Surgical Neurology International

SNI: Neurosurgical Developments on the Horizon, a supplement to SNI

OPEN ACCESS

For entire Editorial Board visit : http://www.surgicalneurologyint.com

Editor: Michel Kliot, MD UCSF Medical Center San Francisco, CA 94143

New and improved ways to treat hydrocephalus: Pursuit of a smart shunt

Barry R. Lutz[1], Pranav Venkataraman[1], Samuel R. Browd[2,3]

Departments of [1]Bioengineering, [2]Neurological Surgery, University of Washington, [3]Division of Pediatric Neurosurgery, Seattle Children's Hospital, Seattle, WA, United States

E-mail: *Barry R. Lutz - blutz@uw.edu; Pranav Venkataraman - pranav@uw.edu; *Samuel R. Browd - sbrowd@gmail.com
*Corresponding authors

Received: 18 September 12 Accepted: 08 November 2012 Published: 19 March 13

This article may be cited as:
Lutz BR, Venkataraman P, Browd SR. New and improved ways to treat hydrocephalus: Pursuit of a smart shunt. Surg Neurol Int 2013;4:S38-50.
Available FREE in open access from: http://www.surgicalneurologyint.com/text.asp?2013/4/2/38/109197

Abstract

The most common treatment for hydrocephalus is placement of a cerebrospinal fluid shunt to supplement or replace lost drainage capacity. Shunts are life-saving devices but are notorious for high failure rates, difficulty of diagnosing failure, and limited control options. Shunt designs have changed little since their introduction in 1950s, and the few changes introduced have had little to no impact on these long-standing problems. For decades, the community has envisioned a "smart shunt" that could provide advanced control, diagnostics, and communication based on implanted sensors, feedback control, and telemetry. The most emphasized contribution of smart shunts is the potential for advanced control algorithms, such as weaning from shunt dependency and personalized control. With sensor-based control comes the opportunity to provide data to the physician on patient condition and shunt function, perhaps even by a smart phone. An often ignored but highly valuable contribution would be designs that correct the high failure rates of existing shunts. Despite the long history and increasing development activity in the past decade, patients are yet to see a commercialized smart shunt. Most smart shunt development focuses on concepts or on isolated technical features, but successful smart shunt designs will be a balance between technical feasibility, economic viability, and acceptable regulatory risk. Here, we present the status of this effort and a framework for understanding the challenges and opportunities that will guide introduction of smart shunts into patient care.

Key Words: Hydrocephalus, shunt, smart shunt, technology

Access this article online

Website: www.surgicalneurologyint.com

DOI: 10.4103/2152-7806.109197

Quick Response Code:

INTRODUCTION

As we approach the 60th anniversary of the first implantable shunt valve, it is instructive to look back and appreciate the advances in technology that have occurred over this time frame all the while realizing significant challenges remain. The concept of diverting cerebral spinal fluid (CSF) from the ventricles to another body location was revolutionary and simplistic in concept and design, but we have learned over the past 60 years that what appeared to be a simple problem is in fact much more challenging.[9] Despite significant advances in technology, hydrocephalus shunting remains fraught with complications leading to an unacceptably high morbidity rate that has not changed appreciably in years. Current technology remains relatively rudimentary with advances coming along every few years

as companies battle to retain market share. Despite these short-comings, several major advances have occurred including the introduction of antisiphoning devices and programmable valves; unfortunately, these technologies have not upheld the promise of reduced complication and failure rates, which remain as high as 40% within the first 1-2 years. As we have advanced from slit valves to differential pressure and antisiphon devices, it has become clear that improved controlling mechanisms are needed to mimic the normal physiologic state.

As early as the 1980s, a robust discussion was happening in the literature regarding improved control of CSF diversion. It has been well known for decades that shunting the cerebral ventricles can lead to complications including over-drainage headaches, subdural hematomas, and slit ventricles syndrome, as well as shunt failure and infection. Even with the introduction of next-generation valves these issues have largely gone without improvement. Additionally, our ability to diagnose shunt malfunction and triage patient symptoms has remained rudimentary at best. Currently available valves provide no feedback regarding patient intracranial pressure (ICP) and provide no self-diagnostic capabilities. Shunt failure remains a clinical diagnosis based on patient symptoms and interpretation of imaging studies. There is increasing recognition of the need for improved devices to treat hydrocephalus. Supportive of these needs is a vocal group of patient advocates demanding improved technology and a healthcare system that increasingly recognizes the enormous costs associated with repeated device failures.

Our collective desire: The "smart" shunt

The desire for a smart shunt, and the common vision for the functions it could perform, is not surprising or new. One would like a device capable of measuring conditions such as ICP or CSF drainage rate and adjusting the CSF drainage through the shunt based on this information. In contrast to mechanical valves, the control algorithms could be arbitrarily sophisticated, which could overcome known deficiencies of mechanical valves (e.g., overdrainage) and allow application of theories for improved CSF management (e.g., weaning from shunt dependence, circadian adjustments, adaptation to patient growth, personalized control). With sensor-based control comes the ability to query the device for data on patient response and shunt function, and some envision transmission of data real-time to the healthcare system, perhaps even with a cell phone. A smart shunt also offers new options to design shunts for reduced failure rates or to reduce the impact if failure does occur. Material modifications have great potential to reduce fouling and obstruction,[31] but one could envision self-cleaning smart shunts or early warning systems that detect impending shunt failure to mitigate risks of unpredictable failure.

Short of a cure, a smart shunt would be one of the most exciting and impactful developments in the treatment of hydrocephalus. But the desire is decades old, and patients are yet to see even a modest version of a smart shunt. Why? To understand this question, it is valuable to review the current state of shunt technology and its failure points, the concept of a smart shunt, technical progress on smart shunt development, and the risk-benefit spectrum that must be considered to bring viable new technology through the regulatory and reimbursement process and into the patient care arena.

Current technology and failure points

The shunt of 50 years ago remains relatively unchanged except for a few advances.[9] A shunt typically has three parts: a ventricular catheter, a valve, and distal tubing. Current devices are available as separate components or unitized. Ventricular catheters have little science to their design and the holes sizes, typically 500 microns, were arbitrarily chosen since they were found to be manufacturable at that size.[30] A few new catheter designs are being discussed in the literature and one new catheter has made it to the market, but there is no data to support improved function.[31] A variety of valves are on the market, largely from four manufacturers who dominate the space, namely Medtronic, Codman, Aesculap, and Integra LifeSciences. These valves come configured as differential pressure valves, siphon-resistant valves, flow-regulating valves, and externally adjustable valves. Distal tubing is also quite unremarkable and typically is marketed as an open silicone tube between 90 and 120 cm in length. While beyond the scope of this paper, several excellent review articles[7,8,22,68] and chapters[6] cover the state of shunt technology; specifically, we refer the reader to *The Shunt Book* by Drake *et al*.[24]

Failure points and rates are also well documented throughout the literature. It is generally estimated that 40% of shunts fail within 2 years and 98% have failed within 10 years.[16,17,40,42-45,63,65,68] Modes of failure include obstruction along any segment, disconnection or migration of tubing, component fractures, and functional modes of failure such as overdrainage, extra-axial fluid collection/hemorrhage, and slit ventricle syndrome. Obstruction is responsible for the majority of failures; about 60% of obstructions occur at the proximal catheter, 30% at the valve itself, and the remainder are due to failure at the distal tubing segment.[6,16,17,20,21,23,41] Unfortunately, few factors, including the type of device and surgeon/hospital experience, currently reduce the rates or mode of failure. A smart shunt conceptually would be able to address various points of failure by design and control improvements.

The smart shunt concept

In the broadest sense, a smart shunt may be defined as an implantable system (including hardware and

algorithms) designed to control CSF drainage based on feedback from one or more measured conditions. Nearly all envisioned smart shunts share a common framework and common set of core components [Figure 1]: one or more sensors (e.g., ICP, CSF flowrate, patient position); a fluid control mechanism (pump or valve); an actuator to move the pump or valve; a housing to isolate electrical components from the body; a power source (battery with or without recharging); and communications (to change device settings and retrieve sensor data). The basic device framework in Figure 1 can in principle enable all of the desirable functions noted above, but there are many variations on the approach.

Smart shunt components

Many components needed to construct a smart shunt exist in isolated forms. Table 1 summarizes core components, examples, and key considerations. Detailed commentary is beyond the scope of this review, but we provide brief comments here.

Sensors

The low pressures (ICP ~10 cm H_2O) and low flowrates (CSF production ~0.3 ml/min) of the CSF system are at the edge of existing sensor technologies;[39] pressure and flow sensor development remains a key challenge. Accelerometers are often proposed to correct for siphoning conditions.[35,37,48] The Linninger group at the University of Illinois is developing a novel ventricular volume sensor based on the difference in electrical impedance between CSF and brain tissue.[11,12,50,51] For all sensors, challenges include isolation from moisture, inability to recalibrate after implantation, and power draw.

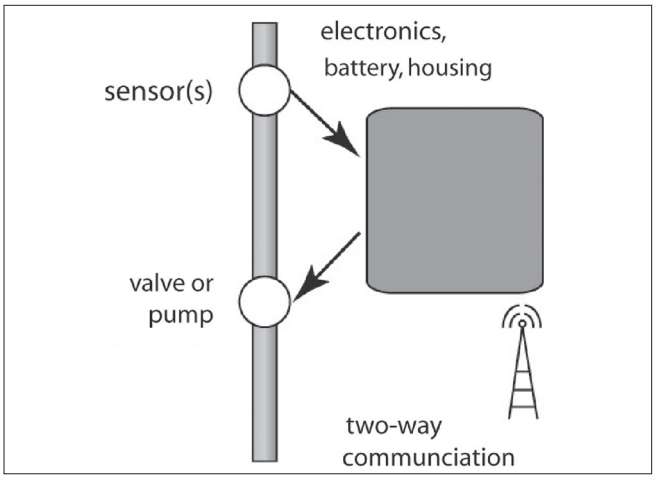

Figure 1: Conceptual framework for a smart shunt. Nearly all smart shunt concepts aim to control CSF drainage based on measurements from implanted sensors (e.g., ICP, CSF flowrate, patient orientation) using a pump or a valve. All smart shunts require a power source (battery with possibility of periodic recharging), and they include implanted electronics (with software). Nearly all smart shunt concepts aim to provide data and allow adjustment or reprogramming of the device

Fluid control mechanism

CSF can be controlled by (1) pumps, (2) on-off valves, or (3) variable resistance valves. Pumps and on-off valves require frequent activation to drain fluid, while variable-resistance valves can drain passively until adjustments are needed. In addition, designs that resist fouling through material selection or fluidic design are highly desirable.

Actuator

Pumps and valves both require some means to generate physical movement. Key considerations are power draw, magnetic resonance imaging (MRI) compatibility (magnets in motors and solenoids), and available force. Smart shunt actuator options have been reviewed.[71]

Power source

Devices may operate on battery power or may be supplemented by periodic recharging (e.g., inductive coupling, but MRI may be problematic). Pacemaker batteries can be replaced on a schedule (roughly 5-8 years), and a similar model may be appropriate for shunts. Battery size impacts viable locations for

Table 1: Core smart shunt components

Component	Example methods	Key considerations and challenges
Sensors	Pressure (ICP), CSF flow rate, ventricle volume	Accuracy for low pressures and flow rates of the CSF system, power draw, MRI compatibility
Fluid control mechanism	Pump, on-off valve, variable-resistance valve	Frequency of activation required (power), avoidance of materials and designs that increase fouling, MRI compatibility
Actuator	Motor, electromagnet, piezoelectric	Power consumption, MRI compatibility
Power source	Battery with or without recharging	Need for long battery life (years) or infrequent recharging; methods have been established in existing implants, but power consumption in smart shunt design is a key challenge
Communications	Radio-frequency (RF), wireless (e.g., bluetooth)	Established methods for two-way communication in existing implants
Housing	Hermetic isolation, bio-compatible components	Established methods for electrical implants, but smart shunts have unique requirements (e.g. sensing and control must interact with a fluid system, need for atmospheric pressure reference)

ICP: Intracranial pressure, CSF: Cerebral spinal fluid, MRI: Magnetic resonance imaging

device placement (on head versus other location). Energy scavenging systems are emerging (mechanical, electromagnetic waves), but available power may be insufficient.

Communications

Communication can include data transmission and commands to manipulate the device. Two-way communication exists in implanted devices (e.g., drug pumps), so this is seen as low risk. External readers/controllers could eventually be operated by the patient (even a smart phone).[58]

Housing

Implantable electrical devices require isolation of electronics from moisture.[38] Smart shunts have the additional challenge that they must interact with a fluid system. Biehl and Scholz[14] elegantly described concepts for hermetic sealing in smart shunts: (1) a flexible hermetic wall; (2) biocompatible actuators; and (3) contactless force transmission (e.g., magnetic force across the housing). Similar issues exist for sensors. Sealing requirements for electrical implants are extreme, and this remains a key challenge for smart shunts.

Activity in smart shunt development

Smart shunt development includes activity from major companies, large academic programs, and individual research groups. Components range from adaptations of existing implanted devices (mechanical valves, drug pumps) to novel valves microfabricated in silicon chips, and proposed control approaches range from preprogrammed drainage schedules to arbitrarily complex feedback control. A complete technical review is beyond the scope of this paper, but we briefly summarize examples of activity from published literature and patents.

As early as 1980, Rekate published rationale for a closed-loop control of CSF drainage[64] and by 1988, Rekate and colleagues published a remarkably complete proposal for a smart shunt design.[46] The description covered key aspects of CSF regulation based on flow control with safety overrides, two-way communications, physician's role in adjustments, hardware and electrical designs, device size and implant location, and device packaging. Two platform concepts were described: (1) on-demand sensor measurement and valve adjustment using an external system for communications and power transmission, and (2) a battery-powered system with flow and orientation sensors, on-demand download of historical data, physician–shunt communication via a modem, and physician-controlled adjustment. Unfortunately, the system was not realized, likely because of technology limitations at the time and nontechnical challenges (regulatory, financial) that persist today. It remains one of the most comprehensive and complete designs reported, and the motivations that drove its development are echoed in current work.

In 1995, Cote *et al*. published a detailed control algorithm in which the drainage set point was varied with ICP to maintain constant flow, and a tolerance zone (10% of set point) and a time delay were introduced to reduce power draw due to unneeded valve activity.[19] The algorithm was tested in computer simulations; and the on-off valve, pressure sensor, and algorithm were tested in bench models of communicating and noncommunicating hydrocephalus including cardiac cycle. Within the past decade, Aschoff and colleagues presented smart shunt concepts (iValve and DigiShunt) that apparently included sensors, accelerometers, data storage, and telemetry; however, we were unable to locate accessible publications.

Patent literature shows recent activity from major shunt companies. In patents from 2006 to 2008, Medtronic described a pump-based smart shunt operated on a preprogrammed schedule or feedback control.[13] The system could use existing implanted drug pumps marketed by Medtronic, and Medtronic has expertise in technology that could be applied directly to complete the system (e.g., communications, sensors). A time delay was suggested to reduce unnecessary changes in settings, but power draw and lifetime were not addressed specifically. In a 2001 patent, Medtronic described a complete sensor-based implantable monitoring system and noted that it could be used for valve control, but it was not the focus of the patent.[55] In a 2012 patent, Codman and Shurtleff described a mechanical valve (e.g., Codman–Hakim) with a pressure sensor and an actuator replacing the magnetic adjustment mechanism.[52] The system could be operated under physician control based on sensor feedback or under control of an internal algorithm. Power draw could be low since the mechanical valve provides the primary control. The algorithm, power management, and nonvalve components were not specified. In a 2006 patent, Integra Lifesciences described a pump-based shunt in which the pump system operated continuously but flow was either drained or returned to the CSF system by a valve as the primary controller.[66] Timed schedules and pressure feedback control were proposed. In another 2006 patent, Integra proposed a control strategy based on the magnitude of ICP oscillations as a measure of ventricle compliance.[67] For all of these systems, it is difficult to know their current status (because of secrecy in the commercial world), and it is likely that other patents exist (obfuscation in patent language makes it difficult to identify relevant work).

The Leonhardt group at Aachen University has published extensively on smart shunts and test systems.[25,26,34-37,48,71,74] They described a smart shunt based on pressure feedback control of a "tube squeezer" valve operated either as an on-off valve or variable-resistance valve. As with Cote *et al*.,[19] control algorithms included a tolerance zone around desired ICP to reduce valve activity. They also

used acceleration sensors to estimate patient position and detect patient activity (to allow rejection of noisy pressure data).[25,26,35-37,48] Various versions of the system were tested in human external drainage cases[26,35,48] and in benchtop models[48] or computer simulations[25,34,35] that included nonlinear brain compliance, ICP dynamics (A-waves, B-waves, P-waves),[34,36] body position[37] and other disturbances (e.g., walking, coughing).[35,36] They also described a system with sensors and telemetry to monitor an existing mechanical shunt; the device was tested in pigs and operated for 70 days on a AA battery.[37]

The Al-Nuaimy group at the University of Liverpool has developed detailed data management architectures and decision-making frameworks for smart shunts[1-3,5,57,58] as well as feedback control algorithms for on-off valves;[4,59,60] in both cases they emphasize advanced strategies including shunt weaning and personalized control. The framework describes the interactions between an implanted smart shunt, patient monitoring system, central database of patient data, and the physician. Unique features of their approach were the use of patient feedback in decision-making (e.g., smart phone questionnaires) and use of mathematical models of the CSF system as a central part of a control algorithm to interpret data and predict responses. Hardware was not developed, but the concepts are applicable to smart shunts in general. Control algorithms for on-off valves were based on a 24-hour time schedule to open–close a valve, with the schedule modified based on feedback and modeling. They also introduced valuable Figures of Merit to quantify the degree of success in reaching control goals (e.g., maintaining target ICP, reducing shunt dependency). An on-off valve proposed by Meithke[56] was used as motivation, but the algorithms would be applicable to any on-off valve.

Several groups are developing microvalves or micropumps that are fabricated using methods adapted from computer chip manufacturing. Yoon *et al.* from Ajou University, Korea, described a silicon/silicone micropump and a microfabricated pressure sensor for closed-loop control as part of a smart shunt concept.[75] Chung, *et al.* from Seoul University, Korea, and collaborating companies described a diaphragm-based microvalve fabricated from silicon and Parylene and tested it using ASTM standards.[18] The Noh group from Drexel University described microfabricated one-way valves[61] and microvalves with microneedles intended to mimic drainage through arachnoid villi.[27,47]

While many groups are developing sensors and dynamic models for the CSF system, a few groups stand out because of emphasis on smart shunts. Medow and colleagues at the University of Wisconsin are developing valves and sensors, Thomas and colleagues at the New Jersey Institute of Technology[72] are developing sensors and obstruction-resistant catheter designs, and the Smart Sensors and Integrated Microsystems (SSIM) Program at Wayne State University has a website that broadly describes smart shunt development activity. Linninger and colleagues are developing a ventricular volume sensor as the core for a smart shunt design.[11,12,50,51] A group centered at ETH Zurich (SmartShunt – The Hydrocephalus Project) is developing core understanding of hydrocephalus dynamics and constructing realistic benchtop models, with an aim to develop smart shunts.[15]

Outlook

Despite a long history of effort and increasing activity in recent years, there is no public evidence that a complete smart shunt has been developed. Rather, smart shunts are often described at a conceptual level (thus the term "smart shunt concepts" used throughout this paper), and reports of smart shunt technology are typically focused on a subset of components with remaining factors left unspecified (other hardware, control algorithms, power management). Thus, various aspects of smart shunts have been reported in isolated form, but a successful smart shunt must be designed as a complete system that balances technical and nontechnical factors. The short-term challenge is to engineer components into complete systems that are technologically feasible, economically viable, and of appropriate risk from a regulatory perspective.

The risk/reward spectrum

Smart shunts have the potential to make critical advances beyond existing mechanical designs, including:

- Providing sophisticated control not possible in mechanical shunts
- Providing data on patient condition or shunt (mal)-function
- Reducing the risk of shunt obstruction

Within each of these areas, contributions range from potential short-term gains based on lower technical and regulatory risk to complex concepts that will require more development (technical and scientific) and may be met with higher regulatory hurdles. Table 2 breaks down potential contributions with examples of implementations from simple to complex and commentary on the risks, challenges, and rewards that should be considered in developing smart shunts.

Sensors, diagnostic feedback, and system monitoring

Most smart shunt concepts include sensors (typically ICP or CSF flowrate) as part of feedback control. Since these parameters are familiar to physicians, any implantable smart shunt that incorporated this technology could provide data that would be immediately useful for better patient management or aid in the diagnosis of shunt malfunction.

Single time point measurements

There has been great progress recently on monitoring and diagnostic systems intended as "add ons" to existing

Table 2: Potential contributions of smart shunts across the risk-benefit spectrum

Potential contribution	Implementations from simple to complex	Risks, challenges, and rewards
Provide data on patient condition or shunt (mal) function	• On-demand, single-time-point data (e.g., ICP, flow) • Continuous recording, physician retrieves data history • Continuous monitoring, integrated alarm functions based on internal algorithms • Continuous monitoring, real-time data transmission interpreted by remote algorithms	• High demand by physicians and patients • Many groups are developing stand-alone monitoring and diagnostic systems • Comes "for free" in most smart shunts • Technical methods for data retrieval exist higher regulatory risk for internal algorithms
Provide sophisticated control not possible in mechanical shunts	• Physician-controlled adjustments based on sensor data • Open-loop control (e.g., preprogrammed time schedule, no need for sensors) • Closed loop control that mimics existing valves (e.g., ICP maintained via sensor feedback) • Closed-loop control with advanced algorithms (e.g. shunt weaning, personalized control)	• Great future opportunity but little consensus on "best control" • Regulatory risk lowest for physician-controlled adjustments or mimicking existing control, higher for untested advanced algorithms • Most smart shunt concepts can provide arbitrary control, but some are less flexible
Reduce obstruction risk	• Improved control (e.g. reduced overdrainage) • Obstruction-resistant valve design • Adjustments to correct for obstruction • Active methods to correct or prevent obstruction	• Largest obvious improvement over existing valves, but almost no attention paid • Obstruction-resistant designs are high priority • Higher regulatory risk for algorithm-based interventions

ICP: Intracranial pressure

valves. These include systems from Radionics (Telesensor), Medtronic (InSite), Transonic Systems (flow sensor), Meithke (SensorReservior), H-cubed, and Issys, as well as sensors in development by Codman,[54] Infoscitex (with Gordon Thomas),[72] and the University of Wisconsin (Josh Medow). These implanted systems are typically powered by an external reader (no internal power source) and measure sensor data on-demand to provide a "snap–shot" of the condition at the time of measurement (e.g., in the physician's office). It has been noted that on-demand measurements can be difficult to interpret since measured values (e.g., ICP, CSF flow) are expected to vary with time, and a single measurement may not accurately identify the patient condition or improper shunt function.[53] One system in development seeks to improve accuracy by creating a driven flow that is then measured to evaluate shunt patency (ShuntCheck with Micropumper, NeuroDx). Challenges remain, but such systems are likely to have important impact in the short-term.

Continuous measurement of sensor data

Most smart shunt concepts are based upon continuous (or at least frequent) sensor measurements to allow feedback control of CSF drainage. Time-course data from these same measurements would allow analysis of trends that could improve physician decision-making and shunt failure diagnosis. They could also generate much needed data for development of next-generation control strategies and could eventually be the basis for personalized control in future smart shunts. However, continuous (or frequent) measurements and data transmission require strategies to keep power draw low. It is worth noting that sensors used in on-demand systems (externally powered) may not be transferable to continuous monitoring in an implant since they have been developed without constraints on power draw. The approach to collecting and using sensor data spans a range of value and risk, which we discuss now.

Tier 1: Historical data retrieved by the physician

Relative to single time point measurements, the first tier of added value would be to allow the physician on-demand access to historical data (e.g., ICP recordings). This approach was noted in the early description by Rekate and colleagues.[46] Analysis of continuous data could improve the accuracy of physician-based diagnosis of shunt failure and could improve the ability to select shunt settings (e.g., valve opening pressure). From a regulatory perspective, providing data to the physician is less risky than interpreting and acting on that data via internal algorithms (described below). Moreover, like the single-time-point systems, on-demand data transmission could allow supplemental external power to reduce battery drain; internal power would still be required to gather sensor readings.

Tier 2: Real-time monitoring with internal alerts

One of the greatest potential impacts of continuous data collection would be the ability to identify problems, such as shunt failure, before they are catastrophic. Alarm mechanisms are already used in implanted devices (e.g., battery warnings), and the specific challenge in smart shunts is to determine how to analyze sensor data and decide when to issue alerts. For example, as has been seen with on-demand diagnostic systems,[53] a single measurement of high ICP or low CSF drainage rate does not mean that the shunt has failed. Smart shunts also have the potential for advanced diagnostics; the ShuntCheck with Micropumper (an external reader design) aims to use a perturbation (driven flow) and measurement (flowrate) approach to improve accuracy of shunt patency diagnosis, and similar concepts could

be implemented in smart shunts. Beyond sensor needs, development of accurate diagnostic algorithms is the key need for implementing diagnostic alarms.

Tier 3: Real-time data transmission to a monitoring system

Many smart shunt concepts note the potential to transmit data to the patient or health care system using a home-based monitoring station[46] or even a smart phone.[58] Like the internal alerts described above, real-time data transmission could allow early detection of problems. It is likely that centrally located algorithms would still be required to screen data and alert physicians to potential problems;[46] thus, accuracy of diagnostic algorithms remains a need. The power requirements for frequent data transmission could be too large to be supported by a battery alone. Some groups envision that an external monitoring station could also be used as a power source, but existing power transmission methods are efficient only for very short physical distances (distant transmission is in development but not yet widely available). In addition, personal medical devices (e.g., using smart phones as medical instruments) and the corresponding regulatory standards (including software and patient data security) are just emerging. Overall, real-time data transmission is appealing and is promoted as a feature of most smart shunt concepts but will likely not be available on the first smart shunts introduced.

Outlook

Early smart shunts will likely allow the physician to retrieve historical data on-demand using an external reader, and the physician will remain in control of interventions. This alone would be a major advance over existing mechanical shunts and on-demand diagnostics. Presumably, the same devices could also provide internal alarms with minor hardware modification, but addition of internally activated alarms will be governed by the need to validate algorithm accuracy and how regulatory agencies view the risk of software-based diagnostics. Real-time data transmission adds to the power burden, would likely require significant hardware changes (perhaps even a need for technology not yet developed), and must contend with regulatory and data privacy issues; it is likely further in the future.

Advanced control algorithms

The most emphasized goal of smart shunts is the potential to provide more sophisticated control than is possible using mechanical valves. Control approaches could simply prevent flow failure modes known in existing shunts (e.g., siphoning, pumping due to cardiac cycle), allow natural ICP dynamics that are typically suppressed by existing valves (e.g., cardiac cycle, natural ICP wave patterns), provide advanced controls that change over time (e.g., shunt weaning, circadian schedule), or provide personalized control for each patient. From a technical standpoint, smart shunts are in principle scalable from simple to sophisticated control with few hardware modifications. But, there is little consensus on what control approach is "best"; perhaps for this reason, discussion of control algorithms in smart shunt literature is almost always left vague. The second entry in Table 2 categorizes smart shunt control strategies based on their level of sophistication, with particular emphasis on how far beyond our current understanding they seek to go. Implicit in this is the regulatory risk associated with control methods that are yet to be clinically validated.

Open-loop versus closed-loop control

Open-loop control could be performed by a preprogrammed schedule operating an on-off valve[58] or a pump.[13] An advantage is that there is no need for a sensor, but there is a risk that the preprogrammed schedule is not appropriate, and dangerous ICP excursions (high or low) would be possible. While open-loop control is often mentioned as an option, it does not appear to be favored even by those who describe it. Medtronic described a preprogrammed schedule for a pump-based system, but also provided for pressure feedback control.[13] The Al-Nuaimy group described an intermediate approach using a timed schedule that would be adjusted by feedback from various sources (patient input, sensor data, physician control).[58] Nearly all smart shunt concepts aim to use closed-loop control based on sensor feedback.

Tier 1: Physician-controlled adjustments based on sensor data

The least risky approach is simply to provide the physician with more data by which to make decisions about valve adjustment. This is a form of closed-loop control but avoids risk questions inherent in software-based algorithms by keeping the physician in the control loop. On-demand diagnostic systems used with conventional adjustable valves offer a similar benefit, but time-course data (described above) would provide a notable advance.

Tier 2: Closed-loop control to mimic existing valves

A higher tier of sophistication could use active feedback control to mimic existing valves (e.g., ICP or flow control) while having the potential to correct for known failure modes. For example, using a positive displacement pump,[13] the control algorithm could maintain a fixed drainage rate that could be overridden if ICP was too high or too low, much like mechanical flow control valves (Orbis Sigma, Phoenix), or the flow rate could be varied based on pressure sensor feedback to maintain fixed ICP, similar to the goal for most existing valves. The clinical effects of simple ICP and flow control, whether adequate or inadequate, are well-established through a long history with mechanical shunts, and complex physiological questions can be largely avoided.

Similarly, a smart shunt that provides conventional control but corrects existing failure modes should be relatively noncontroversial; essentially it would achieve the original

intention that the mechanical shunts failed to meet. Well-recognized control problems in existing valves include (1) overdrainage due to siphoning, (2) overdrainage due to the "pumping effect," (3) hysteresis or drift over time due to imperfect materials, and (4) resetting of magnetic adjustment mechanisms in MRI.

1. Patient orientation (e.g., measured by an accelerometer) can be incorporated into control algorithms to correct for siphoning conditions. Existing antisiphon devices are matched to patient height; a smart system could adjust for patient growth. Most smart shunt concepts suggest orientation sensors to correct for patient orientation but do not specify algorithms. The Leonhardt group has implemented position sensing to good effect.[35,37,48]
2. One-way valves can act as pumps under oscillating pressure (e.g., cardiac pulsations), leading to overdrainage.[62,69,70] In a smart shunt, sensor data could be processed to ignore such effects.
3. Mechanical valves often have hysteresis (e.g., opening and closing pressures differ due to sticking valve parts), and operating curves can change as materials age (e.g., flexibility of diaphragm valves). Active control can better compensate for these problems to maintain a desired set point.
4. Existing "programmable" valves can be unintentionally reset by magnets (e.g., MRI or recently reported iPad use, although locking mechanisms have been developed). It is likely that smart shunts will provide set point adjustment to match existing capability, but adjustments could be made electronically without magnets (e.g., actuator-modified Codman–Hakim valve).[52]

Tier 3: Closed-loop control using advanced algorithms

Most smart shunts should in principle be capable of arbitrarily sophisticated control, but novel control strategies have a high burden-of-proof from a scientific and regulatory perspective. There has been vigorous debate in the literature over advanced control strategies that aim to recreate conditions of the intact CSF system.[64] In addition, many researchers have emphasized shunt weaning (progressive withdrawal of shunt dependency) as a key potential contribution of smart shunts.[3,46,58] The Al-Nuaimy group has described concepts for advanced controls that vary with time of day and patient feedback, and they have suggested modeling as an integral part of predictive and adaptive algorithms for personalized control.[58] It is clear that advanced control offers enormous potential to improve patient outcomes; but validation will take time, and advanced algorithms will likely be encores to less adventurous control strategies.

Outlook.

The opportunity for advanced control is the most emphasized contribution for smart shunts, but the grandest visions stretch well beyond our current scientific or clinical understanding of different control options. Thus, early smart shunts will likely take a conservative approach by adopting control algorithms that mimic existing shunts, with the potential to address some or all of their known failure modes. Even this modest approach could represent a major advance compared with the status quo. Simplified smart shunts introduced early could likely be adapted with little modification to implement advanced control algorithms as they are validated (i.e., reprogramming using the same hardware). In addition, early smart shunts could provide continuous data to better understand real-life dynamics of the CSF system as well as provide a platform for clinical testing of advanced control strategies.

Reduced obstruction risk

Shunt valve obstruction is responsible for 30% of shunt failures,[16,17,21,23,28,41,64] thus reducing valve obstruction is one of the greatest areas of potential impact. A great deal of work has focused on material modifications, especially of the proximal catheter, to reduce obstruction by cells or tissue; these methods have high value and have been reviewed recently by Harris *et al*.[31] Smart shunts could provide methods to complement material-based approaches. The use of sensors and active control mechanisms provides an opportunity for designing valves that are inherently less prone to obstruction or provide active methods to fight obstruction. A smart shunt that did nothing but reduce obstruction would be a major advance, yet there is almost no discussion of this opportunity in the smart shunt literature.

Obstruction-resistant fluidic design

Mechanical valve designs are somewhat constrained in their fluidic design and the choice of materials that are in contact with CSF (e.g., metal springs, adjusting mechanisms). Replacing purely mechanical control with electronic control offers flexibility to design valves that have fewer obstruction-prone features. An example is the tube-squeezer valve described by the Leonhardt group;[25,26,35,48] the fluidic pathway is simple (a tube), and presumably CSF only contacts tubing material (which could be the same silicone used in existing shunts). For these reasons, our group has also chosen a tube-squeezer as the core of our system. Some types of pumps, such as peristaltic pumps (another tube-based device),[13] could be highly resistant to obstruction of their mechanisms. In a very early design, Rekate and colleagues emphasized design goals to reduce obstruction, including absence of small orifices (<0.025 inch diameter) and avoidance of fluid dead spaces.[46] In contrast, many valve designs intended for smart shunts may actually add to the obstruction problem because of complex fluidic design (e.g., small flow passages, delicate actuator parts)

or because of contact of CSF with materials that may promote fouling.

Correction for obstruction or fouling

Mechanical valves cannot correct for fouling or partial obstruction, except via physician-controlled adjustment in programmable valves or potentially by mechanically pumping the shunt. For active systems that maintain a set point (e.g., ICP, flow) by feedback control, such adjustments are inherent and automatic since the system actively changes in response to deviations from the set point. Control adjustments would have finite capacity to correct for progressive valve obstruction, while proximal catheter obstruction would not be overcome by valve or pump adjustment (or mitigation would be only temporary during progressive obstruction).

Active methods to fight obstruction

Components of smart shunts could be used to actively fight obstruction. An early shunt design by Rekate and colleagues included a flushing mechanism to clear obstructions;[46] the system was not tested, but other smart shunts could apply this high value concept. The Judy group at the University of California, Los Angeles is developing proximal catheter microactuators designed to physically disrupt tissue in-growth.[49] Aside from a few examples, active methods are not discussed.

Outlook

Obstruction is one of the most serious problems with existing shunts, and smart shunt designs should place high priority on preventing obstruction (and at least should avoid fluidic designs and materials that would further increase obstruction risk). Development of *in vitro* biological fouling models[32,33] would be extremely valuable for testing obstruction-resistant designs prior to validation in animal or human tests. Conceptually, a smart shunt that offered no advantages other than reducing obstruction would be a major advance; it would offer direct benefits to patient health and reduce healthcare costs by averting revisions and associated diagnostics. Despite the enormous potential opportunity for obstruction-resistant design, there is almost no discussion in the field.

The power problem

For smart shunts to be capable of monitoring and control outside of a clinical setting, the system must be designed for low power consumption to allow operation on battery power for at least a portion of the time. Power draw is affected by hardware selection, but equally important are control algorithm design and decisions about the quality of control it must achieve. Thus, the power management strategy raises many questions: What schedule is acceptable for repowering (recharging or battery replacement)? What are viable locations for device implantation (to allow power transmission for recharging or to accommodate battery size)? What ICP excursions can be tolerated and for how long? Despite the importance of power issues to the viability of smart shunts, attention is largely absent in the literature.

Smart shunts could operate on battery power alone with periodic battery replacement (as in existing pacemakers), or they could be periodically recharged (as in early pacemakers). Recharging would reduce the size of battery needed but recharging methods may not be compatible with MRI and depend on patient compliance with a recharging regimen. Systems without recharging mechanisms will require a larger battery and may require placement at a location other than the head. Thus, potential usage models vary widely, and typically both approaches are claimed as options for smart shunts without further elaboration.

Smart shunts inherently involve a tradeoff between power draw and quality of control. Unlike mechanical valves that automatically and rapidly respond to changes, smart shunt algorithms inherently require decisions about how often to read sensors and how vigorously to respond to those readings. For example, an on-off valve with a normally closed position would require activation roughly every few minutes to maintain ICP within 1 cm H_2O of a set point (rough estimate based on CSF production rate ~0.3 mL/min, ventricle compliance ~1 cm H_2O/mL), and each measurement of ICP likely requires gathering pressure data over several seconds to allow data averaging or filtering to remove undesired transients (e.g., cardiac cycle, noise, pressure spikes). The magnitude of the power–quality tradeoff can vary enormously across designs and control strategies. Low-power components are important, but as important is the design of control algorithms that call these components into action as little as possible to maintain adequate control.

The Al-Nuaimy group provided an excellent framework for evaluating the effectiveness of control.[4,59,60] Using computer models, they simulated control algorithms for on-off valves, and they defined Figures of Merit to quantitatively assess the quality of control (e.g., magnitude and time period of ICP excursions). The Leonhardt group suggested that a Figure of Merit for power draw was needed, and this could be applied to assess specific choices of components (e.g., sensors, actuators).[25] Metrics for performance and power draw can and should be adopted to evaluate other smart shunt designs.

Outlook

Power draw is such a critical factor that many otherwise good designs will fail if they are not designed from the outset to minimize the tradeoff between power draw and quality of control. Despite its critical importance to the feasibility of smart shunts, discussion of power draw is nearly absent, and when noted, details are rarely given. Metrics have been proposed to quantify control quality[3,59,60]

and power consumption,[25] and they should be applied as critical constraints throughout design and testing.

Ex vivo models for development and testing

As described in the previous section, evaluating the quality of control and power draw relies explicitly on accurate dynamic models of the CSF system (virtual and bench models). Existing mechanical shunts are typically tested using simplistic benchtop test rigs to evaluate pressure-flow curves, prevention of reflux (backwards flow), effects of siphoning, etc. An ASTM standard provides standard testing protocols.[10] The methods are static and completely inadequate for testing smart shunts.

There has been extensive literature on dynamic models of the CSF system.[73] Several groups noted above have developed benchtop models or computer models specifically for testing smart shunts that include effects such as nonlinear brain compliance, variations in ICP (cardiac pulsations, respiratory cycles, A-waves, B-waves), and disturbances due to movement (walking, jogging).[4,12,15,19,25,26,34-37,48,50,59,60,74] Of special note, the ETH Zurich SmartShunt group has published excellent work on hydrocephalus and benchtop models with realistic CSF dynamics,[15] with a goal to advance development of smart shunts.

Whether virtual or physical, models of CSF dynamics are essential both for testing effectiveness of algorithms and devices as well as for identifying new goals for advanced control strategies. Especially important will be validation of models that are sufficiently realistic that they increase the likelihood of success when systems are transferred from bench testing to human patients.

Regulatory, reimbursement, and cost

As technology advances it would be most clinicians' hope that the improvements would rapidly find their way to clinical practice. An important rate-limiting step that seeks to ensure safe translation from bench to clinical practice is the national regulatory processes. In the United States regulation of device approval is controlled by the Food and Drug Administration (FDA). An excellent summary and perspective on FDA regulatory history of shunts was published in 2005.[29] Interesting to the history of hydrocephalus treatment, previous valves and components have sought approve via an equivalency argument suggesting the risks associated with new advancements were no greater than existing devices; this is the so-called 510 (k) pathway. A potential paradox of bringing forward advanced shunt technology is the risk of putting new products into a more rigorous device approval category called a Premarket Approval (PMA). If the features of a device are novel and without appropriate predicates, the device risks a requirement for extensive human data with positive outcome measures to obtain regulatory approval. The costs associated with a PMA can be high, requiring investors in later financing rounds to commit enough money to facilitate an appropriately powered study. The financial incentives to angel or venture capital investors become challenging as one seeks to fund shunt device development, since the yearly market of about $200 million dollars is at the lower end of venture capital goals. In spite of these challenges, the inventor/entrepreneur who is able to bring distinguishing advancements to the treatment of hydrocephalus could capture a lion's share of the market, making it a very worthwhile and valuable investment.

While many component predicates (implantable sensors, batteries, telemetry, etc.) exist in other devices, the use of implantable sensors and controlling algorithms in smart shunts has the potential to appear novel, triggering a higher threshold of scrutiny during the regulatory process. The *sine qua non* of shunting, namely real-time physiologically based computer control, would likely lead to a PMA with clinical trials if brought to the FDA today. A PMA would significantly increase development costs and extend agency approval times out 5 years or longer in the best of circumstances. Certain strategies regarding how a smart shunt would function can mitigate much of the approval risk including having early devices maintain static control in the outpatient setting but provide physician-controlled adjustment and interrogation capabilities in the clinic or hospital setting. The ability to simply read an accurate ICP, interrogate the functional status of an implanted shunt, or mechanically clear a fouled valve alone would revolutionize the current state of practice. These simple improvements might meet a lower regulatory standard and set a pathway for future advances that build on these technologies, thus avoiding the huge costs and lengthy time for PMA-approved devices.

With a renewed national focus on health care costs, anyone developing a smart shunt must be cognizant of the cost of goods, that is, the manufacturer's cost of building a device and the associated profit margin obtainable in the current reimbursement environment. One concern is that while technologically possible, the cost of manufacturing an implantable device with all the components necessary to achieve control and communication abilities could lead to a technological wonder that is not economically viable. Strategies to incorporate existing technology, source high-volume parts, and scale manufacturing can all drive down production costs. As improvements in shunt technology lead to documented improvement in outcomes, existing mechanisms to seek higher reimbursement via new coding and payer incentives may provide for higher sales price for devices proven efficacious over time. Since the delay to higher reimbursement can be years in the making, new devices will likely need to be produced and sold within the existing cost structure (approximately US $3500-5000)

until it can be proven that smart shunts lead to reduced shunt revision rates. Once proven superior to the current standard of care, these devices will be rewarded and the likelihood is that a premium price could be achieved as dramatic healthcare cost savings are realized in the form of reduced office visits, complications, reoperations, and readmission rates.

Outlook

While life-saving, the hydrocephalus shunt has undergone limited technological advancement over 60 years. Shunts remain relatively simple devices whose management is often challenging in the best of circumstances. Failure rates remain high and the ability to interrogate the patient's clinical situation is currently limited to clinical exam and imaging studies. All agree the current state of shunting is untenable and needs to be remediated with technological advancements. The desire for a "smart" shunt that addresses these issues is not new, with a description by Hakim as early as the 1960s and with Rekate proving an early description of a complete "smart" system in the 1980s. Realization of a smart shunt has certainly been slowed by the technological challenges, but the economics and regulatory challenges are also significant. Technology has advanced in key areas that are bringing smart shunts closer to reality, and astute choices in commercialization and regulatory strategy will lower the barrier to commercialization of new smart shunt concepts. The past decade has shown a great deal of activity as individuals and corporations seek to develop and protect intellectual property as it relates to smart shunt development.

The most promising developments currently undergoing commercialization and at or near regulatory approval include: (1) the ability to noninvasively assess ICP in the physician office via an implanted pressure sensor, and (2) noninvasive assessment of CSF flow in the clinical setting. Several companies are in late-stage development of systems for on-demand "snap–shot" measurements using an external reader; most systems require implanted sensors that are powered by the reader (ShuntCheck is an exception). These on-demand sensing systems will be a major advance as a supplement to existing mechanical valves.

Near-term devices (<5 years) will likely include implanted sensing systems that record data continuously and perhaps simple electromechanical smart shunts. The ability to record and transmit data on shunt performance and patient condition obtained over extended periods would be a step beyond on-demand "snap–shots" of systems noted above (e.g., time-course of ICP and patient orientation). The first smart shunts to be introduced will be those that cleverly balance technical capability with regulatory risk and other commercial factors. Early smart shunts will likely employ familiar control strategies (e.g., ICP regulation or flow regulation) and on-demand access to recorded data; device autonomy will be limited to keep regulatory risk manageable, and physicians will be integral to interpreting data and making changes to device settings. Compared with mechanical valves, electromechanical shunts provide a new opportunity to design for reduced failure; this is one of the greatest outstanding needs but it receives little attention in smart shunt development.

Long-term advances (>5 years) will likely come in the form of material sciences addressing biocompatibility, infection and fouling issues and introduction of advanced control and diagnostic algorithms in smart shunts. Advanced control strategies, such as shunt weaning and other forms of adaptive control, will require greater understanding of hydrocephalus and significant clinical testing before adoption. Similarly, autonomous diagnostics will require validation of algorithms to differentiate failure from normal variations in the system. Presumably, the earliest ("hobbled") smart shunts will be expandable to some of these advanced functions by reprogramming; once established in clinical practice early smart shunts could provide a platform for testing advanced control and diagnostic strategies.

For all smart shunts, dynamic models of the CSF system and establishment of accepted test methods are essential for device development and preclinical testing.

All of these issues make the development of a reliable and effective smart shunt a daunting, but attainable, challenge as we collectively work to better the lives of children and adults with hydrocephalus.

ACKNOWLEDGMENTS

The authors' work in this area has been supported by The Wallace H. Coulter Translational Research Partnership (TRP), a Commercialization Gap Fund grant from the University of Washington Center for Commercialization (C4C), a Commercialization Grant from the Washington Research Foundation (WRF), a Commercialization Grant from the Life Sciences Discovery Fund Authority (LSDFA, Award Number 4781549), and an STTR grant from NIH/NINDS (1R41NS074616-01). The content is solely the responsibility of the authors and does not necessarily represent the official views of the Coulter TRP, C4C, WRF, LSDFA, or NIH.

REFERENCES

1. Alkharabsheh AR, Momani L, Al-Zubi N, Al-Nuaimy W. A Multi-Agent Approach for Self-Diagnosis of a Hydrocephalus Shunting System. In: Developments in E-systems Engineering (DESE), 2010, p. 39-43.
2. Alkharabsheh AR, Momani L, Al-Zu'bi N, Al-Nuaimy W. An expert system for hydrocephalus patient feedback. Conf Proc IEEE Eng Med Biol Soc 2010; 2010:1166-9.
3. Al-Zubi N, Al-kharabsheh A, Momani L, Al-Nuaimy W. Intelligent shunt agent for gradual shunt removal. Conf Proc IEEE Eng Med Biol Soc 2010; 2010: 430-3.

4. Al-Zubi N, Al-Nuaimy W, Al-Hadidi M. Personalised mechatronic valve time-schedule optimiser for hydrocephalus shunt. In: Biomedical Engineering (MECBME), 2011 1st Middle East Conference on. 2011, p. 359-62.
5. Al-Zubi N, Momani L, Al-kharabsheh A, Al-Nuaimy W. Treatment and Management Methodology of Hydrocephalus: Application of Electronic Shunt Multiagent System (eShunt). In: Developments in eSystems Engineering (DESE), Second International Conference on. 2009, p. 147-50.
6. Anderson RC. Treatment of Hydrocephalus with Shunts, in Principles and Practice of Pediatric Neurosurgery. In: Albright AL, editor. New York: Thieme; 2008.
7. Aschoff A, Kramer P, Benesch C, Klank A, Shunt-technology and overdrainage: A critical review of hydrostatic, programmable and variable-resistance-valves and flow-reducing devices. Eur J Pediatr Surg 1991;1 Suppl 1:S49-50.
8. Aschoff A, Kremer P, Benesch C, Fruh K, Klank A, Kunze S. Overdrainage and shunt technology. A critical comparison of programmable, hydrostatic and variable-resistance valves and flow-reducing devices. Childs Nerv Syst 1995;11:193-202.
9. Aschoff A, Kremer P, Hashemi B, Kunze S. The scientific history of hydrocephalus and its treatment. Neurosurg Rev 1999;22:67-93.
10. ASTM, ASTM Standard F647-94 (2006), Standard practice for evaluating and specifying implantable shunt assemblies for neurosurgical application. 2006.
11. Basati S, Desai B, Alaraj A, Charbel F, Linninger A. Cerebrospinal fluid volume measurements in hydrocephalic rats. J Neurosurg Pediatr 2012;10:1-8.
12. Basati SS, Harris TJ, Linninger AA. Dynamic brain phantom for intracranial volume measurements. IEEE Trans Biomed Eng 2011;58:1450-5.
13. Bertrand W, Harper D, Speckman L, Kiehl A, Scheer R. Implantable cerebral spinal fluid drainage system. U.S. Patent 7309330, issued Dec. 18, 2007.
14. Biehl M, Scholz O, Dössel O, Schlegel WC. Basic Concepts for Active Implantable Valve IFMBE Proc 25/8; 2010:57-60.
15. Bottan S, Poulikakos D, Kurtcuoglu V. Phantom Model of Physiologic Intracranial Pressure and Cerebrospinal Fluid Dynamics. IEEE Trans Biomed Eng 2012;59:1532-8.
16. Browd SR, Gottfried ON, Ragel BT, Kestle JR. Failure of cerebrospinal fluid shunts: Part II: Overdrainage, loculation, and abdominal complications. Pediatr Neurol 2006;34:171-6.
17. Browd SR, Ragel BT, Gottfried ON, Kestle JR. Failure of cerebrospinal fluid shunts: Part I: Obstruction and mechanical failure. Pediatr Neurol 2006;34:83-92.
18. Chung S, Kim JK, Wang KC, Han DC, Chang JK. Development of MEMS-based cerebrospinal fluid shunt system. Biomed Microdevices 2003;5:311-21.
19. Cote GL, Durai R, Zoghi B. Nonlinear Closed-Loop Control-System for Intracranial-Pressure Regulation. Ann Biomed Eng 1995;23:760-71.
20. Drake JM, Kestle J. Rationale and methodology of the multicenter pediatric cerebrospinal fluid shunt design trial. Pediatric Hydrocephalus Treatment Evaluation Group. Childs Nerv Syst 1996;12:434-47.
21. Drake JM, Kestle JR, Milner R, Cinalli G, Boop F, Piatt J, *et al*. Randomized trial of cerebrospinal fluid shunt valve design in pediatric hydrocephalus. Neurosurgery 1998;43:294-303.
22. Drake JM, Kestle JR, Tuli S. Cerebrospinal fluid shunt technology. Clin Neurosurg 2000;47:336-45.
23. Drake JM, Kestle JT. Determining the best cerebrospinal fluid shunt valve design: The pediatric valve design trial. Neurosurgery 1998;43:1259-60.
24. Drake JM, Rose CS. The Shunt Book. John Wiley and Sons; 1995.
25. Elixmann I, Walter M, Kiefer M, Leonhardt S. Simulation of Existing and Future Electromechanical Shunt Valves in Combination with a Model for Brain Fluid Dynamics. Acta Neurochir Suppl 2012; 13:77-81.
26. Elixmann IM, Walter M, Goffin C, Hahne S, Kiefer M, Leonhardt S. Brain Pressure Modelling and Automatic Control of a New Mechatronic External Ventricular Drainage. At-Automatisierungstechnik 2011;59:613-21.
27. Emam M, Abashiya Y, Chareunsack B, Skordos J, Oh J, Choi Y, *et al*. A novel microdevice for the treatment of hydrocephalus: Design and fabrication of an array of microvalves and microneedles. Microsyst Technol 2008;14:371-8.
28. Garton HJ, Kestle JR, Drake JM. Predicting shunt failure on the basis of clinical symptoms and signs in children. J Neurosurg 2001;94:202-10.
29. Haines S, Blount J. Safe Medical Devices for Children, Appendix E: The Regulatory History of Cerebrospinal Fluid Shunts for Hydrocephalus. Field MJ, Tilson H, editors. Washington DC: The National Academies Press; 2005. p. 347-81.
30. Harris CA, McAllister JP. Does drainage hole size influence adhesion on ventricular catheters? Childs Nerv Syst 2011;27:1221-32.
31. Harris CA, McAllister JP. What we should know about the cellular and tissue response causing catheter obstruction in the treatment of hydrocephalus. Neurosurgery 2012;70:1589-601.
32. Harris CA, Resau JH, Hudson EA, West RA, Moon C, Black AD, *et al*. Effects of surface wettability, flow, and protein concentration on macrophage and astrocyte adhesion in an *in vitro* model of central nervous system catheter obstruction. J Biomed Mater Res A 2011;97:433-40.
33. Harris CA, Resau JH, Hudson EA, West RA, Moon C, McAllister JP. Mechanical contributions to astrocyte adhesion using a novel *in vitro* model of catheter obstruction. Exp Neurol 2010;222:204-10.
34. Jetzki S, Kiefer M, Eymann R, Walter M, Leonhardt S. Analysis of Pulse Waves in Intracranial Pressure. Conf Proc IEEE Eng Med Biol Soc 2007; 2007:2863-6.
35. Jetzki S, Kiefer M, Walter M, Leonhardt S. Concepts for a mechatronic device to control intracranial pressure. In 4th IFAC Symposium on Mechatronic Systems. Heidelberg, Germany: 2006, p. 25-9.
36. Jetzki S, Leonhardt S. An electronic implant for Hydrocephalus therapy assistance. Conf Proc IEEE Eng Med Biol Soc 2008; 2008:715-8.
37. Jetzki S, Weinzierl M, Krause I, Hahne S, Rehbaum H, Kiausch M, *et al*. A multisensor implant for continuous monitoring of intracranial pressure dynamics. IEEE Trans Biomed Circuits Syst 2012;6:356-65.
38. Jiang G, Zhou D, Greenbaum E. Technology Advances and Challenges in Hermetic Packaging for Implantable Medical Devices, Implantable Neural Prostheses 2. New York: Springer; 2010. p. 27-61.
39. Jiang G. Design challenges of implantable pressure monitoring system. Front Neurosci 2010;4:29.
40. Kestle J, Drake J, Milner R, Sainte-Rose C, Cinalli G, Boop F, *et al*. Long-term follow-up data from the Shunt Design Trial. Pediatr Neurosurg 2000;33:230-6.
41. Kestle J, Milner R, Drake J. The shunt design trial: Variation in surgical experience did not influence shunt survival. Pediatr Neurosurg 1999;30:283-7.
42. Kestle JR, Drake JM, Cochrane DD, Milner R, Walker ML, Abbott R, *et al*. Lack of benefit of endoscopic ventriculoperitoneal shunt insertion: A multicenter randomized trial. J Neurosurg 2003;98:284-90.
43. Kestle JR, Walker ML. A multicenter prospective cohort study of the Strata valve for the management of hydrocephalus in pediatric patients. J Neurosurg 2005;102:141-5.
44. Kestle JR. Pediatric hydrocephalus: Current management. Neurol Clin 2003;21:883-95, vii.
45. Klimo *P* Jr, Thompson CJ, Drake J, Kestle JR. Assessing the validity of the endoscopic shunt insertion trial: did surgical experience affect the results? J Neurosurg 2004;101 (2 Suppl):130-3.
46. Ko WH, Meyrick CW, Rekate HL. Cerebrospinal-Fluid Control-System. Proc IEEE1988;76:1226-35.
47. Kralick F, Noh H. Implantable micro-system for treatment of hydrocephalus. U.S. Patent 7691077, issued Apr 6, 2010.
48. Krause K, Hahne S, Walter M, Kiefer M, Linke S, Radermacher K, *et al*. Brain Pressure Dynamics and Control with an External Ventricular Drainage, IRMBE Proc 2012; 37:315-8.
49. Lee SA, Lee H, Pinney JR, Khialeeva E, Bergsneider M, Judy JW. Development of microfabricated magnetic actuators for removing cellular occlusion. J Micromech Microeng 2011;21:54006.
50. Linninger A, Basati S, Dawe R, Penn R. An impedance sensor to monitor and control cerebral ventricular volume. Med Eng Phys 2009;31:838-45.
51. Linninger A. Monitoring and controlling hydrocephalus, In: WIPO, editor. US Patent App. 20100130884, filed Jul. 2, 2007.
52. Ludin L, Mauge C. Programmable shunt with electromechanical valve actuator. U.S. Patent US8123714, issued Feb. 28, 2012.
53. Madsen JR, Abazi GS, Fleming L, Proctor M, Grondin R, Magge S, *et al*. Evaluation of the shuntcheck noninvasive thermal technique for shunt flow detection in hydrocephalic patients. Neurosurgery 2011;68:198-205.
54. Mauge C, Dextradeur A, McCusker D, Meyer S, Beodecker V, Kraus R, *et al*. Method for measuring ventricular pressure using a pressure sensing valve. U.S. Patent App 20080214983, filed Mar. 31, 2008.
55. Miesel K, Stylos L. Intracranial monitoring and therapy delivery control device, system, and method. U.S. Patent 6248080, issued Jun. 19, 2001.
56. Miethke C. Hydrocephalus valve. U.S. Patent EP1613388 B1, filed Mar. 22, 2005.

57. Momani L, Alkharabsheh AR, Al-Nuaimy W. Design of an intelligent and personalised shunting system for hydrocephalus. Conf Proc IEEE Eng Med Biol Soc 2008; 2008:779-82.
58. Momani L, Alkharabsheh AR, Al-Nuaimy W. Intelligent and Personalised Hydrocephalus Treatment and Management. In Biomedical Engineering (Barros de Mello CA, ed.). Available from: http://www.intechopen.com/books/biomedical-engineering/intelligent-and-personalised-hydrocephalus-treatment-and-management.
59. Momani L, Alkharabsheh AR, Al-Zu'bi N, Al-Nuaimy W. Instantiating a mechatronic valve schedule for a hydrocephalus shunt. Conf Proc IEEE Eng Med Biol Soc 2009; 2009:749-52.
60. Momani L, Al-Nuaimy W, Al-Jumaily M, Mallucci C. A mechatronic valve in the management of hydrocephalus: Methods and performance. Med Biol Eng Comput 2011;49:121-32.
61. Oh J, Kim G, Kralick F, Noh H. Design and Fabrication of a PDMS/Parylene Microvalve for the Treatment of Hydrocephalus. J Microelectromech Syst 2011;20:811-8.
62. Oi S, Matsumoto S. Morphological findings of postshunt slit-ventricle in experimental canine hydrocephalus. Aspects of causative factors of isolated ventricles and slit-ventricle syndrome. Childs Nerv Syst 1986;2:179-84.
63. Orenstein DM, Yonas H, Bilenker R, Rekate HL, White RJ. Hemangioma thrombocytopenia syndrome. A case masquerading as an encephalocele. Am J Dis Child 1977;131:680-1.
64. Rekate HL. Closed-loop control of intra-cranical pressure. Ann Biomed Eng 1980;8:515-22.
65. Rekate HL. Shunt revision: Complications and their prevention. Pediatr Neurosurg 1991;17:155-62.
66. Rubinstein E, Karshmer D, Levinthal E, Vargas J, Saul T. Internally powered CSF pump systems and methods. IU.S. Patent 7025742, issued Apr. 11, 2006.
67. Saul T. System and method for treating elevated intracranial pressure. U.S. Patent 7025739, issued Apr. 11, 2006.
68. Scott RM, Madsen JR. Shunt technology: Contemporary concepts and prospects. Clin Neurosurg 2003;50:256-67.
69. Serlo W, Heikkinen E, Saukkonen AL, von Wendt L. Classification and management of the slit ventricle syndrome. Childs Nerv Syst 1985;1:194-9.
70. Serlo W, Saukkonen AL, Heikkinen E, von Wendt L. The incidence and management of the slit ventricle syndrome. Acta Neurochir (Wien) 1989;99:113-6.
71. Szczesny S, Jetzki S, Leonhardt S. Review of Current Actuator Suitability for Use in Medical Implants. Conf Proc IEEE Eng Med Biol Soc 2006;1:5956-9.
72. Thomas G, Farrow R, Liu S. No clog shunt using a compact fluid drag path. U.S. Patent 8088091, issued Jan. 3, 2012.
73. Wakeland W, Goldstein B. A review of physiological simulation models of intracranial pressure dynamics. Comput Biol Med 2008;38:1024-41.
74. Walter M, Leonhardt S, Schubert H, Aschoff A. A computer aided test stand for medical microvalves. Conf Proc IEEE Eng Med Biol Soc 1996; 1:157-158.
75. Yoon HJ, Jung JM, Jeong JS, Yang SS. Micro devices for a cerebrospinal fluid (CSF) shunt system. Sens Actuator A-Phys 2004;110:68-76.