designed for endovascular interventions, mapping in deep CNS vascular structures, and the testing of micro-catheter technology on an experimental animal dog model.

Such technology, if successfully developed, would represent a novel approach to for the diagnostics and treatment of the most devastating CNS disorders, such as stroke and epilepsy, with potentially even broader applications, including neurostimulation and implantable monitoring of CNS functions.

METHODS

The experiments were performed at the Cardiovascular Animal Research Center in the Laboratory for Advanced Cardiovascular and CNS Interventions at the School of Veterinary Medicine, University of Veterinary and Pharmaceutical Sciences Brno (Brno, Czech Republic).

Micro-catheter

For the purpose of a remote navigation, we developed a prototype of a very thin catheter, similar in diameter to guidewire (Fig. 1). The micro-catheter is 1.1 Fr. (0.36 mm), and its tip is made of magnetic steel with high permeability. The distal part of the micro-catheter (first 30 mm from the tip) is extremely flexible for safety reasons (to prevent penetration of the vessel wall), and because the lower tip is required to be rigid against the outer magnetic field. There are 4 ring electrodes placed in the proximal part of the micro-catheter capable of scanning the potentials in the vessel.

Technology for magnetically-guided procedures

Our laboratory is equipped with the NIOBE II system (Stereotaxis, Saint-Louis, Missouri, USA) for mag-
netic navigation in combination with AXIOM ARTIS DFC Digital Angiography System (Siemens, Erlangen, Germany).

**Signal Acquisition**

Electrocardiogram (ECG) and electroencephalogram (EEG) signals were recorded by the Prucka EP system (General Electric, Milwaukee, Wisconsin, USA) and by ANNALab MI-3 technology (St. Anne’s University Hospital in Brno and Institute of Scientific Instruments of Czech Academy of Sciences, Brno, Czech Republic) that was developed by our team as an experimental system for comprehensive invasive and non-invasive cardiac and CNS electrophysiology.

**Animals**

A total of two laboratory (beagle) dogs were housed for 14 days before the experiments. The animals were utilized in accordance with the “Guide for Care and Use of Laboratory Animals” (DHHS publ. No. NIH 85-23, revised 1996, Office of Science and Health Reports, Bethesda, Maryland, USA). The experimental protocol was approved by the Ethics Committee of the University of Veterinary and Pharmaceutical Sciences, Brno.

**Anesthesia and Monitoring**

Anesthesia was induced with a mixture of medetomidine (Domitor, Pfizer) and ketamine (Narkamon, Spofa, Czech Republic) applied intravenously via IV catheter into the cephalic vein. Deep anesthesia was induced using intravenous propofol (Propofol, Fresenius). The animals were then intubated and maintained with a mixture of

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**Fig. 3.** Angiogram of intra-cerebral venous system. Arrows show determined targets for micro-catheter placement. The angiogram was subsequently used to compute vectors for magnetic navigation of the tip of the micro-catheter. 1. Transverse sinus of cerebrum; 2. Dorsal petrosal sinus; 3. Cavernous sinus 4. Ventral petrosal sinus.

**Fig. 4.** Example of 3-D reconstruction of the intra-cerebral venous system and computation of magnetic vectors for navigation of the tip of the micro-catheter into target areas as performed by the NIOBE II system.
oxygen and isoflurane (Forane, Fresenius) at the range of 1% to 1.5% of isoflurane. IV infusion was applied (lactated Ringer solution, Baxter) using linear perfusor (Braun Perfusor S, B.Braun, Germany) at a rate of 10 mL/kg/h. The heart rate (HR) was measured by ECG electrodes applied on the thorax, SpO₂ by a sensor applied on the tongue, and respiratory rate (RR) electronically based on thorax-impedance changes. All parameters were sampled and saved by Datex – Ohmeda vital monitor.

Interventions
The experiment was planned and conducted as an acute experiment followed by euthanasia. Each procedure was performed under deep anesthesia to prevent pain and suffering of the animal.

Femoral access was secured by surgical dissection of left groin and separate cannulation of the left femoral artery and vein. A 6-Fr. sheath was inserted into each vessel as a portal entrance for the catheter.

RESULTS

Testing of micro-catheter in the heart
Initially, the micro-catheter was inserted via the venous portal into the femoral vein and through the sinus venosus and navigated down the right atrium and into the right ventricle by using the support of NIOBE II system. This “cardio” part of our experiment was designed to test the mechanical and electrical characteristics of our micro-catheter prototype, particularly the remote navigation of the tip and electrical signal acquisition. The catheter tip was successfully placed into the preselected locations.

Fig. 5. Example of successful micro-catheter placement into a palatine plexus via ventral petrosal sinus with mapping of electrical activity of the brain.

Fig. 6. Example of successful micro-catheter placement into a cavernous sinus with mapping of electrical activity of the brain. Note the tortuosity of venous circulation that was overcome by our technology.
within the right heart (high right atrium, right ventricle outflow tract, right ventricle apex, and annulus tricuspidalis) and recorded intracardiac electrocardiogram (ECG) signals of comparable quality to standard catheters (Fig. 2).

Testing of micro-catheter in the brain

After successful mechanical and electrical testing of our catheter in the heart, the second part of the experiment began with the objective of reaching complex venous structures in the brain and obtaining endovascular recording of electrical activity of the brain, using the support of the NIOBE II system.

The injection of contrast dye into the main venous sinuses was performed (Fig. 3) and two images with a contrast medium (RAO 47° and LAO 37°) were stored in special Niobe II software as shown in Fig. 4. Both main venous sinuses and peripheral venous structures were determined as locations for micro-catheter placement. Subsequently, the 3-D navigation vessel model was computed by the NIOBE system according to our specifications. Parameters for magnetic navigation were set, allowing navigation of the tip of the micro-catheter via tortuositities of the venous cerebral circulation and reaching the predetermined locations in the brain, including deep vein structures. Subsequently, the endovascular navigation of the micro-catheter into CNS structures was initiated by gently pushing the micro-catheter and changing the outer magnetic field. With support of the NIOBE II system, successful navigation of the micro-catheter was performed into the vena cava cranialis, vena jugularis communis, vena maxilaris, sinus temporalis, sinus sigmoideus, sinus petrosus ventralis, sinus cavernosus, and sinus intercavernosus without evidence of venous dissection, acute thromboembolism, or extravascular bleeding during the procedure (Fig. 4 and Fig. 5.)

Electrical activity of the brain was successfully measured via micro-catheter from intracerebral venous locations (Fig. 4 and Fig. 5).

DISCUSSION

To our knowledge, this is the first study demonstrating the ability to reach deep areas of rather complicated canine brain vascularity using the percutaneous endovascular approach. For these first in living dog experiments, our original micro-catheter, in combination with the NIOBE II system, was capable of safely reaching deep venous structures in the brain of the dog which are not accessible using standard techniques, and successfully measuring the electrical signals there. Our group has previously shown that successful EEG recording and radiofrequency ablation can be performed using an endovascular approach in an experimental pig model15. Given the fact that the structure of the venous system in the canine brain is even more complex and fragile than in primates, including humans, our newly developed micro-catheter can be navigated, in combination with the NIOBE II system, to final locations using an external magnetic field, thus representing a potentially new approach for semi-invasive diagnostics and treatment of epilepsy and stroke. Modified versions of the catheter can also be used to damage tumor and other pathological tissues by delivering radiofrequency energy, or for neurostimulation and/or implantable monitoring of CNS functions.

LIMITATIONS

Despite promising results provided by our pilot experiment, it is evident that further testing, particularly on a non-human primate model will be needed to confirm the safety and efficacy of our micro-catheter technology. It is also likely that our prototype micro-catheter will need to be developed for endovascular arterial access due to the smaller diameter of cerebral arteries.

CONCLUSION

Our micro-catheter, specially designed for endovascular interventions in the CNS with support of NIOBE II technology, was capable of safely reaching deep intracerebral venous structures and mapping electrical activity. Such structures have not been accessible with standard catheters. This is the first study demonstrating the successful use of the NIOBE II technology for endovascular interventions in the brain. Further experiments are needed to confirm the safety and efficacy of this new approach for the endovascular treatment of CNS disorders.

ABBREVIATIONS

CNS, central nervous system; ECG, electrocardiogram; EEG, electroencephalogram; RR, respiratory rate; HR, heart rate

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CONFLICT OF INTEREST STATEMENT

The authors stated that there are no conflicts of interest regarding the publication of this article.
Disclosures for Samuel Asirvatham: Honoraria/ Consulting - Abiomed, Biotronik, Boston Scientific, Medtronic, Spectranetics, St. Jude, Sanofi-Aventis, Stereotaxis. Co-patent holder - may receive future royalties from - Nevro: Use of nerve signal modulation to treat central, autonomic, and peripheral nervous system disorders, including pain; Aegis: Appendage ligation; ATP: Atrial fibrillation ablation and coagulum reduction during ablation

REFERENCES


