INTRODUCTION

The use of mobile technologies has given rise to novel ways in which healthcare systems may be strengthened. Innovative applications of such technologies have transformed into a new field of eHealth, known as mobile health (mHealth). According to the Global Observatory for eHealth (GOe), mHealth is defined as 'medical and public health practice supported by mobile devices, such as mobile phones, patient monitoring devices, personal digital assistants (PDAs) and other wireless devices' (World Health Organization, 2011). The increased usage of mobile phones worldwide has led healthcare providers to find more effective methods of monitoring and collecting pertinent patient information (Marcolino et al., 2018) leading to enhanced continuity of care. Telemedicine is the means of delivering medical data and health care via telecommunication technologies. It has the potential for providing continuous healthcare services to patients from a distance (Scott Kruse et al., 2018). In addition to bringing patients and physicians closer, it also has beneficial effects on money and time. Despite the need, monitoring in health care is still in its infancy with cumbersome instruments and restrictive clinical practices. The best example would be the use of a catheter placed in an artery connecting to a transducer to detect and measure blood pressure in the intensive care unit. Besides the poor accuracy of the measurement, the patient is usually sedated to avoid any movement that can cause harm. Currently, there are no simple and...
cost-effective sensing technologies that are capable of continuous and real-time measurements of pressure without sacrificing patient comfort. To take full advantage of mHealth, new methods and technologies (especially implantable microsystem devices that can continuously transfer data via wireless telemetry) must be developed (Mohammadzadeh & Safdari, 2014). Measurement of pressure in the circulatory system, intraocular space, muscle compartments, joints and the brain is clinically relevant as this physical parameter is a critical indicator for detection of many diseases (Aarnoudse et al., 2007). Pressure can vary depending on external and internal factors such as atmospheric pressure, gravity or even the mere actions of muscles. Pressures of interest in the human body range from ultra-low to medium pressures (Yu, Kim, & Meng, 2014). Ultra-low pressures measure < 1 Pa; subtle pressures range from 1 Pa to 1 kPa; low pressures range from 1 to 10 kPa; and medium pressures range from 10 to 100 kPa (Mannsfeld et al., 2010; Zang, Zhang, Di, & Zhu, 2015). Medium pressure values have attracted much interest and are the homeostatic pressure ranges of most of the intra-body functions (Choong et al., 2014; Li & Wang, 2011; Zang et al., 2015). Innovative pressure sensors for applications in health care and medical diagnosis in the low and medium pressure ranges have been developed over the past decades (Zang et al., 2015). Historically, pressure examinations would measure a single snapshot covering only a few seconds (e.g. blood pressure or compartment syndrome) unless manual repetition is performed. Additionally, the device itself may cause artefacts or be position dependant even when long-term monitoring is attempted, such as the case with arterial lines (Kaisti et al., 2019; Li, Mark, & Clifford, 2015). Post-surgery, the patient is delivered a small external device that calibrates the IHM to the mere actions of muscles. Pressures of interest in the human body range from ultra-low to medium pressures (Yu, Kim, & Meng, 2014). Ultra-low pressures measure < 1 Pa; subtle pressures range from 1 Pa to 1 kPa; low pressures range from 1 to 10 kPa; and medium pressures range from 10 to 100 kPa (Mannsfeld et al., 2010; Zang, Zhang, Di, & Zhu, 2015). Medium pressure values have attracted much interest and are the homeostatic pressure ranges of most of the intra-body functions (Choong et al., 2014; Li & Wang, 2011; Zang et al., 2015). Innovative pressure sensors for applications in health care and medical diagnosis in the low and medium pressure ranges have been developed over the past decades (Zang et al., 2015). Historically, pressure examinations would measure a single snapshot covering only a few seconds (e.g. blood pressure or compartment syndrome) unless manual repetition is performed. Additionally, the device itself may cause artefacts or be position dependant even when long-term monitoring is attempted, such as the case with arterial lines (Kaisti et al., 2019; Li, Mark, & Clifford, 2015). Post-surgery, the patient is delivered a small external device that calibrates the IHM to

2 | BIOMEDICAL APPLICATIONS OF PRESSURE SENSORS

2.1 | Cardiac pressure sensors

Blood pressure is among the most important physiological parameters in the living body. It works to control the blood flow in order to transport oxygen and vital nutrients, as well as remove cellular waste, to and from various organs and tissues. Invasive cardiac pressure monitoring has been used since 1959 and numerous epidemiological research studies have determined that there is a strong continuous positive correlation between blood pressures and cardiovascular disease outcomes (Vasan et al., 2001; Yao et al., 2016). Furthermore, high blood pressure has been associated with an increased rate in the development of negative cardiovascular events such as stroke, myocardial infarction, congestive heart failure and death (Vasan et al., 2001). Haemodynamic status of the cardiovascular system can be directly monitored through placement of highly sensitive, yet invasive pressure sensors implanted in the heart or lungs to measure right ventricular pressure (RVP), left atrial pressure (LAP), pulmonary capillary wedge pressure (PCWP), pulmonary artery pressure (PAP) and central venous pressure (CVP) (Abraham & Perl, 2017; Kuck et al., 2013; Lau, Siu, & Tse, 2012; Merchant Faisal, Dec, & Singh Jagmeet, 2010; Wadas, 2005). Additionally, monitoring pressure using implantable pressure sensors in aneurysms post-endovascular repair is key in preventing further rupturing, leaks, vascular damage and ultimately death in patients diagnosed with abdominal aortic aneurysms (Allen, 2005). There are newer sensors that can be surgically implanted post-repair for immediate inspection, or to allow the physicians to deliver personalized therapies (Cleven et al., 2012; Joung, 2013). The sensors can be used to monitor hypertension, repaired aneurysms and more (Potkay, 2008).

RVP sensors estimate the pulmonary artery end-diastolic pressure (ePAPD) using micromanometers in the right ventricle (RV) and pulmonary artery (PA) as RVP is equal to ePAPD when the pulmonary valve opens (Smith & Abraham, 2012). The Chronicle® Implantable Hemodynamic Monitor (IHM) (Medtronic, Inc.) is currently used to measure and record real-time RVPs in heart failure patients. The system consists of a small programmable electrical device which is connected to a transvenous right ventricular lead. The size of the electrical device and the implantation method in the pectoral area are similar to that of a single lead pacemaker (Kuck et al., 2013). The incorporated pressure sensor at the tip of the lead uses a titanium diaphragm and polyurethane window to obtain real-time intra-cardiac pressures and other data (Kuck et al., 2013; Wadas, 2005). The device contains a ‘battery, integrated circuitry and a radio-frequency transmission coil sealed in titanium’ (Figure 1). Post-surgery, the patient is delivered a small external device that calibrates the IHM to changes in barometric pressure, while recording and storing the haemodynamic data (Kuck et al., 2014).

To prevent the risk of pulmonary congestion and heart failure, sensors have been developed to measure mean LAP. Among them, the HeartPOD™ (St Jude Medical, Inc.) device is comprised of an implantable sensor lead coupled to a coil antenna positioned in the subcutaneous tissue (Figure 2b). The sensor lead is implanted in patients through a cardiac catheter via transseptal puncture and fixed directly onto the interatrial septum. No battery is required, and the device is powered with a handheld patient advisory module (PAM) by 125-kHz radio-frequency wireless transmission (Smith & Abraham, 2012). Data are collected, captured in the PAM for periods that last up to 20 s and wirelessly transmitted via the coil antenna (Kuck et al., 2014; Mooney, Fung, Doshi, & Shavelle, 2015).
Pulmonary artery pressure sensors are less invasive than the RVP and LAP sensors as the implant can be placed during a right heart catheterization process. The CardioMEMS heart failure sensor (CardioMEMS™ Inc.) is a wireless radio-frequency sensor that does not use batteries within the device (Abraham et al., 2011) (Figure 2c). It can directly measure systolic, diastolic and mean PAPs using a miniaturized wireless electromechanical sensor (Mooney et al., 2015). The PAP sensor is encompassed in a silicon capsule containing an inductor coil and pressure-sensitive capacitor. These form an electrical circuit, and both resonate at a specific frequency. Changes in resonant frequency of the circuit are caused by direct changes in the blood pressure placed on the silicon membrane. Electromagnetic coupling is achieved through an external antenna placed against the patient’s body in order to take sensor readings.

Abdominal aortic aneurysms (AAAs) are caused by weakening of the endothelial aortic walls in the abdomen. Monitoring their pressure levels with an intrasac pressure sensor is possible (Allen, 2005). Since 1990, endovascular aneurysm repair, also known as EVAR, has become the standard procedure that is used to repair AAAs (Ohki et al., 2007; Toya, Fujita, Kanaoka, & Ohki, 2008). The first implantable device to measure aneurysm sac pressure post-EVAR is the ImPressure™ AAA Sac Pressure Sensor (Remon Medical Technologies, Caesarea, Isreal) (Figure 3). The device (3 × 9 × 1.5 mm) is activated through surface acoustic waves from a handheld probe, which charges a capacitor. This operates through a piezoelectric membrane. The sensor then obtains the ambient pressure and transmits the data via ultrasound signal back to the handheld probe. A signal is collected in real time and translated into a pressure curve for interpretation. Another pressure sensor used to improve EVAR outcomes is the stable batteryless EndoSure™ Sensor, also by CardioMEMS Inc. (Ohki et al., 2007). The working mechanisms of this sensor are similar to the CardioMEMS heart failure sensor used to measure PAP. EndoSure sensors are deployed into the aneurysmal sac during stent deployment. The sensor is composed of flexible plates bearing inductor windings within a hermetically sealed reference cavity. They are fused in silica matrix while the nitinol basket encompasses the electronic components of the sensor. Pressure-dependent changes in resonant frequencies are directly proportional to pressure changes within the aneurysmal sac and are detected using an external antenna activated by the sensor over a radio-frequency impulse. This allows one to monitor the intrasac pressure of the aneurysm, which can avoid arterial obstruction and clot formation. Until today, it is the only sensor that is FDA approved for the implantation and confirmation of abdominal aneurysm progression (Springer, Günther, & Schmitz-Rode, 2008).

2.2 Intracranial pressure sensors

The total volume of the skull is constant and is comprised of the brain (80%), cerebrospinal fluid (CSF) (10%) and cerebral blood volume (10%) (Ghannad-Rezaie, Yang, Garton, & Chronis, 2012). The intracranial pressure (ICP) defines the pressure inside the skull deriving from the flow of cerebral blood and CSF. Maintaining adequate ICP is crucial in order to maintain proper blood flow in the brain and to prevent compression of the brain tissues (Ross & Eynon, 2005). Following traumatic brain injuries or central nervous system (CNS) pathology, ICP increases as a result of swelling, haemorrhaging or abnormal resorption of cerebral spinal fluid, possibly leading to brain stem herniation (Flick, Orgelmeister, & Berger, 1997). Persistence of increased ICP may also result in temporary or permanent brain damage as well as long-term coma. If immediate actions are not taken to decrease the ICP, it can ultimately lead to death (Narayan et al., 2002). Studies have shown that an elevated ICP at or above 15–20 mmHg must be diagnosed early and subsequently treated to prevent brain damage (Smith, 2008). Historically, the standard methods used to obtain direct measurements of intracranial pressure were invasive surgical procedures with high rates of infection and associated with complications including intracranial bleed (Mayhall et al., 1984). Of all the available alternatives to the ventricular drain are the optical pressure transducers, (FISO or Integra LifeSciences) (formerly Camino) and the electronic strain gauge systems. This system utilizes a fibre-optic strand with a pressure-sensitive tip, which is inserted into a ventricular catheter or into the parenchyma (Anderson, 2006) (Figure 4b). The pressure read outs are given by the interferometer instrumentation on the patient bedside. These devices are more expensive than external ventricular drains, with drift and temperature effects also being widely reported with such sensors. Another form of implantable strain gauge systems utilizes wireless electronic sensors composed of soft magnetic material with DC magnetic field created by a permanent magnet (Tan et al., 2008). Commercially available strain gauge sensors that are inserted into the brain parenchyma, such as the Codman™ ICP sensor (Synthes, 2013), have a piezoresistive silicon diaphragm attached to titanium probes and a Wheatstone bridge readout circuit. As the pressure modulates the...
diaphragm, it changes the material’s resistive properties, which is then converted to an electrical current proportional to the change in pressure (Fiorillo, Critello, & Pullano, 2018; Suski et al., 2003). The Codman strain sensors have shown minimal drift (avg. 2 mmHg) and fairly accurate representation of the intraventricular ICP (Koskinen & Olivecrona, 2005; Piper, Barnes, Smith, & Dunn, 2001).

There is a need for an innovative system that allows continuous monitoring of ICP for an extended period while taking into account...
patient comfort, mobility or the possibility of infections and other complications such as leakage or blockage. In 1995, an implantable telemetric endo-system (ITES) was developed, making measurements of intracranial pressure through telemetry feasible for the first time. Capacitive pressure sensors that used the complementary metal oxide semiconductor (CMOS) process with surface micromachining steps (Dudaicevs, Kandler, Manoli, Mokwa, & Spiegel, 1994) led to the Sican F&E Company’s fully implantable intracranial pressure measuring device with transcutaneous telemetric interface (Flick et al., 1997; Schlierf et al., 2007). By the year 2000, a telemetrically powered ITES with low power consumption and a novel hybrid integration approach had been developed using a foil carrier to the telemetry unit under the skin (Eggers, Draeger, et al., 2000; Eggers, Marschner, et al., 2000). More recently, Campus Micro Technologies developed a highly miniaturized implantable sensor with ultra-low power consumption that can be powered transcutaneously via a radio-frequency reader (ISO 1443, 13.56 MHz) (Frischholz et al., 2007). It is wireless with zero drift behaviour and has a life span of over 10 years powered by lithium-ion battery (discharge current 10 mA, voltage window 3–4 V). The device is implanted either in the ventricle or brain parenchyma and is intended for long-term monitoring. Further advancement in the field led to the invention of a pressure sensor with a capacitive pressure transducer. The transducer senses the absolute pressure by converting capacitance to frequency-encoded signal using an application-specific integrated circuit (Ginggen, Tardy, Crivelli, Bork, & Renaud, 2008). The sensor (4.5 × 13 mm) has an accuracy of pressure reading across the range of 600–1200 mbar at body temperature and can be powered telemetrically up to 3 cm (Ginggen et al., 2008). As of the time of writing and to the best extent of our knowledge, there are no commercially available, FDA approved, self-contained implantable bio-pressure sensors for monitoring ICP.

Currently, the closest technologies for wireless pressure monitoring are the ones provided by CardioMEMS™ for cardiovascular pressure monitoring. Blood pressure ranges are typically much higher than that of the ICP (Kuck et al., 2014) likely making the technology non-transferable. Present solutions for quantitatively measuring ICP require surgical intervention for the insertion of a sensor within the skull and limits patient mobility through tethered monitoring within a controlled clinical setting (Table 1). Despite some commercially available solutions (Table 2), a clinical need exists for new innovations to tackle the problem at hand.

### 2.3 Intraocular pressure sensors

Glaucoma is an eye disease affecting 65 million individuals globally often leading to irreversible blindness (Bourne et al., 2014). One of the ways in which optic nerve damage occurs is through the increase of pressure within the eye. The intraocular fluid normally circulates in and out of the eye and is maintained at its homeostatic pressure within the range of 10–21 mmHg (Goel, Picciani, Lee, & Bhattacharya, 2010). However, when there is a blockage of the aqueous humour drainage or excess production, the intraocular...
pressure (IOP) increases within the eye. This increased pressure leads to vision deterioration, National Eye Institute (2019). The excess pressure within the eye causes progressive changes in the optic nerve head and retina gradually leading to peripheral and later complete vision loss (Cosset et al., 2016). The tonometer test is currently the technique of choice to indirectly measure IOP. It involves direct measurement of pressure with a device applied to the outside of the eyeball. However, this lacks the ability to provide continuous real-time IOP measurements as the test can only be performed every hour. The earliest passive wireless sensor was developed by Collins (1967), which contained a gas bubble entrapped in a millimetre-sized glass cylindrical container with flexible polyester diaphragms sealing the ends of the container. Several groups have since developed similar IOP sensors (Chen, 2009; Kakaday, Hewitt, Voelcker, Li, & Craig, 2009; Katuri, Asrani, & Ramasubramanian, 2008; Piso, Veiga-Crespo, & Vecino, 2012). Rosengren, Backlund, Sjöstrom, Hok, and Svedbergh (1992) were the first to focus on miniaturization by linking silicon microfabrication technologies with a passive pressure sensor. This resulted in the fabrication of a sensor with overall dimensions of 3 × 3 × 1 mm³ and an in vitro sensitivity of 4 mV/mmHg (Rosengren et al., 1992). In 1996, a MEMS-coiled passive sensor was proposed as a replacement for the bulky hand-wound coils (Van Schuylenbergh & Puers, 1996) to reduce the implant size and improve the long-term use. Electroplating (Puers, Vandevoorde, Bruyker, Puers, & Vandevoorde, 2000), a ferrite core (Baldi, Choi, & Zlai, 2003) and new packaging (Akar, Akın, & Najafi, 2001; Katuri, Ramasubramanian, & Asrani, 2010) were developed to enhance the quality of coils and telemetry efficiency. The biggest challenges for these MEMS implants are the hardness, poor biocompatibility of materials and long-term reliability of the implantable sensors. After the introduction of polymeric materials to MEMS technology, more flexible devices have been developed that are able to be rolled into catheters (Figure 4c) (Fonseca, Allen, Kroh, & White, 2006). Other active IOP-sensing devices have been reported with increased performance in transmission distance (Eggers, Draeger, et al., 2000; Eggers, Marschner, et al., 2000; Mokwa, 2007), power consumption (Chow, Chlebowski, & Irazi, 2010) and data management (Ghaed et al., 2013; Mokwa, 2007). Although these active IOP-sensing devices exhibit better performance, their design and fabrications are more complex, expensive and less reliable.

Device biocompatibility and its long-term use in biological environments need further investigation. It took until 2014 for the first wireless intraocular pressure transducer to be implanted into a human eye (Melki, Todani, & Cherfan, 2014). The authors used a sensor that had previously been implanted into rabbit eyes (Todani et al., 2011). The device ‘is a digital, ultra-miniature device that combines pressure sensor, temperature sensor, identification encoder, analog-to-digital converter and telemetry into a monolithically integrated circuit (MEMS-ASIC).’ The ASIC used for this device is based on metal oxide semiconductor devices. While many sensors have been developed, few have been successfully patented and among them, even less are being commercially pursued. Nonetheless, the technological companies are becoming increasingly aware of the global trend towards sensors and their prevalence in everyday technology use. Some companies such as Launchpoint Technologies are developing sensors that can easily monitor patients at home (Launchpoint Technologies, 2016). SENSIMED Triggerfish has another novel sensor design—a disposable silicone contact lens—displayed in Figure 4d (Sensimed, 2014). An antenna placed around the eye reads information from the lens sensor, with the antenna connecting to a portable recorder by a cable (Figure 4d).

The recorder stores the data, which can then be transferred via Bluetooth to the healthcare professional that is directly monitoring the patients’ intraocular pressure. The SENSIMED sensor was tested by both healthy subjects (De Smedt, Mermod, & Schnyder, 2012) and patients diagnosed with glaucoma (Mansouri, Medeiros, & Weinreb, 2015). Most patients did not experience any discomfort or irritation from the sensor. Implantdata Ophthalmic Products GmbH also developed a permanent implantable IOP sensor, which is placed by the ophthalmologist during surgery. The ring-shaped sensor is made from eight pressure-sensitive capacitors and a circular microcoil antenna covered in silicone rubber. The device permits self-tonometry by using a device that reads the pressure of the eye.

### Table 1: Advantages and disadvantages of currently used ICP monitoring methods (Popovic, Khoo, & Lee, 2009)

| ICP monitoring technology | Advantages | Disadvantages |
|---------------------------|------------|--------------|
| Intraventricular catheter | • Provides overall ICP and is considered the gold standard | • Increased risk of haemorrhage and infection |
|                           | • Can also be utilized to drain CSF, administer drugs | • Most invasive and difficult to insert |
|                           | • Can calibrate in vivo | |
| Micro-transducer sensor   | • Easy insertion | • Drift of transducer over time |
|                           | • Low risk of complications and infection | • Pressure measurement specific to area placement |
|                           | | • No in vivo calibration |
| Epidural catheter         | • Easy to insert | • Not used commonly due to low accuracy |
|                           | • Low risk of infection | |
| Lumbar CSF pressure       | • Can be performed in emergency settings | • Not reflective of true ICP |
|                           | • Extracranial procedure | • Procedure dangerous to perform with elevated ICP |
transmitted by the sensor. Although some patients were reported not to need anti-inflammatory medication to accommodate sensor usage, the company is adapting design size modifications to reduce the risk of inflammation (Koutsonas, Walter, Roessler, & Plange, 2015).

2.4 | Pressure sensor development in orthopaedics

2.4.1 | Spine

Measuring intervertebral pressure allows us to accurately quantify spinal loads, providing deeper insight on our understanding of degenerative disc diseases and back pain as well as how to prevent them (Dreischarf, Shirazi-Adl, Arjmand, Rohlmann, & Schmidt, 2016; Ledet, Sachs, Brunski, Gatto, & Donzelli, 2000). Synthes Inc. (Bettlach, Switzerland) has developed a Vertebral Body Replacement called Synex (DePuySynthes, 2017), which has 6 load sensors measuring intervertebral pressure (Dreischarf, Bergmann, Wilke, & Rohlmann, 2010) (Figure 5a). In a study conducted by Rohlmann, Graichen, Bender, Kayser, and Bergmann (2008), ‘telemeterized vertebral body replacements’ were implanted to follow the intervertebral pressure for 1 month and assess what positions caused the most strain. Ledet et al. (2000) have also used strain gauges to measure intervertebral disc pressures in the spine of baboons through an implanted box affixed with eight strain gauges. These sensors have significant limitations due to the size of the needle needed for introduction as the current size can damage disc fibres (Al-Fakhir, Abu Osman, & Mahamd Adikan, 2012; Ledet et al., 2012). Fibre Bragg grating sensors (FBGs) are made of silicate, a glass–ceramic material, making it biocompatible. Given the various shape and size, FBGs may potentially be less damaging to the spine and have the advantage of being placed between intimately positioned discs (Al-Fakhir et al., 2012; Dennison, Wild, Wilson, & Cripton, 2008) (Figure 5b). Spinal fusions could also be monitored via MEMS technology designed with ‘two parallel plates forming a narrow gap and a conjoint end’ (Lin et al., 2007; O’Connor & Kiourtì, 2017). Intellirod-Spine™ (2017) has come up with the ACCUVISTA Postoperative Rod Strain Sensor that can detect the strain on a spinal fusion rod, but has yet to receive FDA approval.

2.4.2 | Joint pressure

Balancing tension in the surrounding soft tissue during various orthopaedic procedures like total knee arthroplasty, hip replacement surgeries, anterior cruciate ligament repair and shoulder stabilization is important for high reproducibility, soft tissue healing and musculoskeletal function restoration. Pressure sensors could provide a constant feedback to the orthopaedic surgeons and detect potential issues about soft tissues and the implant before a problem arises (Mouzakis, Dimogianopoulos, & Giannikas, 2009; O’Connor & Kiourtì, 2017; Rowlands, Duck, & Cunningham, 2008). Total knee arthroplasty is challenging in recreating the knee’s form and function (D’Lima, Fregly, Patil, Steklov, & Colwell, 2012), and thus it is crucial to understand the kinematics of knee motion as well as assess the healing of soft and hard tissues around arthroplasties. D’Lima et al. (2012) evaluated the tibial forces of patients after having undergone a total knee arthroplasty by building a prosthesis with a sensor that could measure pressures applied to the prosthesis. These sensors consist of an induction coil, a micro transmitter and antenna (D’Lima, Steklov, Fregly, Banks, & Colwell, 2008). The measurements allowed investigation of knee movements thought likely to cause premature wear for the prosthetic due to altered pressure distributions in the knee (D’Lima et al., 2008, 2012; Ledet et al., 2012). At the same time, Heinlein et al. (2009) used the INNEX FIXUC (Figure 5c) by Zimmer GmbH to detect pressure causing implant deformation, through six semiconductor strain gauges operated with an external magnetic field. MicroStrain Inc. has a strain sensor (Tan et al., 2008) for knee arthroplasty that can wirelessly transmit multi-axis torque and force information.
They have developed a second-generation implant that advances the capabilities of the first smart knee implant in 2004 that measured only knee compressive forces. The new implant potentially monitors bending, compressive and shearing loads across the human knee. This device has yet to make it out of the laboratory. Measurements of contact forces and moments on the glenohumeral joint with sensors may be important indicators to help with physiotherapy following a shoulder operation (O’Connor & Kiourti, 2017) as well as an effective method to determine a gold standard (Westerhoff, Graichen, Bender, Rohlmann, & Bergmann, 2009).

Graichen, Arnold, Rohlmann, and Bergmann (2007) have developed a chip placed on a titanium implant that can record pressure and temperature and transmit the data to a database outside the body. Another sensor, influenced by the Bio-Modular Shoulder System, focuses on collecting contact forces and moments on the glenohumeral joint (Bedoya-Serrano, 2017; Westerhoff et al., 2009). The limits of these devices mostly concern the power supply. Because of the inductive mode of powering, the sensors tend to be less effective than a direct source of power. The distance between the device and the monitor to enable recording the measurements is also limited to half a metre (Bedoya-Serrano, 2017). In addition to their high cost, the biocompatibility of these sensors in the long-term remains highly questionable (Healio, 2008).

2.4.3 | Intra-compartmental pressure

Anatomically, the muscles in human limbs are divided into compartments formed by unyielding fascial membranes (Elliott & Johnstone, 2003). Compartment syndrome (CS) is the process that occurs when increased pressure in a compartment compromises the circulation and function of the tissues (Perron, Brady, & Keats, 2001). If left untreated for only a few hours, CS can lead to tissue necrosis, severe intractable pain, paralysis, sensory deficits, long-term disability or even death. Clinical evaluations are seriously limited, and the findings may generally be inconsistent or even impossible to gather. Three conventional methods exist for measuring intra-compartmental pressure (ICP): a handheld manometer (Stryker Pressure Monitor Instrument), a simple manometric IV pump and the wick or slit catheter technique (Whiteside technique). However, these methods must be repeated over a short timeframe as they only provide static measurements of pressure. Although the Stryker device seems to be a compact handheld instrument (Figure 5d), any advantages of its portability over the other methods are negated by its inaccuracy (Large, Agel, Holtzman, Benirschke, & Krieg, 2015) and it has been pulled from the market. Recently, a pressure sensor based on MEMS technology has been developed (Merdassi, Allan, Harvey, & Chodavarapu, 2017) (MY01™ from NXTSens Inc). This implantable prototype measures 2 × 3 mm and consists of a capacitive pressure sensor, a readout, an antenna and radio-frequency identification (RFID) to transfer the data. Although the readings are more accurate than the Stryker device, the major advantage of this new sensor is the ability to continuously monitor intra-compartmental pressure without the need for repeated needle sticks.

2.5 | Bladder pressure sensors

Urinary incontinence (UI)—the loss of bladder control—is a common and undertreated affliction associated with significant reduced quality of life (Coyne et al., 2008), morbidity (perineal infections from moisture and irritation, falls in the elderly and fractures) (Brown et al., 2000) and sexual dysfunction (Cohen, Barboglio, & Gousse, 2008). Diagnosis relies heavily on urodynamic studies, from which cystometry (measurement of intravesical bladder pressure) is the cornerstone in the evaluation of UI (Bradley, Smith, & Kreder, 2008). Currently, catheters are inserted through the urethra and rectum (or vaginal) while the bladder is forced filled with saline. This method is evidently invasive, uncomfortable, and needs to be performed by a physician. It also relies on subjective questionnaires (Avery et al., 2004). Other techniques include ultrasonic-based Novioscan, Care (2019), DFree (2019) or near-infrared spectroscopy (systems) to quantify bladder volume. However, bladder volume measurement only provides limited data and cannot provide a definitive picture of bladder urodynamics, whereas bladder

![Figure 5](image-url)
pressure is widely accepted as the most reliable indicator of bladder function (Artibani, 1997). Novel diagnostic procedures using wireless, catheter-free, implantable bladder sensors capable of transferring data to an external receiver have been recently developed to allow continuous pressure measurement (Table 3). Currently, CardioMEMS is the only commercially available implantable pressure sensor that has not yet been tested on bladder.

There are two categories of sensors: free-floating and submucosal devices. A free-floating device is capable of being inserted during a minimally invasive procedure such as during cystoscopy, thereby providing immense potential for ambulatory diagnostic procedures or for chronic implants. The major drawback of intravesical devices is the poor retention rate, with the vast majority of devices being expelled within 1 month during voiding (Majerus et al., 2016, 2017). To prevent expulsion, Wille, Tenholte, and Engelmann (2013), Wille et al. (2014) developed a C-shaped sensor with a handheld device capable of registering voiding desire and micturition coupled with an alarm pad device detecting any urine loss. Others have added an expandable balloon to prevent expulsion (Siwapornsaithain, Lal, & Binard, 2002; Wang et al., 2008). The lifesaving sensor for full bladders (Figure 6) is the smallest piezoresistive single-crystal silicon MEMS (820 × 1820 μm; final diameter of 1.2 mm after packaging) for bladder pressure sensing (Clausen, Moe, Tvedt, Vogl, & Wang, 2011; SINTEF), with a thin and biocompatible packaging (20 nm-thick TiO₂) demonstrating minimal shift when soaked for 30 days in human bodily fluid (Clausen, Tvedt, Moe, & Vogl, 2013).

This device is currently wired to an external electronic Sensor Data Logger (SDL), also providing microSD storage card and power supply. Studies are focusing on wireless recharge and on minimally invasive percutaneous suprapubic injection. Preliminary results demonstrated technical safety and sensitivity compared with others (Clausen, W. Tvedt, & Glott, 2018), with functionality and feasibility after 17 hr duration (Clausen, Tvedt, Hellandsvik, Rognlien, & Glott, 2017). To prevent misalignment that occurs with batteryless sensors (Lee & Choi, 2015, 2016), a bladder pill sensor measuring 5 × 30 mm (Soebadi et al., 2016), made of a commercial ferrite rod and a custom magnetic snap-on tool, has been developed (Bakula, Soebadi, De Ridder, & Puers, 2016) and now miniaturized (Soebadi et al., 2017). New devices are being introduced in pre-clinical models and look promising. An approach using a piezoelectric cantilever made of lead zirconate titanate (PZT) with a working frequency of 350 Hz acts as an acoustic receiver that converts sound vibration into electrical power to charge a capacitor. The stored charge eradicates misalignment issues encountered with inductive powering (Kim, Powell, & Ziaie, 2014) (Figure 7). The feasibility, deep penetration, depth of acoustic vibrations, adequate pressure measurement and absence of loss of sensitivity caused by misalignment were confirmed in a pig’s bladder (Kim et al., 2014).

Intravesical implants have been associated with health issues such as stone formation, infection and haematuria (Tyagi, Kashyap, Hensley, & Yoshimura, 2016). These can be overcome with packaging by completely isolating the pressure sensor, or by encasing the sensor in a silicone-filled medical-grade polyurethane balloon (Kim, Powell, & Ziaie, 2016).

Submucosal devices have been proposed to reduce baseline drift by implanting sensors in the bladder wall beneath the mucosal layer, thereby preventing any contact with the urine. In addition to its invasive abdominal approach, submucosal pressure sensors are usually associated with a significant damping effect on pressure measurements (correlation coefficient 0.89) compared with free-floating intravesical devices (correlation coefficient 0.95) (Majerus, Garverick, Suster, Fletter, & Damaser, 2012; Melgaard & Rijkhoff, 2011; Roth et al., 2016). Ambulation was a major contributor of artefacts (Majerus et al., 2012; Makovey et al., 2015; Takayama, Takei, Soejima, & Kumazawa, 1987), partially explained by the biomechanics of the relatively thick muscular layer of the bladder impeding on pressure measurement. Previously published examples are the wireless implantable micro-manometer (WIMM) (Figure 8) (18 × 7 × 4 mm) and a lens-shaped sensor (13.6 × 2 mm) developed by Melgaard and Rijkhoff (2011).

The latter consists of a wired piezoresistive MEMS pressure sensor which demonstrated reliable detection of the onset of bladder contraction in vivo. However, any deviation of the sensing membrane from the bladder lumen caused unreliable signals in anaesthetized animals, thus bladder wall biomechanics are likely to prevent reliable measurements. UP-Link is also an ultra-low power wireless manometer device (5 mm × 3cm) (Kim et al., 2016; Roth et al., 2016), exhibiting considerable improvement in power management by measuring pressure only intermittently (Lee, Kim, Ziaie, Raghunathan, & Powell, 2014). The major threat to submucosal implantation is erosion of the detrusor, with animal studies revealing expulsion of sensors within 1 month of implantation (Basu et al., 2018; Majerus et al., 2016, 2017). To prevent erosion through the bladder wall, a catheter-lead pressure sensor tethered through the detrusor has been proposed. Gaeltec pressure transducers (model 1 CT/b) have broken due to movement after 64-day implantation without erosion of the detrusor (Takayama et al., 1987). Initially developed for blood pressure monitoring, a commercially available transmitter using radiotelemetry technology from Data Science International, 2019 (strain gauge sensor, PhysioTel PA-C40) (International) demonstrates exceptionally low signal drift (<2 mmHg per month) (Potkay, 2008) and high-quality recordings comparable to conventional cystometry, even if implanted within the bladder dome. There was no associated erosion (Guiol, Ledoussal, & Surge, 1992; Monjotin et al., 2017). Recently, despite a short measurement period, a fully implantable wireless pressure sensing catheter-lead demonstrated physiological data without bladder wall erosion or inflammation (Tan et al., 2009).

3 | CHALLENGES AND OUTLOOK

There are a number of common limitations that must be addressed when examining the usage of sensors placed within the human body. Such limitations include sensor drift (which occurs...
| Sensor technology                                      | Size                      | Sleep mode | Power   | Lifespan | Wireless telemetry | References                                      |
|--------------------------------------------------------|---------------------------|------------|---------|----------|-------------------|-------------------------------------------------|
| Piezoresistive MEMS (Bosch BMP180)                     | 45 × 5.5 mm C-shaped      | Free-floating | Battery | 1–3 days | Yes               | Wille et al. (2014), Wille et al. (2013)         |
| Piezoresistive MEMS                                     | 2 × 2 mm + balloon        | Free-floating | Battery | 115 hr   | Yes               | Siwapornsathain, Lal, and Binard (2002)          |
| Piezoresistive MEMS                                     | 25 mm diameter            | Free-floating | Battery | 14 days  | Yes               | Wang et al. (2008)                              |
| Piezoresistive pressure (MEMS) from SINTEF              | 1.2 mm diameter           | Free-floating | Wired   | 17 hr    | No                | Clausen et al. (2011), SINTEF                    |
| Capacitive pressure sensor                              | 9 × 7 × 15 mm             | Free-floating | Inductive | N/A     | Yes               | Lee and Choi (2016)                             |
| Piezoresistive pressure (MEMS; Bladder Pill)           | 5 × 15−30 mm              | Free-floating | Inductive | N/A     | Yes               | Bakula et al. (2016)                            |
| Single capacitive absolute pressure                    | 17.6 × 6.8 × 3.4 mm       | Free-floating | Inductive | N/A     | Yes               | Coosemans and Puers (2005)                      |
| Inductive or capacitive                                | 8 × 40 mm                 | Free-floating | Mechanical vibrations | N/A | Yes               | Kim et al. (2014)                               |
| UP-Link (piezoresistive MEMS)                           | 5 mm × 3 cm               | Submucosal  | Battery | 2–13 years | Yes               | Lee et al. (2014) and Roth et al. (2016)         |
| WIMM (piezoresistive MEMS)                              | 18 × 7 × 4 mm             | Submucosal  | RF      | 24 hr with 4 hr recharge | Yes | Basu et al. (2018); Majerus, Fletter, Zhu, and Damaser (2015) |
| Piezoresistive MEMS                                     | 13.6 × 2 mm               | Submucosal  | Wired   | 2–3 weeks | No                | Melgaard and Rijkhoff (2011)                     |
| Radiotelemetry (strain-gauge sensor; DSI PhysioTel® PA-C40) | (with transmitter secured to abdominal wall) | Yes | Battery | 4 months | Yes | Monjotin et al. (2017) |
| Piezoresistive (MEMS)                                   | N/A Submucosal (with transmitter secured to abdominal wall) | N/A | Battery | 4 days | Yes | Tan et al. (2009) |
| Gaeltec pressure transducer (Model 1 CT/b)              | N/A Submucosal (with transmitter secured to abdominal wall) | No | Battery | <1 month | No | Takayama, Kawai, Kanesaki, Date, and Fukada (1987) |
| LM pressure sensor                                     | 11.5 × 17 × 8 mm          | Submucosal  | Battery | 12–24 hr | Yes               | Weaver, Alspaugh, & Behkam (2010)                |
when monitoring over an extended period of time), power consumption, heat emission within surrounding tissue and the associated risk of tissue damage, dislocation of the device, on device clotting or blood coagulation, biocompatibility, biodegradability, the mechanical lifespan of the sensor within a physiological environment and the most problematic issue at hand—the invasive approach of delivering and removing dislodged pressure sensors within delicate tissues. Another issue of significant importance is sterilization procedures, which must be performed prior to any in vivo applications.

A significant study conducted by Ferrara, Fleischman, Dunning, Zorman, and Roy (2007) tackled the issue of implantable sensor sterilization and the potential effects on device performance. It was found that the use of steam and gamma radiation sterilization, an already established and leading method of sterilization, had negligible effects on sensor performance (Ferrara et al., 2007). Drift remains one of the major challenges of a reliable sensor applied for long-term monitoring. Different strategies are emerging to minimize offset and sensitivity drifts. To reduce the impact of the adsorption of biological substances to the membrane and minimize drift, researchers are focusing on designing membranes with a greater mechanical stiffness than the potential attached biofilm. Nevertheless, this might in turn decrease the sensor sensitivity. Other strategies involve the use of a biomaterial nano-layer to prevent cell growth (Frischholz et al., 2007) or to contain the sensor in a structure filled with silicone oil or other uncompressible liquid (Flick & Orglmeister, 2000). The design of a robust biocompatible packaging for a pressure sensor that can resist the human environment is very challenging. Several typical MEMS materials have been studied, and their poor biocompatibility has been reported (Kotzar et al., 2002). However, other biocompatible material packaging like titanium and its alloys, noble metals, stainless steels and others can be successfully implanted with a hermetic package to avoid moisture ingress.

The power consumption for the pressure sensor to operate, in addition to the radiating power losses, should both be minimal. Currently, implantable batteries or radio-frequency (RF) links are used depending on the medical application, size and lifetime. Researchers envisage to power the pressure sensors from the heat of the human body (Bogue, 2009) or other in situ energy sources such as biofuel cells (Habrioux et al., 2008; Merle et al., 2009). Other design challenges lie in data transfer/collection. The largest majority of the pressure sensors are composed of an implantable component, and one or more external components for controlling and/or collecting the data from the implanted part. Indeed, having a wire attached to an implant could have repercussions on daily activities. Nevertheless, the wireless option is strongly dependent of the implant size, its location and the data rate (Boutry et al., 2012). As seen in the rest of this review, these methods vary from inductive coupling, wireless antennas or ultrasound communication (Clausen & Glott, 2014; O’Connor & Kiourt, 2017). As with any foreign object placed in the human body, implantable devices pose the risk of colonization and infection. Device colonization, sepsis and death as a result of infection are an increasing risk as continuous monitoring becomes an optimal method in obtaining necessary pressure measurements. Some researchers are looking into sensors that could detect the corrosion or degradation of the materials. To diagnose implant failures, Mouzakis et al. (2009) have developed a sensor with a coil that uses an electromagnetic pulse, which may be able to determine implant breakdown.

Researchers are looking at developing biodegradable pressure sensors in order to avoid invasive surgical removal, which could damage directly interfaced tissues. Most pressure sensors use the piezoelectric material lead zirconate titanate (PZT) due to its excellent electromechanical coupling (Nain, Rathore, & Sharma, 2018). However, PZT is brittle and highly cytotoxic given its lead component. On the other hand, the piezoelectric material polyvinylidene difluoride (PVDF) has been shown as a lead-free alternative...
providing good biocompatibility while also being light, flexible, cheap and low acoustic impedance (Fiorillo, Pullano, & Critello, 2019; Nain et al., 2018; Zang et al., 2015). With the emergence of transient electronic technology and implants (Boutry et al., 2012), conventional biodegradable polymers, biodegradable metals and biodegradable conductive polymer composites have made a fast development (Li, Wang, Kong, & Yin, 2018). Biodegradable metals include Mg, Fe (and their alloys), which are used for electrical circuits (Boutry et al., 2013; Hänzi, Gerber, Schinhammer, Löffler, & Uggowitzer, 2010). Traditional biodegradable polymers include poly(l-lactide) (PLLA) and polycaprolactone (PCL). They can be used as substrate or packaging material (Middleton & Tipton, 2000). To the best of our knowledge, there are no fully biodegradable conductive polymers available. Usually, the so-called ‘biodegradable conductive polymer’ is a mixture of PLLA or PCL with polypyrrole (PPy) nanoparticles (Boutry, Sun, Strunz, Chandrahalim, & Hierold, 2010). In 2014, the first biodegradable pressure sensor was reported by Luo, Martinez, Song, Herrault, and Allen (2014). The sensor was made of zinc/iron bilayers with PLA and PCL as dielectric and structural materials. However, the very simple design of this biodegradable RF wireless LC resonant pressure sensor dictated a poor sensitivity at low-pressure ranges (below 10 kPa). Boutry et al. (2015) fabricated a fully biodegradable and flexible pressure sensor array for cardiovascular monitoring from microstructured poly(glycerol sebacate) (PGS) films. The device had a high sensitivity in the low-pressure regime in combination with its fast response time. A biodegradable piezoelectric force sensor using FDA-approved piezoelectric PLLA was recently developed and tested by researchers (Curry et al., 2018) (Figure 9). The sensor was made with 5 × 5 mm² of PLLA film with molybdenum electrodes, encapsulated by polylactic acid (PLA) layers and sealed with biodegradable PLLA glue. With a total thickness of 200 µm and ability to sense a wide range of force from 0 to 18 kPa, the envisioned sensor allows for flexibility and is beneficial for measuring a variety of biophysiological forces, such as diaphragmatic contraction pressures as well as other intraorgan pressures (Curry et al., 2018).

The study showed decreased levels of inflammatory responders by 4 weeks; however, further testing and observation are needed to optimize biocompatibility. Most recently, a biodegradable silicon electronic sensor has been designed and tested for its efficacy in predicting intracranial pressures in rat models (Kang et al., 2016). The sensor was successful in measuring relevant intracranial pressures ranging from 0 to 70 mm Hg, and the materials were shown to naturally resorb through hydrolysis (Irimia-Vlada, 2014). In one model, a completely bioresorbable pressure sensor with degradable wires and wireless transmitter showed long-range data transmission (10 m). Additionally, they implanted a partially resorbable near-field communication (NFC) system composed of a magnesium inductive coil, silicon nanomembrane, NFC microchip and poly(lactic-co-glycolic acid) (PLGA) encapsulation. Although the sensor was placed extracranially under the scalp, the researchers successfully showed transient increases in intracranial pressure. The sensor was completely implanted without any protruding wires, eliminating any further complications of skin-based infections during intracranial pressure monitoring. Finally, a fully biodegradable and stretchable strain and pressure sensor have been developed, which can monitor in real time the mechanical forces on tendons after surgical repair (Boutry et al., 2018) (Figure 10). The sensor was made of stretchable and biodegradable elastomers on which magnesium was evaporated and can also be evacuated via natural tracks. The sensor exhibited excellent biocompatibility and functionality in a rat model, opening the concept of this new technology to real-time monitoring of tendon healing.
Pressure is among the most interesting physiological parameters to monitor when assessing the state of organs or biological systems in the body. Being aware that pressure measurement procedures are routinely used in clinical practice and understanding the issues of current monitoring systems and how they fail is critical to address the remaining challenges. This review not only highlights the pressure sensors that are widely used in clinical practice but also describes the progress made on implantable pressure sensors. Depending on the biological environment, the sensor design must cautiously take into account certain factors such as interactions between the implanted sensor and the body (biocompatibility), surgical placement and patient comfort. Engineering performances such as continuous monitoring, drift and telemetry are also pertinent issues that must be addressed when designing a sensor. Although the rapidly developing MEMS field has overcome some challenges of biocompatibility and size constraints (while also offering long-term monitoring), the current level of performance and invasiveness of pressure sensors are for the most part still below requirements for practical applications. Further work is required to properly assess and improve long-term monitoring performance with new strategies focusing on telemetry and drift management.

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