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LONG-TERM PERFORMANCE OF A CE-APPROVED TELEMETRIC INTRACRANIAL PRESSURE MONITORING

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Abstract—**Telemetric intracranial pressure (ICP) monitoring has been a challenge throughout several decades. Major obstruction was to minimize zero drift of absolute pressure sensors. A new promising product demonstrating in-vitro excellent long-term stability has been tested for its reliability in an animal model with a follow-up of up to 2 years. In "minipigs" subdural (Raumedic-STel®, Helmbrechts Germany) and intraparenchymal (Raumedic-PTel®) telemetric ICP probes have been inserted. Standard ICP probes (Raumedic Neurovent P®) served as controls. In regular intervals of 3 months the telemetrically and conventionally measured ICP have been compared. For each control a new conventional ICP probe has been inserted frontally to the telemetric device in the generalized anesthetized minipigs, resulting in overall 38 comparisons. Bland-Altman-plots, Chi2-tests and matched pair T-tests (significance level < 0.05) were used for data-analysis.**

The zero-shift was -1.7±7.6 mm Hg (limits of agreement: 4.4±1.9 mm Hg) and -3.0±6.0 mm Hg (limits of agreement: 3.6±2.6 mm Hg) in STel and PTel respectively meeting well the devices specification of ±2 mm Hg drift per year. The reliability of both telemetric probes has been proved as quite comparable (p=0.2). These new telemetric ICP probes demonstrate reliable data during at least the first 6 months after implantation.

I. INTRODUCTION

INTRACRANIAL pressure (ICP) monitoring is of outstanding importance in the clinical management of patients suffering from various different cerebral diseases (e.g. after severe traumatic brain injury or intracranial bleeding).

Hydrocephalus stands for another disease in which ICP monitoring is of utmost importance. It is characterized by a imbalance of cerebrospinal fluid (CSF) production and absorption resulting in ventricular enlargement (physiological CSF-filled space within the brain) ending in chronic brain destruction if it remains untreated. Standard treatment for more than 80% of all patients suffering from hydrocephalus is the implantation of a shunt. Shunts are thin silicone rubber tubes allowing CSF drainage from the ventricles into a different low-pressure compartment (preferentially into the peritoneal cavity). Mechanical differential pressure valves as part of such shunts serve to control for the drainage volume to ensure physiological intracranial pressure. After its implantation yet, the performance of shunts remains a "black box" for clinicians, as there are no options allowing its proper function. Moreover, it has been found that imaging (computerized tomography, magnetic resonance imaging) are also not suitable for shunt performance assessing [1]-[2], as ventricular shrinking must not occur in patients with favorable outcome. ICP monitoring remains the only reliable way for checking questionable shunt performance. Yet, it loads major burden and additional risks on patients, as they have to undergo another surgical intervention. As, - up to now -, such measurement can be performed only with non-full implant devices, ICP monitoring can become performed in in hospital patients only and during 5 – 10 days maximally due to increasing infection risk thereafter [3].

Full-implant devices for long-term ICP-monitoring were demand note of clinicians accordingly since several decades. Yet minimally 14 different according designs failed to fulfill the clinicians' prerequisites.

In cooperation with the Raumedic AG (Helmbrechts, Germany) a new designed telemetric ICP measurement device has been developed seemingly providing the major clinical specifications according to its long-term in-vitro performance (e.g.: minimal long-term drift, reliability). The purpose of this study was to assess its in-vivo performance.

II. MATERIAL AND METHODS

A. The Telemetric ICP Measurement Device

For the implantable telemetric probes housing ceramic has been used. It contains all electronics and the antenna for data and energy transfer (Fig. 1). The sensor tip contains a piezoresistive strain gauge silicon-based absolute-pressure sensor with build-in Wheatstone bridge and a temperature sensor. Its signals are digitized and processed by an ASIC within the ceramic housing. As it has been designed as a passive implant, signal measurement and processing requires external power supply which is realized by a modified Raumedic-Datalogger® having an antenna for energy transmission and data receive. RFID (radio-frequency identification) technology allows individual implant identification to provide its specific calibration data. Actually data can be sam

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pled at 5 Hz at resolution of 1 mm Hg within a pressure range between -40 to +400 mm Hg. To compute relative ICP, absolute pressures measured by the implant and by a second absolute pressure sensor within the Datalogger measuring atmospheric pressure have to be processed. ICP data with time-stamps are stored on a build-in solid-state drive (SSD). Details of the technology have been described earlier [4]-[6]. Two different designs of the implant have been realized optimized for subdural or intraparenchymal application.

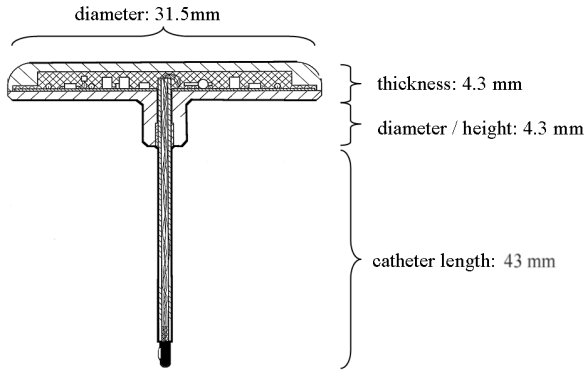

Fig. 1. Sematic graph of the implant of a parenchymal telemetric probe. The diameter of the intraparenchymal catheter measures 1.3 mm.

A. Study Design and data analysis

All operative procedures and all measurements have been performed under general anesthesia and complete monitoring (rectal temperature, capillary oxygen saturation ($S(O_2)$) and ECG) of the animals. Anesthesia has been induced with Ketavet® (10%; / 1mg / 10 kg i.m.) and 2.6-Diisopropylphenol (Propofol®) (dosage depending on individual reaction). Thereafter the animals were intubated, artificially ventilated (30% O_2, nitrous oxide at 2.5 Vol.%) and anesthesia sustained with i.v. N-(1-Phenethyl-4-piperidyl)propionanilid (Fentanyl®) (45 – 90 µg/kg/h) and vaporized (RS)-Difluormethoxy-1-chlor- 2,2,2-trifluorethan (Isofluoran®) at 1.5 to 2.5 Vol%. For hydration, left-ear vein i.v. line has been used to administer Ringer-Lactate and 0.9% NaCl-solutions. Amoxicillin i.v. (weight adapted), - administered 30 min. before skin incision -, served as perioperative antibiotic prophylaxis and has been continued for further 3 days. (RS)-2-(6-Chlor-9H-carbazol-2-yl)propan-acid (Carprofen®) has been given as post-interventional pain killer.

The study has been done in male, adult "Goettinger" minipigs. Details of the operative procedures have been described earlier [5]. To assess the long-term performance of telemetric devices 8 animals were implanted with two telemetric probes under strict sterile conditions. One was inserted subdurally (Raumedic STel®) and the other intraparenchymally (Raumedic PTel®). For control measurement a conventional Raumedic Neurovent-P® pressure sensor has been inserted via a more frontally to the telemetric probes placed borehole. To estimate potential hydrostatic pressure differences between reference and telemetric probe, X-rays have been performed to assess the probes' insertion deep. If necessary, according corrections have been performed. According to protocol every 3 months after implantation control measurement comparing telemetrically and conventionally measured ICP have been performed in 3 randomly selected animals, resulting in 1 to 5 controls in each minipig. After reference probes' implantation resting ICP has been measured during 10 minutes. Thereafter ICP has been altered by inkling the operating table ± 20° for another 10 min.

Measured data were processed with the Raumedic-Datalog® software. Data analysis has been performed with Microsoft-Excel 2003 (Redmond, USA), PASW Statistics 18 (SPSS Inc, an IBM Company, Chicago, USA), and WinSTAT® for Excel Version 2009.1 (R.Fitch Software, Bad Krozingen, Germany). Bland-Altman plots, Kaplan-Meier charts, Log-rank test, Mann-Whitney-U-test, F-test and regression analysis were used for statistical workup. The significance level has been adjusted at $p < 0.05$.

As biocompatibility was another aspect to address in this study, we implanted in a further animal another two telemetric devices, but these were never used for control measurements allowing to analyze effects on the surrounding tissue effectuated purely by the implants without the potential bias which could have brought in during the insertion of the conventional ICP probe for reference measurements and eventually by transcutaneous energy transmission.

The study was approved by an independent animal welfare committee and monitored by the institutional animal welfare delegate. Veterinarians supervised all procedures and performed anesthesia.

III. Results

A. General findings

Overall 10 subdural and 8 intraparenchymal telemetric probes have been inserted in 8 minipigs assigned to undergo control measurements. Another 2 intraparenchymal probes were inserted in the animal serving to study biocompatibility only. In two animals only one control measurement has been performed, while in another 2, 3 and 1 animals 3, 4 and 5 controls were performed respectively. According to study protocol 1, 1, 2, 3 and 4 animals were finalized 1, 6, 9, 12, 18 and 24 months after PTel and STel implantation respectively to study biocompatibility after different time intervals resulting in an overall average follow-up of 15 ± 5 months. During the observational period 7 STel probes and 2 PTel probes were lost after aseptic skin necrosis of the skin covering the implants between days 56 until day 443 after insertion. The always-preceding signs of skin injury resulted from inter-individual violations due to rank fights as part of the animals' natural behavioral repertoire. These findings could be substantiated by the histopathological examinations performed after finalization demonstrating clear signs of signifi-

cant violations even resulting in skull fractures in these animals. Probes positioned under necrotic skin have been removed regarding them as potentially contaminated by bacteria. After wound debridement the skin was sutured again. No case of general infection or meningitis occurred and the remaining telemetric probe served for further controls. It has to be emphasized that primary wound healing could be achieved in all animals initially.

B. Functional survival

On day 98 and 156 after insertion STel probes of two animals failed allowing no further ICP measurement. The overall functional survival of all studied telemetric probes has been calculated as 88% after a maximum of 24 months when computed according to the Kaplan-Meier method. In a log-rank test the functional survival of PTel and STel differs not significantly ($p = 0.136$). Yet, with respect of the small sample size (due to the explorative character of this study and with regard of maximal animal welfare) such data have to interpret with care as sufficient rigor for funded statistical conclusions addressing functional survival seems not given.

C. Reliability of measurement and comparison of STel and PTel

Overall 25 control measurements have been performed. Due to the intentioned "lost" of 7 STel compared with only 2 PTel probes, 11 and 14 controls have been performed in STel and PTel probes. The follow-up period of both probe types did not differ significantly (STel: 16±5 months; PTel: 15±6 months; $p = 0.747$).

While providing accurate data before implantation, 2 STel and 2 PTel probes (each in different animals) met not its specifications during the control measurements performed immediately demonstrating significant differences when compared with measured ICP by the reference and the second implanted telemetric probe. We assume incidental, inappropriate operative insertion technique as underlying reason for its failure.

Excluding the later from further analysis, the overall difference between telemetric and reference calculates as 4±2.4 mm Hg (range: 1 – 8 mm Hg) throughout the whole follow-up. Interestingly, when calculating Pearson's product-moment coefficient, the differences between probes meeting the specification ($R = 0.933±0.09$) and those not meeting it ($R = 0.924±0.07$) directly after implantation were minimal ($p = 0.541$) indicating that dynamic signal characteristics remained unchanged or mildly affected only despite significant differences regarding static ICP.

To analyze the long term performance of telemetric ICP measurement we regarded the evolution of the differences between measurement done during the first 6 and 12 months (control 1, 2) and compared it with control 3-5 performed 15 – 24 months after telemetric probes' implantation (Fig. 2). It is obvious that probes' performance remains within the reference during the first year after implantation with minimal zero-based drift. Thereafter yet, the static ICP of PTel probes differs increasingly when compared with the reference. Apparently PTel probes trend to underestimate ICP after an implantation period exceeding 12 months. In contrast, STel probes (while demonstrating comparable well reliable value as PTel probes during the first year after implantation) overestimated and underestimated ICP during control 3 and 4 respectively, but demonstrated no trend of increasing discrepancy between reference and control as STel probes (Fig. 2). Interestingly, the difference of the STel probe and reference is higher (yet still acceptable from clinicians' viewpoint) during the first year after insertion when compared with PTel probes ($p = 0.002$).

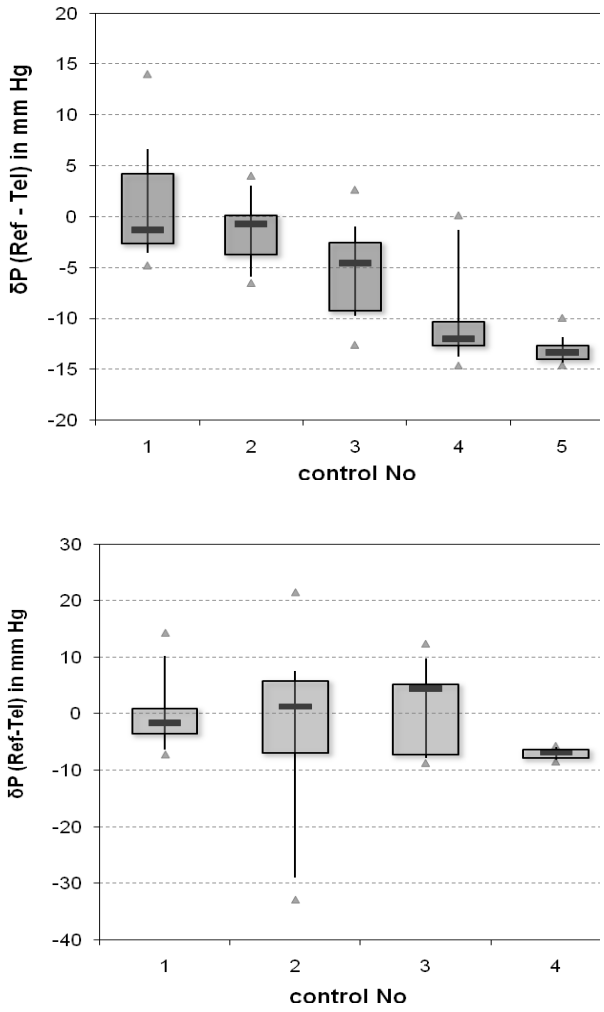

Fig. 2. BoxWhisker plots of the evolution of the difference (in mm Hg) between STel (upper chart) / PTel (lower chart) compared with reference measurement. The differences are low during the first year (control 1, 2) but increases later.

Clinician regards specifically results of Bland Altman plots when comparing Gold standards with new devices. The clustered overall data from all measurements (after excluding data from devices with initial worse performance) demonstrate an average difference between reference and telemetrically assed ICP exceeding not more than -1.7 mm Hg appearing well acceptable at the first glance.

Yet, the limits of agreement, - ranging between 9 mm Hg

to -12 mm Hg still appear as too large from clinicians' perspective. Another interesting aspect becomes obvious analyzing the Bland-Altman plot (Fig.3): While the discrepancy between reference and telemetric ICP is small at ICP-levels up to 15 mm Hg, the differences between reference and telemetric probe increase as more as ICP exceeds values of 15 mm Hg. This might indicate some sensor non-linearity at higher ICP. With a more detailed analysis it can be found that mainly STel probes seem responsible for such finding, while PTel probes were found with well linearity throughout the whole covered ICP rage. Up to now we have no explanation for this phenomenon.

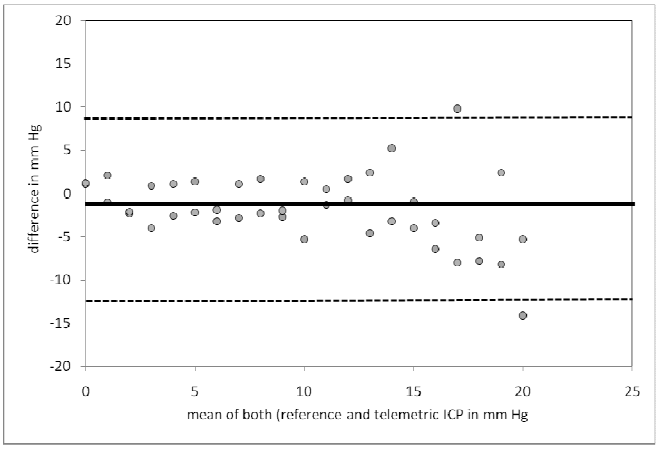

Fig. 3. Overall performance of all telemetric probes and all measurement plotted as Bland-Altman chart. For improved illustration data have been mildly clustered in advance.

IV. Discussion

With the Raumedic telemetric ICP measurement devices a first commercially available technology has become CE-approved which can be using during 4 weeks in clinical practice (up to now). Despite longer usage would be desirable, its availability despite such restriction marks a new milestone in hydrocephalus treatment allowing ICP-based, individualized setting of adjustable shunts according to patients' specifical demands. Moreover, it is well known that most shunt adjustment must be done within the first months after shunt implantation. In contrast to the past era without such feature, clinicians had to wait for the clinical course of patients before eventually further necessary adjustment could be done to optimize clinical outcome. Accordingly, despite restricted to 4-weeks implantation, the available CE-approved telemetric devices add major advantage in clinical practice and help to shorten hospitalization.

Yet, to analyze late clinical deterioration, which might come from shunt failure as well as from other Comorbidity, longer telemetric monitoring could be valuable too. The aim of the study was to evaluate its long-term performance accordingly.

Based on our findings as well Ptel as STel probes have been proven to provide reliable data for at least 12 months, sufficiently supporting its clinical usage and approval for up to 12 months. Thereafter yet, both (especially the PTel probes) demonstrate increasing zero-based shift. Especially PTel probes seemingly trend to underestimate ICP when implanted longer than 12 months. Contrary the sensor linearity of STel probes seems questionable at ICP level > 15 mm Hg, while it seems much more favorable in PTel probes. Underlying reasons for such phenomena have not yet been fixed, but have to be solved if implantation periods exceeding 12 months should be aimed.

The effect of the impact brought in by the animals behavior can hardly estimated, but remains a strong drawback of this study. For larger series an animal model has to be established which excludes such bias.

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