MONITORING OF PHYSIOLOGICAL FLOW WITH A MICROFABRICATED ELECTROCHEMICAL PARYLENE FLOW SENSOR

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ABSTRACT

A microfabricated electrochemical impedance-based flow sensor for inline monitoring of physiological fluid flow was demonstrated to track cerebrospinal fluid (CSF) flow changes in a week-long, live porcine study. This impedimetric sensor was benchmarked against a Sensirion LD20 thermal liquid flow sensor at the benchtop, followed by a CSF drainage study using an external ventricular drain (EVD) in the pig. Sensor resolution was improved ~2× to 26.2 µL/min at low flow versus previous work, and operation expanded to 0-1000 µL/min. Using separate calibrations for low and high flow ranges, accuracy at low flow rates (0-200 µL/min) was improved more than six-fold compared to prior work. High sensitivity, resolution, accuracy, and stable RMS error were demonstrated in the porcine study. The performance of the impedimetric sensor was comparable to the LD20 benchmark showing the sensor's capability of monitoring flow dynamics in implanted hydrocephalus shunts.

KEYWORDS

Parylene C, flow sensor, impedimetric sensor, hydrocephalus

INTRODUCTION

Elevated intracranial pressure (ICP) in hydrocephalus patients resulting from the imbalance between production, absorption, and circulation of cerebrospinal fluid can be treated using an implanted drainage shunt to remove excess CSF. However, shunts fail often due to clogging, which is challenging to detect from symptoms including headache, nausea, and vomiting; these are general, nonspecific, and may be indicative of other maladies [1]. A suspected shunt malfunction can involve a hospital visit for diagnostic imaging, including magnetic resonance imaging, computed tomography, and plain X-rays. The additional imaging is costly and can expose patients to radiation.

Sensors have been developed to monitor CSF flow dynamics for detecting such shunt malfunction. The only FDA-approved device in the market is ShuntCheck from NeuroDx Development which measures CSF flow rate. This device is positioned on the skin and aligned to the implanted shunt catheter. An ice pack is set upstream, cooling the flowing CSF, which is detected via the induced temperature gradient downstream using a thermistor. This approach can cause discomfort but, more importantly, has limited resolution and accuracy. Other sensors being developed include ultrasonic sensors, which measure volumetric flow in shunts transdermally [2] but have low resolution and are impractical to wear.

The ideal sensor would be implanted in line with the shunt, be able to measure both CSF flow and ICP, and have a life span of decades. An external handheld device would be used to record flow and pressure as well as being able to recalibrate for drift, as both CSF flow and ICP can vary from second to second depending on body position, fluctuations in blood pressure, and respiration. Thermal flow sensors can be implanted [3], but most have a silicon construction which is subject to corrosion, fracture, and exposure to the body environment while operating *in vivo* [4]. Sensors having biocompatible construction, such as Parylene, could perform better for *in vivo* applications over time [4].

We developed a sensor made from biocompatible and non-corroding Parylene C, capable of measuring flow and temperature in real-time through electrochemical impedance transduction of biological saline solutions. Here, sensor calibration and resolution were improved for CSF flow monitoring, and the first demonstration of the sensor in the pig is reported.

MATERIALS AND METHODS

The impedimetric sensor consists of an upstream, resistive, serpentine platinum (Pt) heater (~400 Ω) and downstream sensing electrode pairs (exposed Pt) on a Parylene substrate (Fig. 1) [5]. Multilayer micromachining on a silicon support wafer was used to fabricate the sensor [6]. A 10 µm thick Parylene insulation layer was deposited through chemical vapor deposition (CVD). To define the metal features, a 2 µm thick AZ 5214-IR photoresist layer was spin-coated, and Pt (2000 Å) was deposited through e-beam deposition followed by lift off in heated acetone and rinses in isopropanol alcohol (IPA) and deionized (DI) water. Another 10 µm thick Parylene layer was then deposited. 15 µm thick AZ 4620 photoresist was spin-coated to serve as the sacrificial layer. The metal pad, electrode sites, and device shape were etched out through deep reactive ion etching. Photoresist was removed by sequential acetone, IPA, and DI water baths, and the individual sensor was released using a razor blade to cut along the etched shape. The device was thermoformed in a vacuum oven at 200 °C for 48 hours to enhance the adhesion between Parylene and metal layers.

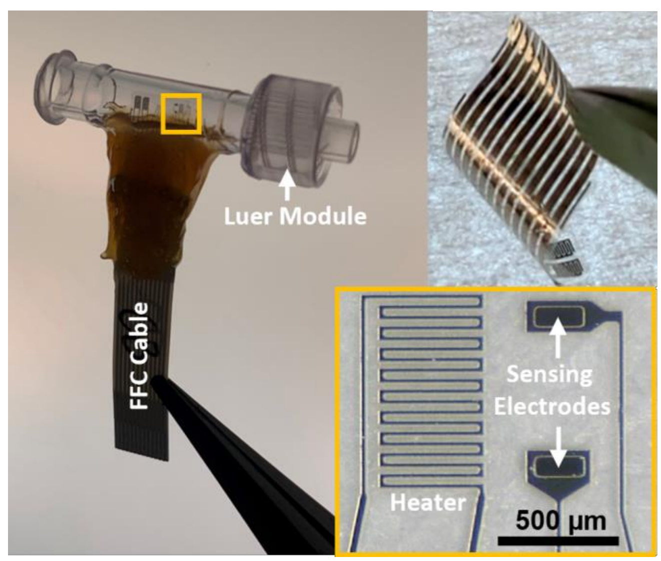

Figure 1. Low profile, flexible sensor die packaged in a Luer module. Fabricated Parylene impedimetric sensor after release from the silicon substrate. Inset shows a close-up of the flow sensor elements (yellow box).

The flow was detected using a time-of-flight approach: the upstream heater was activated by a voltage pulse, then heat transfer downstream was detected via the electrolyte's impedance response, which is sensitive to thermal changes. Specifically, the maximum rate of impedance change – defined here as the heating slope (HS, %/s) – during the 10-second heater activation was used to transduce the flow rate (Fig. 2) [6][7]. Measurements were acquired every 80 s (including 60 s for cooling between measurements) to minimize the overheat temperature (~2 °C). Impedance was acquired at 50 kHz to maximize the contribution from solution resistance.

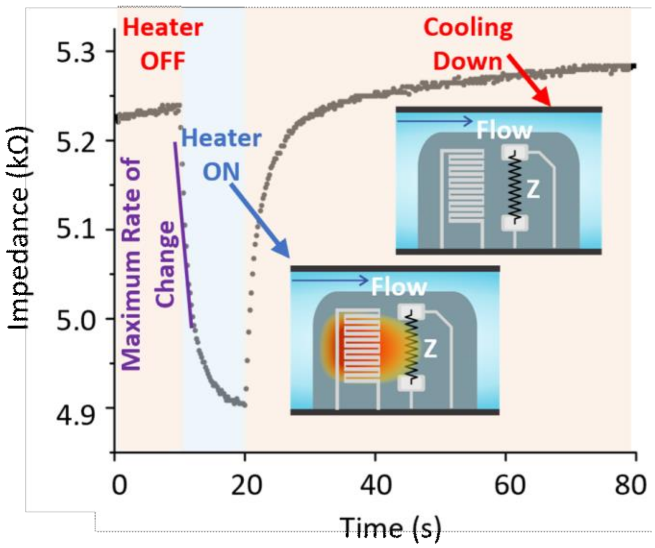

Figure 2. Impedance response of sensor over a heating cycle. Flow rate is transduced from the normalized maximum rate of impedance (Z) change during the "Heater ON" phase (10-20 s).

The contact pad region was attached to a PEEK adhesive backing and mated to an FFC cable through a zero-insertion force (ZIF) connector. This assembly was packaged with the sensor positioned in the lumen of a luer module and affixed with epoxy (EpoTek 353 ND-T) for integration into the EVD system (Fig. 1). The sensor was connected to a printed circuit board (PCB) with a commercial flow sensor LD20 (Sensirion) via the FFC (Fig. 3). A cable interfaced the PCB to the power source and recording system, allowing both the impedimetric and LD20 sensors to be activated to acquire simultaneous flow measurements.

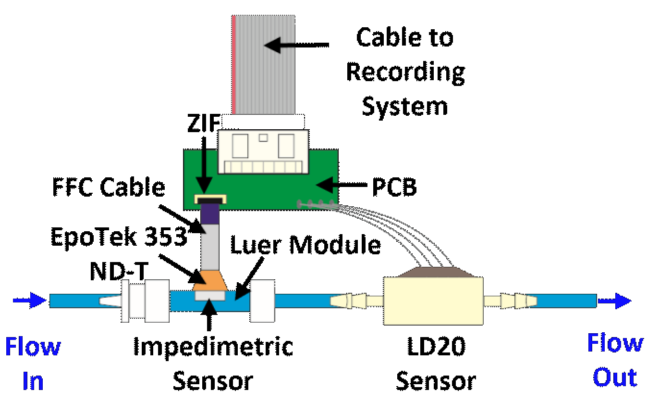

Figure 3. Schematic of fully packaged impedimetric and LD20 sensors. Blue arrows indicate the direction of CSF flow.

The sensor was calibrated at the benchtop using phosphate-buffered saline and compared against the LD20 sensor over the flow range of 0 to 1000 µL/min. For the low flow range of 0 to 200 uL/min, one calibration measurement was taken every 20 µL/min. The measurement was taken every 250 µL/min for the higher flow rate. To simulate *in vivo* conditions, the testing setup was placed in a temperature-controlled chamber (Fig. 4). A temperature probe was used to actively monitor the temperature of the reference PBS to ensure the liquid flowing through the sensor reached the expected temperature. The fluid temperature was varied around body temperature (37 °C), 20, 30, and 40 °C specifically to investigate the impact of temperature on sensitivity.

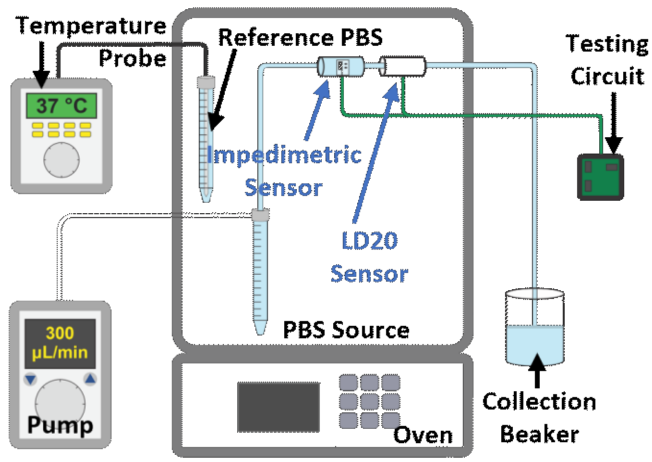

Figure 4. Benchtop testing setup for calibrating the sensor. Phosphate-buffered saline (PBS) flow and an oven were used to mimic the body's warm saline environment.

RESULTS AND DISCUSSION

Flow sensor calibration curves at various heater power settings (10, 20, and 40 mW) were evaluated (Fig. 5). At 10 mW, the sensitivity (slope of the plotted curve in Fig. 5) was low for flow

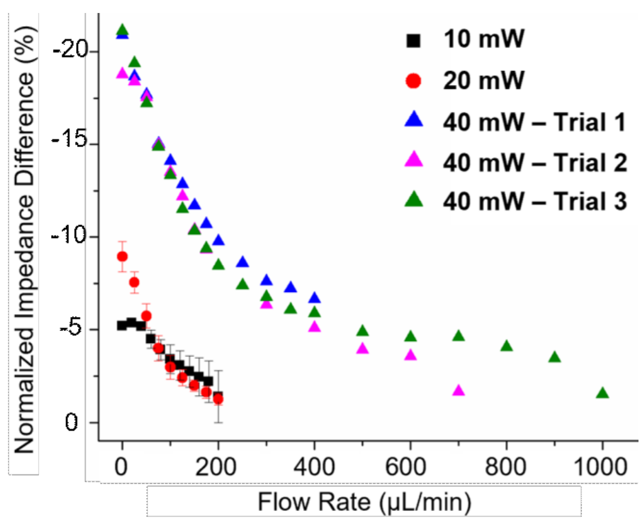

Figure 5. Impedimetric sensor calibration at different heater input powers. The sensitivity (Δ%/µL/min) increased significantly, especially in the low flow range when input power doubled from 10 to 20 mW but did not improve beyond 20 mW.

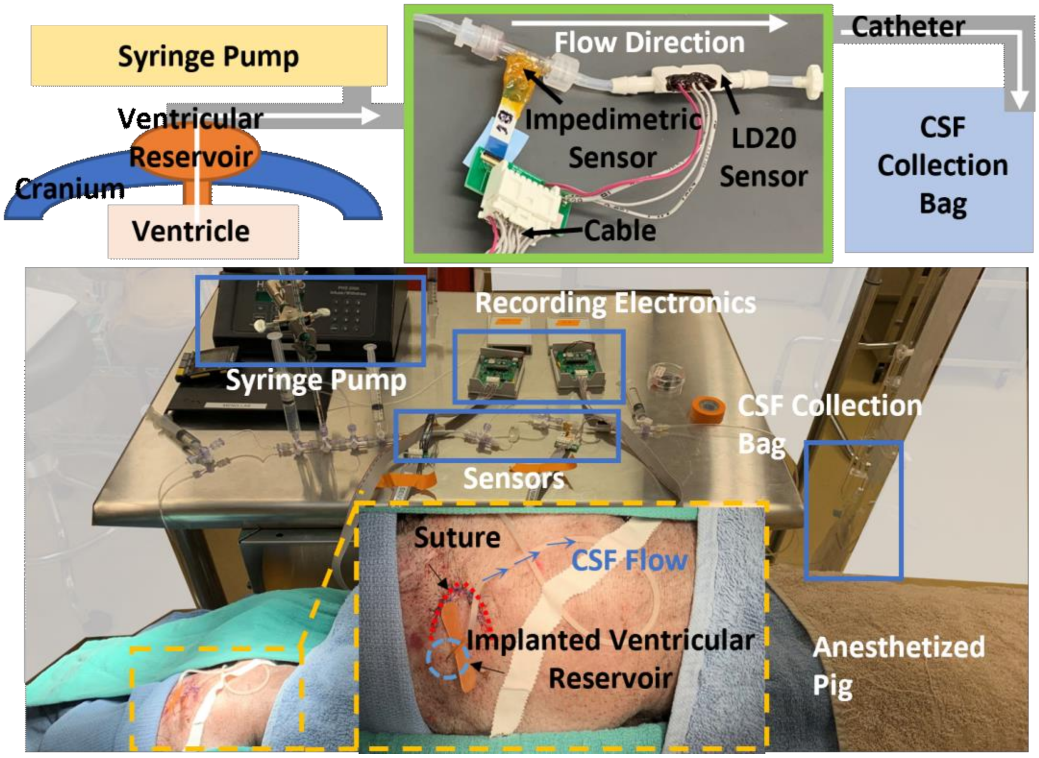

Figure 6. Testing setup for the porcine study. The ventricular catheter was implanted into the ventricle with the reservoir under the scalp then the wound was sutured. A needle with a catheter was connected to the reservoir (yellow dashed box) to access CSF via the shunt either for draining or infusing. Flow sensors were connected to the output for measuring the flow rate and temperature of CSF.

rates under 100 µL/min. Curves at 20 and 40 mW had similar slopes. Sensitivity did not improve above 20 mW; this heater setting was selected to conserve power.

A non-linear response with flow rate was recorded, requiring two separate calibrations. For flow > 200 µL/min, HS was linearly correlated with flow rate (R^2=0.94) but quadratic for lower flow rates (R^2=0.95). By considering different regression curves by flow range, the sensor accuracy (% error) improved over sixfold compared to previous work [6] for the low flow rate domain, which corresponds to the typical CSF flow range observed in patients with an EVD [2]. Longer response times are expected at low flow, further supporting two separate calibrations [8].

An impedimetric sensor and LD20 were connected to an EVD, installed in a 36 kg 10-month-old Yucatan female pig, and used to take periodic CSF flow measurements for one week (Fig. 6). An incision was made on the pig's scalp, and a burr hole (diameter of ~1.5 - 3 cm) was drilled for inserting the ventricular catheter to target the pig's left lateral ventricle. The burr hole was placed on the coronal suture ~1 - 1.5 cm from the midline. Proper ventricular catheter placement was confirmed by the outflow of CSF from the sidearm of the silicone reservoir. The ventricular catheter reservoir was sutured to the pericranium with the sidearm plugged. The skin was closed with two layers of sutures and marked over the reservoir for future access.

CSF was drained from the ventricle through the reservoir, directing flow through the sensors to a collection bag. Access to the CSF was achieved using a 25-gauge butterfly needle to puncture through the reservoir. The same line was connected to a syringe pump to infuse artificial CSF (aCSF) into the pig's ventricle to modulate ICP for mimicking the hydrocephalus condition. Impedimetric sensors successfully tracked temperature and flow

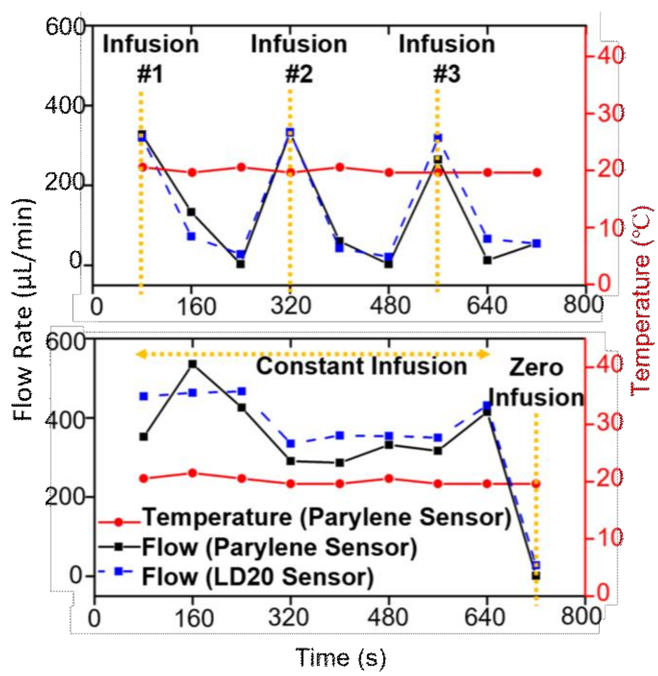

Figure 7. Flow and temperature of pig CSF acquired by impedimetric Parylene and LD20 sensors. (Top) Results for sequential aCSF bolus infusions at 80, 320, and 560 s, respectively. Measurements were obtained after infusion. (Bottom) Results for constant aCSF infusion. The infusion was stopped after 640 s, and measurements were taken during infusion.

rate (Fig.7) under bolus and constant aCSF infusion. Comparison to LD20 flow measurements showed good agreement (Fig. 8). The impedimetric sensor reliably tracked flow at different time points over one week: day 1 (surgery day), 6, and 7 (Fig. 9). A stable RMS error of 21.39, 36.62, and 32.25 µL/min was recorded.

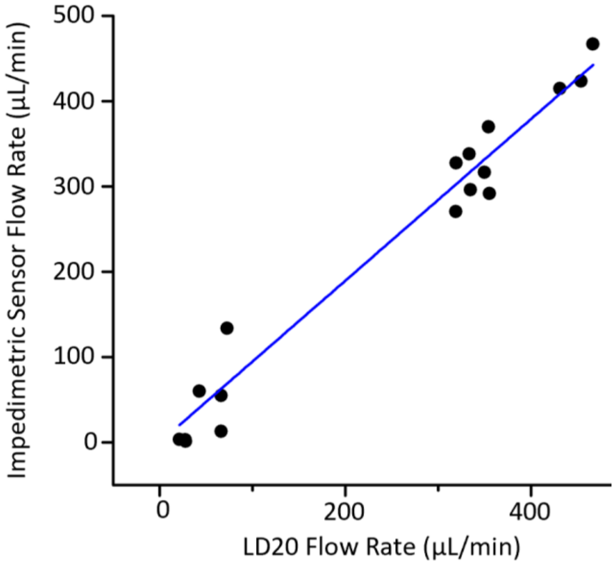

Figure 8. The measured flow rate of the impedimetric sensor (y) was linearly correlated to the LD20 sensor (y=0.95 x, R^2=0.99).

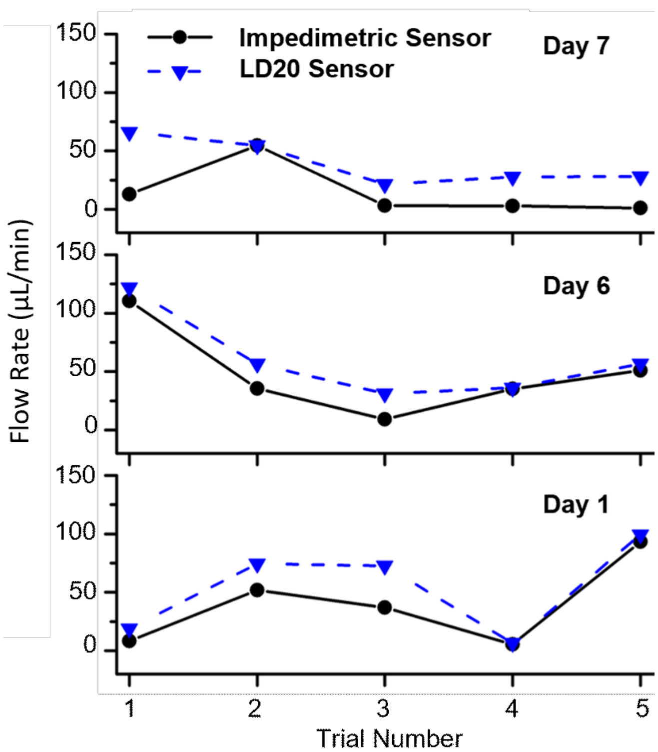

Figure 9. Comparison of flow measurements over one week for the impedimetric and LD20 sensors (implantation on Day 1).

The sensor system used for the porcine study was wired to a recording PCB with an SD card slot for storing the data. A lithium polymer battery was used to power up the PCB and sensors. Future work involves developing a fully implantable sensor system, including miniaturization of the recording electronics.

CONCLUSION

This work demonstrated a Parylene flow sensor based on electrochemical impedance transduction and successful flow and temperature measurements in a live shunted pig for one week. The sensor tracked CSF flow in real-time from the pig brain ventricle with good agreement with a commercial sensor (LD20). This paves the way for the application of the sensor for *in vivo* long-term monitoring of physiological flow in hydrocephalus patients.

ACKNOWLEDGEMENTS

The authors would like to thank Dr. Bradley Ahrens, Dr. Lynlee Stevey, and Vivian La for their assistance in the animal study. The authors also express special thanks to Dr. Donghai Zhu for his input on fabrication and the USC Biomedical Microsystems Laboratory members for their assistance. This work was supported in part by the National Science Foundation under award numbers EFRI-1332394 and IIP-182773, USC Coulter Translational Research Partnership Program, and the USC Ming Hsieh Institute Award.

REFERENCES

[1] J.M. Spirig, M. N. Frank, L. Regli, and L. H. Stieglitz, "Shunt Age-related Complications in Adult Patients with Suspected Shunt Dysfunction. A Recommended Diagnostic Workup", *Acta Neurochirurgica*, 159, 8 (2017).

[2] T. Pennell, J.L. Yi, B. A. Kaufman, and S. Krishnamurthy, "Noninvasive Measurement of Cerebrospinal Fluid Flow Using An Ultrasonic Transit Time Flow Sensor: A Preliminary Study", *Journal of Neurosurgery: Pediatrics PED*, 17, 3 (2016).

[3] T. Bork, A. Hogg, M. Lempen, D. Müller, D. Joss, T. Bardyn, P. Büchler, H. Keppner, S. Braun, Y. Tardy, and J. Burger, "Development and *In-Vitro* Characterization of An Implantable Flow Sensing Transducer for Hydrocephalus", *Biomedical Microdevices*, 12, 4 (2010).

[4] K. Scholten and E. Meng, "Materials for Microfabricated Implantable Devices: A Review", *Lab on a Chip*, 15, 22 (2015).

[5] A. Baldwin, L. Yu, and E. Meng, "An Electrochemical Impedance-Based Thermal Flow Sensor for Physiological Fluids", *Journal of Microelectromechanical Systems*, 25, 6 (2016).

[6] T. Hudson, A. Baldwin, A. Samiei, P. Lee, J.G. McComb, and E. Meng, "A Portable Multi-Sensor Module for Monitoring External Ventricular Drains", *Biomedical Microdevices*, 23, 45 (2021).

[7] T. Hudson, A. Baldwin, E. Christian, J.G. McComb, and E. Meng, "Testing A Multi-Sensor System for Hydrocephalus Monitoring in External Ventricular Drains", 2019 20th International Conference on Solid-State Sensors, Actuators and Microsystems & Eurosensors XXXIII, Berlin, Germany (2019).

[8] C. Sosna, T. Walter, and W. Lang, "Response Time of Thermal Flow Sensors", 2010 Eurosensors XXIV, Linz, Austria (2010).

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