Ventriculovenous shunts are predisposed to thrombotic complications

Jelle Vandersteene



Faculty of medicine and health sciences

Ghent University

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Ventriculovenous shunts are predisposed to

thrombotic complications

Jelle Vandersteene

Promotor: prof. dr. Dirk Van Roost

Co-promotor: prof. dr. Filip De Somer

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PROMOTOR

Prof. dr. Dirk Van Roost Ghent University, Belgium

CO-PROMOTOR

Prof. dr. Filip De Somer Ghent University, Belgium

DOCTORAL ADVISORY COMMITTEE

Prof. dr. P. Segers Ghent University, Belgium Prof. dr. S. Van Vlierberghe Ghent University, Belgium

MEMBERS OF THE EXAMINATION AND READING BOARD

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KU Leuven University, Belgium
Dr. S. Bhatti
Ghent University, Belgium

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List of Abbreviations

CSF	cerebrospinal fluid
CFD	Computational Fluid Dynamics
DVSAD	dural venous sinus access device
ETV	endoscopic third ventriculostomy
ICP	intracranial pressure
IJV	internal jugular vein
MRI	magnetic resonance imaging
NPH	normal pressure hydrocephalus
Psss	pressure in the superior sagittal sinus
RL	Ringer's Lactate
RVS	retrograde ventriculosinus
SSS	superior sagittal sinus
VA	ventriculoatrial
VP	ventriculoperitoneal
VS	ventriculosinus
VV	ventriculovenous (including VA and VS)

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Chapter 4

Treating hydrocephalus with the retrograde ventriculosinus shunt. Prospective clinical study.

E. Baert, F. Dewaele, <u>J. Vandersteene</u>, G. Hallaert, Jean-Pierre Okito Kalala, D. Van Roost

Submitted to World Neurosurgery; A1; Q2 (60/197) in General surgery; Impact Factor 2.592.

Chapter 5

A non-hydrocephalic goat experimental model to evaluate the ventriculosinus shunt.

<u>J. Vandersteene</u>, E. Baert, S. Schauvliege, K. Vandevelde, F. Dewaele, F. Desomer, D. Van Roost Accepted in Laboratory Animals; A1; Q1 (33/136) in Veterinary sciences; Impact Factor 1.532

Chapter 7

A new non-occlusive roller pump model for in-vitro evaluation of intravascular devices.

E. Baert, <u>J. Vandersteene</u>, F. Dewaele, F. De Somer, A. Van Tilborg, D. Van Roost

To be submitted to Artificial Organs; A1; Q2 (28/77) in Engineering Biomedical; Impact Factor 2.403 A method for improved quantitative evaluation of scanning electron microscope images of cylindrical surfaces.

<u>J. Vandersteene</u>, T. Van Den Berghe, G. Planckaert, E. Baert, F. Dewaele, F. De Somer, D. Van Roost

Submitted to Physiological Measurement; A1; Q2 (37/77) in Engineering Biomedical; Impact Factor 2.058

The influence of cerebrospinal fluid on blood coagulation and the implications for ventriculovenous shunting.

<u>J. Vandersteene</u>, E. Baert, G. Planckaert, T. Van Den Berghe, D. Van Roost, F. Dewaele, M. Henrotte, F. De Somer Accepted in Journal of Neurosurgery; A1; Q1 (16/197) in General Surgery; Impact Factor 4.059

Chapter 8

A hydrocephalic goat experimental model to evaluate the efficacy of hydrocephalus treatments.

E. Baert, S. Schauvliege, <u>J. Vandersteene</u>, K. Vandevelde, F. Dewaele, F. Desomer, D. Van Roost

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Chapter 1. Rationale and overview

Rationale

Cerebrospinal fluid (CSF) is produced by the choroid plexus, and flows through the cerebral ventricles to the subarachnoid space where it is absorbed to the superior sagittal sinus (SSS) (1). Hydrocephalus develops when the CSF flow is hampered or the absorption capacity is diminished (2). When the CSF flow is obstructed at the level of the third or fourth ventricle's outflow ('obstructive hydrocephalus'), it can be treated by an endoscopic third ventriculostomy (ETV). If the CSF flow is obstructed more proximally or distally, it is treated by draining CSF to the peritoneal cavity or to the right atrium of the heart with a ventriculoperitoneal (VP) or ventriculoatrial (VA) shunt (3). Although these techniques are frequently used since the 1950's, they suffer from a failure rate up to 50% in the first two years after implantation (4-8). An important cause of shunt failure is siphoning, which means that the CSF column within the catheter exerts suction through gravity when the patient is in a sitting or standing position (9). Complex and expensive devices to counteract siphoning exist but are not always sufficient (5, 10). Shunt failure is an important burden for patients and it has a high economic impact, hence, there remains a valid rationale for ongoing hydrocephalus research (11).

A promising, but still experimental treatment of hydrocephalus is the ventriculosinus (VS) shunt (11). The VS shunt drains CSF to its natural resorption site, preserves the anti-siphon effect of the internal jugular vein (IJV) and theoretically restores a physiological intracranial pressure (ICP) (12-15). The shunt system is short, simple and confined to the skull, which

minimizes the risk of mechanical failure and infection. After unsuccessful early attempts, El-Shafei and Børgesen independently pioneered the technique in the early 2000s (14, 16, 17). They report, based on retrospective data, a shunt survival rate of up to 95% after a mean follow up of over 6 years (13, 14).

We felt inspired by the new technique and, as prospective studies were lacking, we started a monocentric prospective clinical trial. This study was interrupted due to an unacceptable high obstruction rate of the sinus catheter, caused by a thrombotic and/or endothelial sleeve around the distal end of the shunt (15). What caused this early and frequent thrombotic obstructions is not clear. We respected the technical recommendations of previous literature (13, 18, 19) and the surgeon who performed all implantations even travelled to Cairo to learn the technique from professor El-Shafei. Therefore, it seems highly unlikely to us that the results are due to a deviant surgical technique. Also, more generally, we noticed that, despite the substantial theoretical advantages and the excellent clinical results that were reported, the VS shunt did not break through. On the contrary, it has become very quiet about this technique that neurosurgeons seem to be reluctant to use.

Therefore we suspect that certain characteristics of VS shunts predispose this technique to thrombotic complications (20). This hypothesis is endorsed by the fact that thrombotic complications are also encountered – and well documented - in ventriculoatrial (VA) shunts, a classical treatment of hydrocephalus (3, 21, 22). The incidence of these complications has proven to be higher than would be expected on the basis of the presence of a foreign body in the blood vessel alone (20).

The goal of the present thesis is to identify characteristics that predispose ventriculovenous (VV) shunts (VS and VA shunts) to thrombotic complications. This will be a first step in a bigger research project aiming at the development of a new, long-lasting VS shunt.

Overview

The present thesis is structured as follows:

Chapter 2, 'General introduction', gives a general introduction on the production, circulation and absorption of CSF as well as on the medical condition hydrocephalus.

Chapter 3, 'Ventriculoperitoneal shunts', describes the principles and results of this technique, currently the most used treatment of hydrocephalus. It addresses common causes of shunt failure with special attention to siphoning.

Chapter 4, 'Ventriculovenous shunts', gives a general introduction on the technique and results of VA and VS shunting and discusses how VS shunts theoretically prevent siphoning. Next, it reports on the methodology and results of the prospective clinical trial to evaluate VS shunts, that was conducted at our department and interrupted due to frequent and early thrombotic shunt obstructions. It concludes that specific factors probably predispose ventriculovenous (VV) shunts to thrombotic complications.

Chapter 5, 'Factors that predispose to thrombotic complications', reports on the results of a non-hydrocephalic experimental goat model, that was developed to identify factors predisposing VV shunts to thrombotic complications. During the experiment we observed pulsatile reflux of blood into the shunt system, despite the presence of a one-way valve and regardless of shunt orientation (anterograde or retrograde). We also found that adding CSF to blood enhances blood coagulation. Both issues were further explored by the in vitro models described in the following chapters.

Chapter 6, 'Pulsatile backflow of blood into the shunt', identifies the interaction between pressure waves in the brain ventricles (proximal end of the shunt) and in the SSS or the right atrium (distal end of the shunt), as a potential cause of pulsatile backflow. It discusses the methodology and the results of a dynamic experimental set-up, that was developed to evaluate whether these pressure waves are effectively responsible for pulsatile backflow of blood into the shunt system.

Chapter 7, 'Procoagulant effect of CSF', explores if this effect, observed in the animal model, also exists in humans. First the influence of adding CSF to blood of the same patient was evaluated in a static coagulation assay. Next, a new dynamic in vitro model (modified Chandler loop) was applied to verify whether the blood-CSF-foreign material interaction effectively results in more clot formation on the shunt surface.

Chapter 8, 'Evaluation of the efficacy of novel hydrocephalus treatments', discusses an attempt to develop a hydrocephalic experimental goat model. Such a model might be a necessary step in the development of a novel VS shunt, as the non-hydrocephalic model, presented in chapter 5, does not allow to evaluate efficacy nor long term shunt survival.

Chapter 9, 'Discussion', integrates the findings of the previous chapters, and focuses on the future development of a new VS shunt.

Chapter 10, 'Summary – Samenvatting', provides English and Dutch summaries of the present thesis.

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Chapter 2. General introduction

Cerebrospinal fluid

CSF, found in the cerebral ventricles (Figure 1) and in the subarachnoid space surrounding the brain, offers hydromechanical protection of the central nervous system, plays a prominent role in brain development, and regulates interstitial fluid homeostasis (1-3). In order to enable CSF to fulfill these functions, its production, circulation, and absorption processes should be unhindered and carefully balanced. These processes are summarized in Figure 2 and discussed in more detail below.

CSF secretion

400 to 600 ml CSF is secreted daily, of which 60 to 70 % is produced by the choroid plexuses of the lateral ventricles and the tela choroidea of the third and fourth ventricles (4). Choroidal secretion of cerebrospinal fluid comprises two steps: the first step is passive filtration of plasma from choroidal capillaries to the choroidal interstitial compartment according to a pressure gradient. The second step consists of active transport from the interstitial compartment to the ventricular lumen, across the choroidal epithelium, involving carbonic anhydrase and membrane ion carrier proteins (5). The active transport of CSF results in a composition that is more than a passive ultrafiltrate of plasma (4). The secretion of CSF is exquisitely modulated so that the intracranial pressure (ICP) is stable when CSF absorption is normal (1).



Figure 1. Brain ventricles

Upper left, ventricles viewed from lateral surface of the brain; upper right, ventricles viewed from anterior surface of the brain; lower left, ventricles viewed from apical surface of the brain; lower right, details of ventricular structures. Reproduced from (6) with permission.

The choroid plexuses receive cholinergic, adrenergic, serotoninergic and peptidergic autonomic innervation. The sympathetic nervous system reduces CSF secretion, while the cholinergic system increases CSF secretion. Monoamines and neuropeptide factors have also been shown to play a role (1). 30 - 40 % of the CSF production results from a transporter-mediated extrachoroidal fluid transport that occurs at the cerebral capillary wall (7) and ventricular ependyma (8).

Despite the daily production rate of around 500 ml CSF, only 80-180 ml of CSF is present around the brain and spinal cord at any given moment. The CSF volume is thus renewed 4-5 times every day (1). This high turnover rate relies on unhindered circulation and absorption of CSF.

CSF circulation

After its production, CSF travels through the interventricular foramina of Monro to the third ventricle and then through the cerebral aqueduct of Sylvius to the fourth ventricle and finally to the subarachnoid space through the lateral apertures of Luschka and the median aperture of Magendie. It then circulates rostrally to the villous sites of absorption or caudally to the spinal subarachnoid space. CSF that enters the spinal subarachnoid space, might be absorbed by spinal arachnoid villi (see below) or might circulate back to the cranial subarachnoid space (1, 9).

Circulation of CSF is driven by static and dynamic pressure gradients (1, 9). The static pressure gradient is generated by the production of CSF (volume transmission) while the dynamic pressure gradients originate from the cardiac and respiratory cycles. Due to the dynamic pressure gradients, CSF flow or movement is neither laminar nor constantly unidirectional. Pulsatile CSF movement during each cardiac pumping cycle occurs as anterograde caudal flow is followed by retrograde cranial flow (1).



Figure 2. CSF 'secretion-circulation-absorption' model

CSF is mainly secreted by the choroid plexus and, to a lesser extent, by the interstitial compartment. It circulates rostrocaudally inside the ventricles and drains into the cerebellomedullary cistern (cisterna magna) through the median aperture (foramen of Magendie) of the fourth ventricle. CSF circulates in cranial and spinal subarachnoid spaces. In the cranial subarachnoid space, CSF flows towards arachnoid villi in the wall of venous sinuses from which it is absorbed. Part of the CSF is absorbed by the olfactory mucosa and cranial nerve sheaths (implying optic, trigeminal, facial and vestibulocochlear nerves) and is drained by the lymphatic system. In the spinal subarachnoid space, the CSF that is absorbed by the epidural venous plexus and spinal nerve sheaths enters the lymphatic system, while the remaining CSF circulates rostrally towards the cranial subarachnoid space. Reproduced from (1) with permission.
CSF absorption

CSF absorption to the dural venous sinuses by arachnoid granulations (Pacchionian granulations; arachnoid villi) is supported by both older (10-12) and more recent studies (13). Arachnoid granulations are projections of the arachnoid membrane into the SSS allowing drainage of CSF to the venous system (Figure 3) (11). The pressure gradient between the subarachnoid spaces and the venous sinus, necessary to ensure CSF drainage, is between 3 and 5 mmHg (14).



Figure 3. Cranial arachnoid granulations

Arachnoid granulations are endothelium-lined finger-like meningeal protrusions through the dura mater of the superior sagittal sinus that ensure CSF drainage whenever the pressure gradient between the subarachnoid spaces and the venous sinus is over 3 to 5 mm Hg. Reproduced from (1) with permission.

The proportions of CSF that efflux through each of these major pathways have yet to be determined with any certainty in humans. The existing evidence, derived from animal studies, indicate that the relative importance of the major pathways varies between species (15). For example, the lymphatic system seems to account for up to 15 % of the CSF absorption in cats, 30 % in rabbits and almost 50 % in sheep (15).

The CSF outflow pathways may evolve throughout development. A tracer injected to observe CSF drainage through the lymphatic system in embryonic and postnatal pigs was detectable as early as the 92 nd day of the embryonic period (16). Given that arachnoid granulations are scarcely visible in fetal and newborn sheep (17) and are not easily observed in humans until 18 months after birth (18), it might be speculated that the lymphatic pathway plays an especially important role in CSF drainage during embryonic and early postnatal development but takes a proverbial backseat as the arachnoid granulations mature and become more capable of supporting CSF absorption (19), (20).

CSF absorption by spinal arachnoid granulations: CSF is also absorbed from the spinal compartment by spinal arachnoid granulations (1). These are typically found adjacent to spinal nerve roots and protrude through the dura mater (21). Spinal arachnoid granulations evacuate CSF to the epidural venous plexus or to the lymphatic system (22). Spinal absorption of CSF increases in the upright position and during effort (22).

Absorption by spinal nerve sheaths: CSF absorption surfaces have been identified on meningeal sheaths, particularly the meningeal recesses of spinal and cranial nerve roots (Figure 4). The best-known example is the optic nerve. In pathological conditions, such as hydrocephalus and benign intracranial hypertension, fluid thickening of the optic nerve sheaths can be visualized by magnetic resonance imaging (MRI). This finding suggests that the optic nerves participate in CSF absorption when the capacity of the usual absorption pathways has been exceeded (1).



Figure 4. Cerebrospinal fluid absorption by spinal arachnoid villi and meningeal sheaths of spinal nerves

Spinal absorption of CSF may occur by arachnoid villi in contact with the epidural venous plexus (a), arachnoid villi adjacent to spinal nerve roots (b). or absorption surfaces in the meningeal recess of spinal nerve roots (c). Reproduced from (1) with permission.

Absorption through the cribriform plate: this pathway, that was studied in animal models, successively involves perivascular spaces, the arachnoid sheath of olfactory nerve fibers through the cribriform plate, and the nasal submucosa and cervical lymph nodes (23). Stains injected into CSF are subsequently found in the nasal submucosa and cervical lymph nodes (24). In sheep, occlusion of the cribriform plate of the ethmoid bone increases the intracranial pressure (25, 26), and lymphatic absorption of CSF increases with increasing intracranial pressure (27). Ligation of cervical lymph vessels of the dog induces cerebral edema (28). Despite such evidence from animal models, the functional role of this lymphatic pathway in man remains unknown. Presumably, it provides an accessory pathway that becomes active when the capacities of the cranial arachnoid villi are exceeded. It may be especially active in neonates, as immature arachnoid villi only become fully functional after the age of 18 months, and in the elderly due to fibrous changes of arachnoid granulations (1).

Movement of water in the central nervous system and CSF physiology

Water can diffuse freely and bidirectionally between blood, brain and CSF (29, 30). This fast water flow relies on the presence of aquaporins. The brain contains 3 types of aquaporins (31). Aquaporin 1 is expressed in the apical membrane of the choroid plexus, and plays a role in CSF formation (32). Although highly expressed in peripheral endothelial cells, aquaporin 1 is not found in normal brain capillary endothelium (33). As shown in Figure 5, aquaporin 4 is strongly expressed at the borders between brain parenchyma and major fluid compartments including astrocyte foot processes (brain–blood) and glia limitans (brain–subarachnoid CSF), as well as ependymal cells and subependymal astrocytes (brain–ventricular CSF) (34, 35). This pattern of distribution suggests that aquaporin 4 controls water flow into and out of the brain. Aquaporin 9 has been observed in rat brains and may play a role in controlling the cerebral energy metabolism (31).

Despite the evolving knowledge about the movement of water in and out of the brain and about the distribution and function of aquaporins, the exact mechanism of the huge bidirectional flux of water through the brain capillaries and choroid plexus remains unknown (31). In adults there are no obvious

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aquaporins in brain capillary endothelium or on the basal side of the choroidal epithelium (36). Brain capillary endothelium however does contain tight junctions which prevent paracellular transport of water (31).



Figure 5. Routes of water flow out of the brain

(a) Excess water moves from the brain, through several layers of astrocyte processes comprising the glia limitans externa and pia into subarachnoid CSF. (b) Excess water also moves from the brain, through layers of subependymal astrocyte processes (glia limitans interna) and ependyma into ventricular CSF. (c) Some excess water moves directly from the brain through astrocyte foot processes and endothelial cells into the blood. Note that all exit routes strongly express aquaporin 4 (AQP4). Image reproduced from (31), with permission.

Recently a brain-wide pathway for fluid transport in mice was identified. This pathway includes the para-arterial influx of subarachnoid CSF into the brain interstitium (along the Virchow Robin spaces), followed by the clearance of interstitial fluid along large-caliber draining veins. Interstitial convective bulk flow between these influx and efflux pathways is driven by aquaporin 4 dependent trans-astrocytic water movement and probably by the arterial and venous pressure waves (37). This system, called the glymphatic system (or g-lymphatic system as it depends on glial cells), is summarized in Figure 6.

Recent literature shows that the secretion of CSF is volumetrically less than 1 % of the total central nervous system water diffusional exchange (38, 39). Based on this fact an alternative model of CSF physiology was proposed (40). In this model it is presumed that CSF is exclusively formed and absorbed by water filtration across arterial capillary walls throughout the entire central nervous system. The model thus contradicts the contribution of the choroid plexus to the production of CSF as well as the contribution of the arachnoid granulations to the absorption of CSF (40, 41). By consequence there is no 'volume transmission' and thus no 'CSF bulk flow' from the brain ventricles to the subarachnoid space. Instead there is a pulsatile 'to and fro' movement of CSF resulting in local mixing and diffusion. Based on this alternative model of CSF physiology it is claimed that hydrocephalus is not the result of hampered CSF circulation or absorption, but is caused by intraventricular fluid accumulation due to increased blood vessel permeability in combination with a permanent increase in CSF osmolarity caused by pathological changes (40).



Figure 6. Glymphatic pathway

The glymphatic system supports interstitial solute and fluid clearance from the brain. In this brain-wide pathway, CSF enters the brain along para-arterial routes, whereas interstitial fluid is cleared from the brain along paravenous routes. Convective bulk flow between these influx and clearance routes is facilitated by the aquaporin 4 (AQP4) dependent astroglial water flux and drives the clearance of interstitial solutes and fluid from the brain parenchyma. From here, solutes and fluid may be dispersed into the subarachnoid CSF, enter the bloodstream across the postcapillary vasculature, or follow the walls of the draining veins to reach the cervical lymphatics. Reproducced from (37), with permission. This alternative model of CSF physiology is inconsistent with over 60 years of experimental data obtained for animals and humans (3) as well as with clinical observations like the effectiveness of resection/ablation of the choroid plexus in case of CSF overproduction (42) and of ETV in case of obstructive hydrocephalus (43). It is also in contradiction with iconographic data proving a net CSF flow through the Sylvian aqueduct (38). It is shown that, although the total water exchange is considerably higher at the blood brain barrier, the *net* fluid generation capacity is importantly higher at the choroid plexus barrier (3).

In the light of the above, we support the opinion that the recent insights in molecular exchanges (including water) between CSF, interstitial fluid and brain capillaries, complement rather than contradict the traditional and well documented bulk flow model (3).

Cortical veins and dural venous sinuses

Anatomy

Blood is supplied to the brain by the internal carotid- and vertebral arteries. It then flows through smaller arteries and arterioles (resistance vessels) towards the capillary bed. Capillaries join to form venules and veins. The venous drainage of the brain can be separated into two subdivisions: superficial and deep. The superficial system contains cortical veins that drain towards the dural venous sinuses (Figure 7).

The most prominent of these sinuses is the SSS which is located in the sagittal plane under the midline of the cerebral vault. It has a triangular section that augments from anterior to posterior (44-46). From the SSS, blood flows caudally towards the confluence of sinuses, where the SSS joins the inferior sagittal sinus that primarily drains the deep venous system. From the confluence, two transverse sinuses originate that travel laterally and inferiorly. Before leaving the skull, the sinuses describe an S-shape, called the



Figure 7. Anatomy of the cortical veins and dural venous sinuses

The cortical veins enter the SSS under individual angles. The SSS runs towards the confluence where it is joined by the inferior sagittal sinus and bifurcates to give rise to the transverse sinuses. These run laterally towards the sigmoid sinuses and the internal jugular veins. Reproduced from (6) with permission.

sigmoid sinuses. The sigmoid sinuses drain in the internal jugular veins that finally deliver the blood to the superior caval vein and right atrium of the heart.

Cortical vein - dural venous sinus junction

The cortical veins drain in the SSS under individual angles. The angles shift from cranially to caudally. At the cranial side of the SSS, the veins drain in the direction of the blood flow, in the middle of the SSS perpendicular to the blood flow, and in the caudal part against the direction of the blood flow (Figure 8) (44-46).



Figure 8. Angle between cerebral veins and the SSS

Left, at the cranial side of the SSS, the veins drain in the direction of the blood flow; middle, in the middle of the SSS the veins drain perpendicular to the blood flow; right, in the caudal part of the SSS the veins drain against the direction of the blood flow

This is the result of brain development. In the fetal brain, the cerebral veins run from the Sylvian fissure upwards to the SSS, which they join under a straight angle (90 °). However during the further development of the central nervous system, the frontal pole is moved anteriorly and the rest of the brain posteriorly, while the entry of the veins in the SSS remains fixed (46).

The thin walled cortical veins are surrounded by CSF and subjected to the ICP. Whenever the transmural pressure (pressure inside the vein – pressure outside the vein) becomes negative, the vein collapses (47, 48). This happens at the junction with the SSS (Figure 9) (48).



Figure 9. Volume changes of the cerebral veins in response to ICP or Psss alterations

As Psss < ICP in physiological conditions, and as the thin walled cortical veins collapse when the transmural pressure is negative, these veins are partly collapsed in physiological situations. The combination of resistance and flow through the collapsed vessel results in a pressure gradient over the segment. Therefore, the transmural pressure becomes positive in the more proximal part of the vein. Proximal to this point, the vein will remain open. When volume is added to the intracranial compartment, the ICP rises and venous blood is 'squeezed' out of the cerebral veins, reducing the blood volume and lowering the ICP again. When the Psss increases, the cerebral veins dilate, increasing the intracranial volume and thus the ICP. The pressure in the SSS, that is embedded within the stiff dura mater, is lower than the ICP. By consequence, the transmural pressure in the most distal part of the cortical veins will be negative, causing these veins to collapse (47, 48). The combination of resistance and flow through the collapsed vessels, results in a pressure gradient over the segments. Therefore, the transmural pressure becomes zero or slightly positive in the more proximal part of the veins. The veins will remain open proximal to this point (47, 48).

Intracranial pressure

The normal ICP is the result of CSF formation, the total resistance of CSF circulation and absorption and the pressure in the dural venous sinuses. It can be calculated by Davson's equation (49):

 $ICP = I_f x R_o + P_{sss}$

I_f, formation rate of CSF (ml/min); Ro, resistance to circulation and absorption of CSF (mmHg/ml/min); Psss, pressure in the SSS (mmHg)

The upper limit of normal ICP in adults and older children is considered to be 15 to 20 mm Hg, although the usual range is 5 to 10 mm Hg (49).

In an adult human being, approximately 87 % of the volume of the intracranial space, typically 1500 ml, is occupied by the brain, 9 % by CSF and 4 % by blood (50). To protect the brain from physical injury, the intracranial elements are encased in a rigid structure, the skull. The intracranial elements contain mainly water and are considered to be incompressible. By consequence, any change in volume of one of the three intracranial components (blood, brain, CSF) or the addition of a pathological element (hematoma, tumor, ...) must occur at

the expense of the other two, if ICP is to be maintained. This relation is referred to as the Monro-Kellie doctrine (49).

V_{blood} + V_{CSF} + V_{brain} (+ V_{other}) = V_{intracranial space} = constant

V, volume

A sudden increase in volume can be compensated by displacement of cranial CSF to the spinal compartment (distension of the spinal dural sac) and/or by drainage of venous blood to the dural venous sinuses (Figure 9Figure 9). Due to such mechanisms, the intracranial system has some compliance. This is reflected in the characteristic pressure-volume curve, that is hyperbolic in healthy adults (Figure 10) (49).

Along the flat portion of the curve, an increase in volume will affect the ICP only minimally because compensatory mechanisms can effectively keep the ICP within normal range. This part of the curve is called the 'period of spatial compensation'. As more volume is added, the compliance progressively lessens; this portion is called the 'period of spatial decompensation' (49). For ICP values over 50 mm Hg, and as it approaches the mean arterial pressure ('critical ICP'), the curve tends to flatten again; thus, the complete curve is not hyperbolic but rather sigmoid (49).

It is important to note that even the physiologic ICP is far from static; it rather constitutes a dynamic equilibrium. This is reflected by the ICP waveform not being flat, but pulsatile (Figure 11). The baseline, or average, level is commonly referred to as the ICP, whereas rhythmic components superimposed on this level are associated with cardiac and respiratory activity. 2 General introduction



Figure 10. Intracranial pressure-volume curve.

The relation of the ICP (y-axis) to the intracranial volume (x-axis) follows a sigmoid curve, that has three zones: a flat zone, expressing good compensatory reserve (period of spatial compensation; 1), an exponential zone, depicting poor compensatory reserve (period of spatial decompensation; 2), and a flat zone again, seen at very high ICP values (above the "critical" ICP) depicting derangement of normal cerebrovascular responses. The intracranial blood volume varies during the cardiac cycle resulting in a pulsatile intracranial pressure wave. In the first zone, the pulse amplitude of ICP is low and does not depend on the mean ICP value. The pulse amplitude increases linearly with the mean ICP in the zone of poor compensatory reserve. In the third zone, the pulse amplitude starts to decrease when the ICP is rising. Reproduced with modifications from (49), with permission. Cardiac and respiratory activity creates pulsatile components by cyclical changes in cerebral blood volume (49).

During the heart cycle, left ventricular contraction causes an arterial pulse, that results in a sudden increase in the cerebral arterial inflow. Due to vascular resistance, the arterial inflow is not directly compensated by venous outflow and the total intracranial volume and thus the ICP will rise transiently (49, 51). As in the extra-cranial vasculature, the arterial pulse is damped by the resistance and compliance of the arterioles and the capillary flow is nearly pulseless (52). Although a pulseless flow is delivered to the veins, the intracranial cortical veins do pulsate. This is due to the transmittance of the arterial pulse, through CSF and brain, to the thin walled cerebral veins, resulting in a pulsatile venous compression and venous outflow (53-55). The cyclic alteration in venous outflow towards the venous sinuses results in a pulsatile flow in the SSS (53).

The respiratory contribution to the ICP waveform is the result of fluctuations in cerebral venous outflow during the respiratory cycle, generated by pressure changes in the thoracic cavity. During inspiration there is a negative intrathoracic pressure that increases the pressure gradient between the cerebral veins and the superior caval vein, therefore driving cerebral venous return, with a concomitant drop in cerebral blood volume and ICP (49).

A sudden rise in thoracic pressure (Valsalva maneuver) is transmitted through the jugular veins and dural venous sinuses towards the cortical veins. These veins will dilate in response to the increased transmural pressure, thereby increasing the intracranial volume and ICP (49).



Figure 11. ICP waveform

Upper: the rhythmic components of the ICP waveform associated with cardiac and respiratory activity.

Lower: detail of the ICP waveform originating from the cardiac cycle. Several small components can be seen, the most constant of which are the percussion wave (P1), the tidal wave (P2), and the dicrotic wave (P3). The percussion wave, the most constant in amplitude, derives from pulsations in large intracranial arteries. The tidal wave has a more variable shape and is thought to arise from brain elastance. The tidal wave and the dicrotic wave are separated by the dicrotic notch, which corresponds to the dicrotic notch in the arterial pulse waveform. Reproduced with modifications from (57) with permission.

This results in a fixed relation between the pressure in the dural venous sinuses and the ICP: in physiological circumstances the ICP is 1.6 times higher than the Psss (48, 56).

Hydrocephalus

Definition

Hydrocephalus, the accumulation of CSF in the brain (Figure 12), has been recognized as a clinical entity since the days of Hippocrates. Surgical treatment strategies however were only developed after Walter Dandy almost singlehanded established the true pathology between 1913 and 1929 (58). At present, it continues to be one of the most common neurosurgical conditions, both in children and adults (59). The incidence of congenital hydrocephalus is 0.82-1.1 per 1,000 live births (60-62). The overall incidence of acquired hydrocephalus is not well documented. Studies typically address certain types or specific causes. The incidence of hydrocephalus after community-acquired meningitis is around 5% (63), after severe head trauma 0.7% (64) and after subarachnoid hemorrhage around 20% (65). The incidence of normal pressure hydrocephalus (NPH) is 0.2%. It increases to 5.9% in the population aged 80 years and older (66). Although hydrocephalus is common, there is still no generally recognized definition of the condition. We prefer the definition proposed by Rekate: "Hydrocephalus is an active distension of the ventricular system of the brain resulting from inadequate passage of CSF from its point of production within the cerebral ventricles to its point of absorption into the systemic circulation" (67). Note that this definition excludes passive enlargement of the ventricles due to cerebral atrophy or due to other causes (68). Theoretically, one should add a distinct form of hydrocephalus, without

ventricular dilatation, to the definition. If the obstruction of the CSF flow is distal, near (or in) the SSS, CSF will accumulate under pressure outside as well as inside the brain. In this situation, no pressure difference between the intraventricular and the peripheral subarachnoid space will develop and the ventricles will not enlarge at all or only slightly (68).



Figure 12. Appearance of hydrocephalus on magnetic resonance imaging (MRI)

T2 axial MRI images at the level of the interventricular foramen of Monro. Left: normal ventricles.

Right: marked dilatation of the ventricles in a patient with hydrocephalus.

Etiology

Hydrocephalus may develop at any age due a variety of etiologies. The most frequent causes are subarachnoid or intraventricular hemorrhage (24%), myelomeningocele (21%) and brain tumors (9%). Less frequent causes are (peri)aqueductal stenosis, trauma, and central nervous system infection (68).

Hydrocephalus can be categorized according to where, along the CSF pathway, the obstruction occurs (Table 1) (67).

Site of obstruction	Pathology	Treatment
None	Choroid plexus papilloma	Removal
Foramen of Monro	Tumor, congenital anomaly,	Tumor removal,
	post shunt ventricular	septostomy, VP or VA
	asymmetry	shunt
Aqueduct of Sylvius	Congenital lesion, tumor,	ETV, VP or VA shunt
	secondary to extraventricular	
	obstruction	
Outlets of fourth	Chronic meningitis, Chiari II	ETV, VP or VA shunt
ventricle	malformation	
Basal cisterns	Meningitis, post subarachnoid	ETV, VP or VA shunt
	hemorrhage	
Arachnoid	Hemorrhage or infection	VP or VA shunt
granulations		
Venous outflow	Skull base anomalies,	VP or VA shunt,
	congenital heart disease	treatment of vascular
		anomaly if possible

Table 1. Classification of hydrocephalus, modified from (67) with permission

Signs and symptoms

Hydrocephalus gives rise to various clinical syndromes depending on the age of the patient and on how fast the pathology develops (68).

In the newborn, hydrocephalus is objectified by progressive ventricular enlargement observed by sequential transfontanellar ultrasound. If hydrocephalus develops before fusion of the cranial sutures, this is before the age of 3, it causes enlargement of the head. It can be objectified by a deviation of the head circumference from the growth curve (usually a deviation of 2 standard deviations from the mean is being used as cutoff) and by tense anterior and posterior fontanels. The hydrocephalic infant is irritable, feeds poorly, and may vomit frequently. With continued CSF accumulation, lethargy develops and the infant appears faint, uninterested in its surroundings and unable to sustain activity. Later the "setting-sun sign" develops. This paralysis of upward gaze (Parinaud syndrome) is due to compression on the mesencephalic tegmentum. If still untreated, the condition may evolve to coma and death (68).

In older patients, the skull is closed and the accumulation of CSF will directly increase the ICP. Depending on the residual absorption rate of CSF the condition may develop in an acute or indolent way (68).

Clinical symptoms of acute hydrocephalus include headache, nausea, vomiting, and visual disturbance. If not treated it may progress rapidly to drowsiness, coma and death (68).

When there is still some absorption capacity left, hydrocephalus may develop more insidiously and reach a stable state. At this point, CSF formation equilibrates with absorption and the ICP gradually drops to reach a mildly higher than normal level of 150 to 200 mm H₂O. Although the hydrocephalus has been 'compensated', the patient nonetheless will develop symptoms. The name given to this condition by Adams, Fisher, and Hakim is normal pressure hydrocephalus (NPH) (69). NPH is manifested by a triad of clinical findings. A slowly progressive gait disorder is usually the earliest feature, followed by impairment of the mental function and, later, sphincter incontinence (69).

Treatment

When the CSF flow is obstructed at the level of the third or fourth ventricle's outflow, it can be treated by ETV (Figure 13).



Figure 13. Endoscopic third ventriculostomy

Hydrocephalus caused by obstructed CSF flow out of the third or fourth ventricle (obstructed aqueduct in this example) can be treated by endoscopic third ventriculostomy. During this procedure the floor of the third ventricle is perforated (red arrow). This allows CSF to flow from the third ventricle directly to the interpeduncular cistern, thus bypassing the aqueduct, fourth ventricle and apertures of Luschka or Magendie. Image reproduced with modifications from Version 8.25 from the Textbook OpenStax Anatomy and Physiology, published May 18, 2016 and protected by Creative Commons 4.0.

During this endoscopic procedure a perforation is made in the thinned floor of the third ventricle, allowing movement of CSF out of the blocked ventricular system and into the interpeduncular cistern (43, 67). ETV will not help when the obstruction is located proximal to the third ventricle or distal to the outflow of the fourth ventricle. In those cases, CSF is typically drained to the peritoneal cavity by a VP shunt or to the right atrium of the heart by a VA shunt. These techniques are discussed in detail in Chapter 3 and Chapter 4.

Reference values

Table 2 summarizes some generally accepted reference values that are relevant for the remainder of this dissertation.

Value	Reference
400-600 ml/day	(1)
80-180ml	(1)
12 mmHg/ml/min	(70)
5 – 15 mmHg	(49)
3-4 mmHg	(71)
0,008 ml/Pa	(51)
252 mm	(44, 72)
0 mm, 0 mm	(72, 73)
4 mm, 4mm	(72, 73)
10 mm, 7mm	(72, 73)
11 on each side	(44, 46, 73)
6 - 7.5 mmHg	(74)
150 – 450 ml/min	(72, 75)
150 mm/s	(76)
1103 kg/m3	(72)
3.75 mPa s at 25 °C	(72)
	Value 400-600 ml/day 80-180ml 12 mmHg/ml/min 5 – 15 mmHg 3-4 mmHg 0,008 ml/Pa 252 mm 0 mm, 0 mm 4 mm, 4mm 10 mm, 7mm 11 on each side 6 - 7.5 mmHg 150 – 450 ml/min 150 mm/s 1103 kg/m3 3.75 mPa s at 25 °C

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M Ventriculoperitoneal shunts

Chapter 3. Ventriculoperitoneal shunts

Technique

In 1955 Scott, Wycis, Murtagh and Reyes described the VP shunt (Figure 1). This shunt consists of a silicone tube that is led from one of the lateral ventricles of the brain, out of the skull through a burr hole and then under the skin towards the peritoneal cavity (1).



Figure 1. VP shunts

A VP shunt connects one of the lateral ventricles of the brain with the peritoneal cavity. The shunt system consists of a proximal (ventricular) catheter [1], a one-way differential pressure valve [2] and a distal (peritoneal) catheter [3]. Left: schematic drawing. Right: X-ray of a VP shunt in a baby.

Results

Until now, VP shunts remain the standard treatment for hydrocephalus (2). However, the percentage of shunt failure remains high. The overall 1- and 2year shunt survival rates for all age groups are 50–70% and 47–67%, respectively (3-7).

Factors that influence the shunt failure rate, include patient age and shunting technique (6). Comparison of the results of different clinical series is difficult because of the variation in terms of patient population, surgical technique and shunt hardware.

Most studies that assess shunt survival focus on the pediatric population. Within this population, shunt failure is significantly higher in infants younger than 6 months of age. One study found a 45% shunt failure for such infants, versus a 37% shunt failure in the other age groups (6).

Studies focusing on the adult population report lower shunt failure rates. In this population the rate of shunt failure is about 15 to 30% (8-11).

NPH patients are a specific group that consists of mainly elderly patients. Not all patients who fulfill the criteria for NPH will benefit from a CSF shunt even if it is fully functioning. One should thus differentiate between shunt response and shunt survival. Shunt response is around 85% after 1 year and 75% after 6 years (12), while shunt survival is around 80% (13).

Shunt failure rates are particularly high in the first 6 months after implantation, followed by persistent but lower failure rates in the 2 years thereafter. The early (within 6 months) failures result from both shunt infection and mechanical failure (3, 14, 15).

Shunt infection may be caused during surgery or be due to local or hematological spreading of another infection. The infection rate drops from 8.6 % to 5.5 % when shunt catheters impregnated with antibiotics are used (16).

Mechanical failure includes obstruction, disconnection and retraction of the shunt system. The latter two are especially caused by growth of the – young – patient (15).

Obstruction may occur in any part of the shunt system (proximal catheter, valve, distal catheter) with aspiration of choroid plexus into the proximal catheter being the most common cause of shunt failure in general (15).

Another, particularly important cause of shunt failure is siphoning (6, 14, 17, 18). Because of its importance, siphoning is discussed in more detail below.

Siphoning

When a shunt patient is sitting or standing, the CSF column within the distal (peritoneal) catheter exerts suction through gravity (Figure 2) (19, 20), leading to shunt-related intracranial hypotension and aspiration of choroid plexus into the proximal catheter (6, 14, 17, 18). Intracranial hypotension causes headaches, nausea, vomiting and even subdural hematomas while aspiration of choroid plexus is a major cause of shunt obstruction (6, 14, 18).

Chronic excessive drainage of CSF may also cause a slit-ventricle syndrome (6, 14, 18, 21).

'Slit' or collapsed ventricles are typically a manifestation of chronic overdrainage. Not all patients have symptoms, but it is generally agreed that

this state increases the risk for ventricular shunt obstruction. The apposition of the ventricular catheter to the ventricular wall increases the chance of ingrowth of ependymal cells or choroid plexus (21).



Figure 2. Siphoning of VP shunts

Left: schematic drawing of a VP shunt. When the patient is sitting or standing, the highest point of the CSF compartment is situated above the tip of the peritoneal catheter. Right: when two buckets are filled with liquid and connected with a tube, the liquid will flow because of gravity, from the bucket with the higher fluid level into the bucket with the lower level until both levels are equal (20). h: height difference between fluid level at the proximal and distal end of the tube

The adult slit-ventricle syndrome is an ill-defined disorder. We prefer the definition of Rekate (22): "The slit-ventricle syndrome consists of the triad of intermittent headaches lasting 10–30 min, smaller than normal ventricles on imaging studies, and slow refill of shunt-pumping devices." Its incidence is
about 5% of the non-NPH patients (23). Although relatively few in number, these patients represent a disproportionate amount of clinical effort expended, with frequent emergency department visits and requests for office visits (21). The syndrome occurs more commonly in patients who have been shunted for many years, either as an adult or in childhood. Additionally, it is suggested that a significant proportion of patients with adult slit-ventricle syndrome previously had unrecognized non-communicating hydrocephalus. Common symptoms of adult slit-ventricle syndrome include intermittent headaches that become more frequent and intense over time (21). The etiology of these intermittent headaches has been unclear but may be related to periods of insufficient CSF drainage. In addition, collapse of the ventricular system lowers intracranial compliance. According to the law of Laplace, relatively high pressure is needed to expand the collapsed ventricles (like blowing a balloon, the first blows are the hardest). Thus, when the ventricular catheter is temporarily obstructed by the ventricular wall and/or choroid plexus of the collapsed ventricle, the pressure in the ventricle has to become quite high to dilate the ventricle and free the catheter. At shunt revision, the typical intraoperative finding is near-total, but not complete, obstruction of the ventricular catheter. Therefore, the slit-ventricle syndrome is actually an underdrainage syndrome created by a preceding period of overdrainage (21).

Valves and medical devices that counteract siphoning

Up to 70% of all shunt patients will develop symptoms of excessive CSF drainage when only a standard low resistance valve is used (17). This led to the development of various medical devices meant to counteract siphoning (18). These devices include: differential pressure valves, flow regulating

devices, siphon control devices and gravitational valves. Basically, all these devices can be classified in two groups: the differential pressure valves and the flow regulating valves (24). In clinical practice, programmable differential pressure valves are often used alone or in combination with a gravitational or flow regulating valve.

Differential pressure valves

The standard valves (Figure 3) operate as differential pressure devices allowing unidirectional flow (25). These devices only open when the pressure difference across the valve surpasses a certain threshold ('opening pressure'). There are a number of different mechanisms, including slit valves, diaphragm valves, miter valves, and metallic spring ball valves (26). However, all of these valves will essentially produce the same pressure/flow curve (Figure). Once the valves open and as long as the differential pressure is present, they provide very little resistance to flow. Depending on the posture of the patient, siphoning will thus still occur (24).

Originally, the standard valves were supplied as low-, medium-, and highpressure valves. At present neurosurgeons are in favor of using – expensive – programmable valves. These allow the surgeon to noninvasively adjust the opening pressure in accordance with clinical or radiological findings (18, 27-29).



Figure 3. Standard differential pressure valve

Left: schematic image of a spring ball valve as an illustration of a standard differential pressure valve. The valve is either closed (upper image) or open (lower image). The thickness of the arrow relates to the magnitude of the intracranial pressure. Right: pressure flow characteristics. Once the valve is open (opening pressure in this image is 100 mm H₂O), the resistance to flow is very low and large flow rates are possible. When the patient assumes an upright position, the valve may open due to the siphoning effect and excessive drainage of CSF may occur.

A gravitational valve (Figure 4) consists of a ball that in a vertical position – by gravity – rolls into a conical socket, thereby increasing the differential pressure over the valve. When the patient is in the horizontal position, the ball leaves the socket, resulting in a lower differential opening pressure. A drawback of gravitational valves is that these have to be implanted (and stay in this position) with their longitudinal axis exactly along the vertical axis of the patient, both in the coronal and sagittal planes, to have the desired effect (20).



Figure 4. Gravitational valve

Left: flow characteristics of a shunt system containing a standard differential pressure valve with an opening pressure of 80 mm H₂O and a gravitational valve (0 – 200 mm H₂O). The flow is shown in function of the degrees of verticalization. When the ICP is low, the flow will only gradually increase when the patient verticalizes, however excessive drainage may still develop. When the ICP is high, the flow rate will decrease during the first 30 degrees of verticalization. This is due to a fast decrease in ICP following the rapid evacuation of CSF and an increase in the differential pressure of the valve due to gravity. Beyond 30 degrees of verticalization, the siphon effect becomes dominant and the flow rate increases again (30). Image reprinted with modifications from (30) with permission. Right: when the patient is supine the balls roll away from the socket, allowing for undisturbed CSF flow. In this position the differential pressure needed to initiate flow over the device is minimal (almost zero). When the patient verticalizes, the balls roll into the socket through gravity, augmenting the opening pressure of the device.

Flow regulating valves

Various flow regulating devices exist.

The 'anti-siphon devices' or 'siphon controlling devices' consist of a flexible membrane that closes the CSF drainage pathway – due to the atmospheric pressure – when siphoning starts to occur (Figure 5) (31). The device reduces the tendency to excessive drainage in the upright position; however, the pressure required to maintain the same flow rate actually only slightly increases (Figure 5) (24). By consequence, the anti-siphon device acts functionally more like a gravitational valve than as a flow regulating valve.



Figure 5. Anti-siphon device

Left: an anti-siphon device containing a flexible membrane [M] overlying a socket [S] Middle: when the transmural pressure (pressure in the valve – atmospheric pressure) becomes negative, the membrane is pressed against a central socket, hampering the CSF flow.

Right: pressure flow characteristics. When the membrane is pressed against the socket, the differential pressure necessary to cause a certain flow is only slightly higher than when the membrane is in a neutral position.

A drawback of anti-siphon devices is that, to function properly, the diaphragm must be freely mobile and the pressure outside the membrane must be atmospheric (32). This may be hampered due to scar tissue around the valve.

The position of the siphon controlling device along the distal column of fluid is also important (33). The lower the device is placed along the shunt path, relative to the ventricles, the greater the negative pressure that may still occur in the ventricles. If the device is placed at the level of the abdomen, the siphon control portion would never be active and the valve would function exactly as a differential pressure valve (24).

The Sigma valve (Integra Plainsboro, New Jersey, United States) (Figure 6) has quite different flow/pressure characteristics from those of a standard valve (34). A flexible diaphragm moves along a piston of variable diameter, basically resulting in three pressure/flow stages. In Stage 1, the valve functions in the same way as a standard differential pressure diaphragm valve, with a certain opening pressure and a low resistance to flow. In Stage 2, as the differential pressure increases, the diaphragm descends along the piston, with a progressively larger diameter. This reduces the flow orifice and significantly increases the resistance to flow. Consequently, the flow rate will only slightly increase in response to increased differential pressure, which prevents siphoning. Stage 3 is a high-pressure `safety release mechanism'. When the ICP reaches a high level, of around 400 mm H₂O, the diaphragm moves beyond the end of the piston, and the resistance to flow becomes very low. The transition between the above stages is gradual, so the pressure curve is sigmoid in shape (hence the name 'Sigma valve') (20, 24).



Figure 6. Sigma valve

When the patient is in horizontal position and the differential pressure is low, the resistance to flow is also low [stage 1]. When the patient verticalizes and the differential pressure increases, the membrane is pushed to a wider part of the central piston, increasing the resistance to flow [stage 2]. When the intracranial pressure becomes very high (e.g. Valsalva maneuver), the membrane will surpass the piston and the resistance to flow will substantially decrease [safety release, stage 3].

The Siphon Guard (DePuy Synthes, Raynham, Massachusetts, United States) (Figure 7) is a valve with a high and a low resistance pathway. When the flow increases beyond 0.7-1.8 ml/min, the low resistance pathway closes and the high resistance pathway opens. Although the latter pathway limits the flow rate, it still may increase beyond 20 ml/hour. As this is higher than the CSF production rate of most patients, intracranial hypotension may still occur (20).

Switching from the high- back to the low resistance pathway occurs when the differential pressure decreases below a certain threshold (4 to 6 mmHg). A possible drawback concerns locking of the device in the high resistance state:

due to the high hydrodynamic resistance in the vertical position, the differential pressure may remain higher than 6 mmHg. Hence the device will not switch back to the low resistance state when the patient moves to a horizontal position. In that case, the device may cause underdrainage (35).



Figure 7. Siphon Guard

Right: when the patient is supine and the flow is low, the ball moves out of the socket, leaving the low resistance pathway open. When the patient verticalizes the ball moves into the socket due to the increased flow rate. In this position the low resistance pathway is closed, forcing the CSF to flow through the narrow channel which offers high resistance.

Left: pressure flow curve. An increase in differential pressure is initially followed by an increased flow rate [1]. The increased flow rate moves the ball into the socket, thereby closing the low resistance pathway which causes the flow rate to drop. Further increase in differential pressure results in a more gradual increase in flow rate [2].

Clinical results

The development of new valve designs has had only a limited effect on the clinical results so far (3, 36).

The Sigma valve is the only device to have been reported to present a 1 year failure rate lower than that of standard valves (20 % versus 40 % in the first year) (37). The lower failure rate is due to the lower incidence of too small ventricles (24). Only 8.2 % of the patients with a Sigma valve developed slit-ventricles, compared to 30.9 % of the patients with a standard valve (37). The larger ventricles may prevent plugging of the catheter holes due to coaptation of the ependyma and plexus with the ventricular catheter. However, these promising results from uncontrolled series were not confirmed by more recent data stemming from a randomized controlled trial. This trial showed no overall beneficial effect of any valve on overall shunt survival rates. Although the use of a Sigma valve resulted in fewer ventricular catheter obstructions, more mechanical failures occurred at other sites along the Sigma shunt, including the valve (3).

Clinical series also show that, even with the use of (a combination of) the most advanced valves and anti-siphon devices, symptomatic overdrainage still occurs in 5-10% of all shunt patients (17, 38-40). This group of patients is seriously incapacitated by symptoms of disturbed ICP and is typically subjected to a high number of shunt revisions (21).

The high cost of programmable valves and anti-syphon devices, combined with the reported incidence of shunt failure, causes the economic impact of hydrocephalus treatments to be high (41). In the United States, surgical revisions of VP and VA shunts are a billion-dollar-a-year cost (41).

In conclusion, further research to optimize hydrocephalus treatments is still needed, as physiological CSF dynamics are not restored in a satisfactory way by the current shunting techniques (3, 20, 42).

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Chapter 4. Ventriculovenous shunts

Ventriculovenous (VV) shunts draining CSF to the venous system may be an alternative to VP shunts. The most interesting techniques, VA and VS shunting, are discussed below.

Ventriculoatrial shunts

In 1952 Nulsen and Spitz described the VA shunt. At present, this shunt consists of a silicone tube that is led from one of the lateral ventricles of the brain, out of the skull through a burr hole and then under the skin toward the right auricle of the heart. An essential part of the shunt system is a one-way (Holter) valve (1).

The technique has some advantages over VP shunts. First, verification of the correct placement of the distal catheter is possible intraoperatively (2). Second, the right atrium provides a consistent low pressure outlet: an advantage that gains progressively more importance, as obesity, that may cause high abdominal pressure which may result in dysfunction of VP shunts, becomes a global epidemic (2, 3).

VA shunts have similar effectiveness and complication rates as VP shunts (2, 4-6). However, the nature and severity of the complications are different (2). Several studies have reported that VA shunts suffer from thrombotic complications that include thrombus formation at the distal catheter as well as jugular or caval vein thrombosis (4, 7). Thrombus formation may result in

shunt failure due to obstruction of the distal catheter (30-50 % of the revisions of VA shunts are due to distal catheter obstruction) but may also cause thromboembolic complications. Thromboembolic complications may occur early after shunt insertion (8). These complications manifest only seldom clinically (0,3 % of patients), whereas necropsy series suggest an incidence up to 60 % (9). However, it may also cause late complications that occur typically after 10-20 years (2, 8-10). The most important late complication is pulmonary hypertension (8, 10). Although the process of micro-embolization appears to be intermittent and mild, patients with VA shunts often develop severe pulmonary hypertension, that, once diagnosed, is almost universally fatal (8-10) . The seriousness of this complication has urged surgeons to routinely screen patients with a VA shunt for pulmonary hypertension with echocardiography and pulmonary function tests. If this screening is performed, pulmonary hypertension is found in 8% of the VA shunt patients (10).

The high incidence of thrombotic complications in patients with VA shunts is not explained on the basis of a foreign body in the right atrium alone, as patients with for example pacemaker leads do not suffer from equivalent rates of thromboembolism (9). The factors that predispose VA shunts to thrombotic complications are not clear.

Thrombotic complications are the main reasons that VA shunts have fallen in disuse in such a way that, at present, most neurosurgeons reserve VA shunts to patients in whom VP shunts are contra-indicated or not successful (11).

It should be noted that VA shunts, like VP shunts, suffer from siphoning.

Ventriculosinus shunts

The many frustrating complications of VA shunts and VP shunts, their incapacitating impact on the life of patients and their high financial cost urged neurosurgeons to search for a better, physiologically adapted treatment for hydrocephalus. Pioneers such as Gartner (cited in (12)) and Ingraham (13) were the first to drain CSF to its natural resorption site, the dural venous sinuses. However, they abolished the technique due to reflux of blood and obstruction of the distal catheter. Later, after the introduction of one-way valves and silicone catheters, new attempts to VS shunting were reported by Sharkey (14), Hash (15) and Wen (16). Finally, El-Shafei and his son were the ones to understand 1) the role of the collapsible IJV in preventing siphoning and 2) the advantages of introducing the sinus catheter against the blood flow ('retrograde') to prevent thrombotic shunt obstruction. Their extensive experimental work led to the development of the retrograde ventriculosinus (RVS) shunt (6, 17-21). This shunt was evaluated in several retrospective clinical series (22-24). Similar efforts were realized by Børgesen, Gjerris and Eklund leading to the development of the SinuShunt[®] (SinuShunt A/S, Glostrup, Denmark) (25-27).

This chapter gives a comprehensive overview of the experimental and clinical work regarding VS shunting. The theoretical advantages and promising clinical results of the RVS shunt inspired us to conduct a monocentric prospective clinical trial at our department. The methodology and results of this trial are discussed in manuscript 1 that is included at the end of this chapter.

Advantages

Draining CSF to the natural resorption site, the SSS, theoretically reduces the risk of shunt failure in several ways (19, 20). A first reason is that excessive drainage is prevented by preservation of the natural, self-regulating anti-siphon effect of the IJV (19). Second, the shunt system is short, less complex and confined to the skull, which minimizes the risk of mechanical failure and infection. As the VS shunt is hardly affected by growth of the patient, it is especially suited for infants.

Anti-siphon effect of the IJV

When CSF is reabsorbed to the SSS, blood and drained CSF form a fluid column between the SSS and the right atrium of the heart. In a sitting or standing position, it could be expected that the difference in height between the proximal and distal end of this fluid column would cause siphoning and intracranial hypotension, in analogy to the previous discussed liquor shunts. However, in physiological conditions, siphoning is counteracted and the ICP is not permitted to drop excessively (19).

El-Shafei was the first to identify that the IJV might act as a physiological antisiphon device (19). He based this hypothesis on previous literature on venous hydrodynamics (28). Veins have a soft, thin wall that is unable to withstand even small negative transmural pressures (transmural pressure is defined as the pressure inside the vessel minus the ambient pressure). The pressure in larger veins fluctuates around the atmospheric pressure and situations in which the transmural pressure becomes negative are not uncommon. In these situations the veins collapse, which contributes to the regulation of the venous flow (28).



Figure 1. In vitro set-up

The IJV [1, dark blue] of a human cadaver was attached in the horizontal position to an iron bar [2]. Proximally the vein was connected to a flow meter [3] and a constant head tank [4], distally to a rigid tube [5]. Pressure transducers were connected upstream and downstream to the IJV [A and B respectively]. Also, the ambient atmospheric pressure was measured [C]. The height of the constant head tank was adjusted until the flow through the horizontally positioned IJV equalized 400 ml/min. The distal end of the tube was lowered as to adjust the downstream pressure to 1.5 cm H₂O. The IJV was then rotated in such a way that the proximal end remained fixed while the distal end progressively was lowered. Image reproduced with modifications from (19) with permission To substantiate his hypothesis, El-Shafei performed an in-vitro experiment. The set-up is shown in Figure 1. A constant head tank assured a flow rate of 400 ml/min through the horizontally positioned IJV of a human cadaver.

The vein was then progressively verticalized by lowering the distal end while keeping the proximal end fixed. During this maneuver, the flow rate initially increased and the proximal pressure decreased. By consequence, the transmural pressure decreased and the transection of the vein, that was circular at the start, changed to oval and further to biconcave (Figure 2).

Figure 2. Transection of the IJV in function of the transmural pressure

The transection of the IJV is shown in function of the transmural pressure (mm H₂O). As the pressure decreases the section becomes oval and finally biconcave. The collapsed vein segment exerts a high resistance to flow.

Image reproduced with modifications from (19) with permission



Collapse started at the proximal end and progressed downward as the rotation angle increased. Due to the progressive collapse, the resistance to flow in the vessel increased causing the flow rate and the proximal pressure to stabilize from 40° rotation onwards. In this stable situation the flow rate was 400 ml/min and the proximal pressure 2.1 cm H_2O . Decreasing the downstream pressure did not affect the flow rate nor the proximal pressure (19).

The results of this in vitro study endorse the hypothesis of El-Shafei that the IJV acts as a natural, self-regulating anti-siphon device. It counteracts gravity and regulates the pressure in the dural venous sinuses and consequently the ICP within narrow limits, regardless of the position of the patient (19).

As the ventriculosinus shunt does not bypass the jugular vein, it – theoretically – restores a physiological ICP. In the absence of siphoning, the drainage of CSF is expected to be constant without moments of active suction (18). This prevents aspiration of the ventricular wall or choroid plexus into the proximal catheter and thus avoids the most frequent cause of proximal shunt obstruction (29).

It also prevents the development of slit-ventricles and might be a (or the only) satisfying solution for the 5-10% of shunt patients who experience intracranial hypotension despite the usage of resistance valves and anti-siphon devices (30-33).

Besides being simple and physiological, ventriculosinus shunting is also affordable. The superfluity of programmable valves and anti-siphon devices reduces the cost of the shunt system from around \in 1700 - 2200 (e.g. programmable valve, with or without anti-siphon device, antibiotic impregnated silicone catheter system) to around \in 900 (e.g. fixed pressure valve, same catheter system). Postoperatively, there is no need for adjustments of the valve pressure. This results in an additional saving of

around \notin 100 per patient (mean number of 1.5 adjustments per patient with a VP- or VA shunt (34), counting visits to an outpatient clinic (\notin 25) and skull x-rays (\notin 45)).

Surgical technique

4 Ventriculovenous shunts

Based on experimental and clinical experience, the cited authors have modified the technique. This led to the two most important strategies that exist at present: the RVS shunt or El-Shafei shunt (23) and the commercially available SinuShunt (SinuShunt A/S, Glostrup, Denmark) (26).



Figure 3. 'Retrograde' position of the shunt and definition of impact and wake side

The tip of the shunt is directed against the blood flow or in a 'retrograde' fashion. The solid black arrows represent the direction of the blood flow in the vessel (SSS), whereas the white arrows represent the drainage of CSF. The impact and wake sides of the shunt are defined relative to the direction of the blood flow.

The El-Shafei shunt is characterized by the retrograde - with the tip aimed against the blood flow – implantation of the sinus catheter (Figure 3). In this position the ICP is kept above the static pressure in the superior sagittal sinus (Psss) by the blood flow that 'hits' the draining CSF column. This is called the 'impact effect' by El-Shafei (35). According to El-Shafei, the impact effect

assures that the ICP remains higher than the Psss regardless of the patient's position, thus preventing backflow of blood to the shunt at all times (20). The experimental work concerning the hydrodynamics of the RVS shunt is discussed in detail in chapter 6.

The retrograde position is believed to have, besides the impact effect, two other advantages.

First, stream lines of the blood flow will hit the shunt's impact zone (facing the blood stream), deflect and move on. However, in the wake zone (the 180° opposite site, facing away from the incoming flow), some of the running fluid separates from the stream lines and stagnates. Stagnation of blood promotes clot formation (Figure 4) (24). Second, in the retrograde position, drained CSF is deflected to flow over the shunt's surface, forming a constantly renewing CSF sleeve (Figure 5). According to El-Shafei, this sleeve discourages clot formation (20).

Besides the retrograde implantation, El-Shafei stresses the importance of a strict watertight junction between the ventricle catheter and the dura mater. If CSF leaks through this connection, the ICP drops below the Psss and, when no valve is present, blood will regurgitate to the shunt and the ventricular system. In case a valve is present, leakage of CSF will cause the drainage to the SSS to become intermittent, which promotes distal shunt obstruction (6). When no watertight junction could be obtained, El-Shafei did not proceed with the RVS shunt implantation. This was the case in 8.5% (10/119) of his patients. An interesting modification of the technique to implant the sinus catheter was published by Samadani et al. (36).



Figure 4. Hydrodynamic principles of flow past a cylindrical object

Blood hitting an object placed in the bloodstream will deflect to wrap around the object. Downstream of the object, blood will detach from the surface. At this point it will be dragged towards the wake side which causes slow and non-laminar flow (upper image). If the shunt is positioned retrograde, streamlines of the blood flow will hit the shunt tip, deflect and move on (middle image). However, when the shunt is positioned anterograde, the tip is situated in the wake zone where the flow is slow and non-laminar. Note that this schematic representation is generic. The actual shape of the streamlines is entirely dependent on the velocity of the flow. A realistic image, based on CFD (Computational Fluid Dynamics), is provided in Chapter 6 (Figure 7).

The authors used the Seldinger technique to introduce the sinus catheter. The Seldinger technique consists of several steps: puncturing the SSS with a

needle, advancing a guide wire through the needle into the SSS, removing the needle, dilating the opening in the sinus with appropriate dilatators, introducing the sinus catheter over the guidewire into the sinus and removing the guidewire. This technique theoretically decreases the risk of bleeding and air embolism (36).

The SinuShunt (Figure 6) was developed by Børgesen (Denmark) (25, 26). The device contains a one-way valve with a built-in resistance tube and is designed to have a total resistance equal to the physiological resistance to CSF absorption (8 mmHg/ml/min) (26). The intravascular catheter is implanted in the direction of the blood flow ('anterograde') in the transverse sinus. Børgesen stresses the importance of a perfect central position of the shunt tip in the sinus. A groove, drilled at the posterior border of the burr hole, serves to guide the drain to the center of the sinus, and to keep it there after closure of the wound (26).



Figure 5. CSF sleeve effect

The white arrows represent the CSF 'sleeve'. This sleeve is formed by CSF draining along the shunt surface due to the blood flow that is oriented in the opposite direction. The solid black arrows represent the direction of the blood flow in the blood vessel. The ventriculosinus shunt has been evaluated in several clinical series (>150 patients in total) (13, 15, 16, 23, 26, 37).

The technique has been proven to be safe and effective, both in pediatric and adult patients, to treat high- and normal pressure hydrocephalus (23, 26, 38, 39). None of these patients developed venous sinus thrombosis, clinically significant air embolism, or excessive intra-operative sinus bleeding (23, 26, 38). Postoperative shunt response was similar to the conventional shunts in terms of immediate improvement of acute hydrocephalus signs and symptoms (23, 26, 38).



Figure 6. The SinuShunt

The device consists of a titanium inlet cone for attaching the ventricular drain [1], a valve mechanism preventing back-flow from the transverse sinus to the shunt or the ventricles [2], a pre-chamber made of silicone rubber for puncture and testing of the performance of the shunt [3], a resistance tube made of titanium and dimensioned to create a resistance to outflow equal to normal values (8 mmHg/ml/min) [4], a housing for the valves and the resistance tube made of silicone rubber, and a silicone rubber drain, diameter 2.1 mm, leading into the transverse sinus [5] (26). Image reproduced from (27) with permission.

In patients with closed craniums, the ventricle size diminished, but not to the same extent as seen following shunting with standard devices (26). In infants with open craniums, the head circumference continued to increase but at a slower rate than before surgery (23).

The shunt survival rates during the follow up period of the most recent clinical series are listed in Table 3.

Table 3. Methodology and shunt survival of the most recent clinical seriesevaluating the VS shunt.

Retro., retrograde or against the direction of the blood flow; Orient., orientation; Antero., anterograde or in the direction of the blood flow; Cent., tip of the shunt stabilized in the center of the sinus by a guiding channel in the skull; TS, transverse sinus; N, number of patients; w, weeks; y, years; m, months; NS, not stated; Diagnosis, type or etiology of hydrocephalus; OC, open cranium; CC, closed cranium; HPH, high pressure hydrocephalus; T, tumor; SAH, subarachnoid hemorrhage; MMC, myelomeningocele; FU, follow up; d, days; Sh. Surv., shunt survival.

Author	Orient.	Sinus	Ν	Age	Diagnosis	FU	Sh. Surv.
El-Shafei	Retro.	SSS	11	6 w – 48 y	OC 66*;	6уЗ	95 %
			9		CC 44*	m	
Børgesen	Antero.	TS	17	NS	NPH 19;	344 d	53 %
Børgesen	Antero.	TS	28		HPH 3; T 7;	145 d	90 %
	Cent.				SAH 11		
Oliveira	Retro.	SSS	5	3 m – 6 m	MMC	1 y	80 %

During surgery, El-Shafei measured the ICP before and after opening the VS shunt in 90 patients. The pressure decreased from $500 \text{ mmH}_2\text{O}$ to $120 \text{ mmH}_2\text{O}$. When the patient was brought in the sitting position, the ICP initially dropped

but stabilized at 40 mmH₂O. When the patient was brought in the recumbent position again, the pressure was restored to 120 mmH₂O (6).

Another study evaluated the ICP in 1 patient using a telemetric sensor (40). The ICP was recorded when the patient had a VA shunt and later after the VA shunt was converted to a VS shunt. The ICP curve during chance of posture from a supine position (0° rotation) to the sitting position (90° rotation) is shown in Figure 7 (40).





We felt inspired by the theoretical advantages and the promising early clinical results of the VS shunt. However, long-term clinical studies are scarce and the RVS shunt, nor the SinuShunt[®] are gaining terrain in the treatment of hydrocephalus. This urged us to perform a monocentric prospective clinical

trial (department of neurosurgery, Ghent University Hospital). The retrograde technique of El-Shafei was withheld as this was the best substantiated method, both clinically and experimentally. The methodology and results of the prospective clinical trial are discussed in Manuscript 1.

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Manuscript 1. Treating hydrocephalus with the retrograde ventriculosinus shunt. Prospective clinical study

E. Baert¹, F. Dewaele¹, <u>J. Vandersteene¹</u>, G. Hallaert¹, J. Okito Kalala¹, D. Van Roost¹

World Neurosurgery, submitted

¹Department of Neurosurgery, Ghent University Hospital, Ghent, Belgium.

Abstract

Since the 1950's, hydrocephalus can be treated with CSF shunts, usually to the peritoneal cavity or to the right cardiac atrium. However, due to their siphoning effect, these shunts lead to non-physiological CSF drainage, with possible co-morbidity and high revision rates. More sophisticated shunt valve systems significantly increase costs and technical complexity and remain unsuccessful in a subgroup of patients. In an attempt to obtain physiological CSF shunting, many neurosurgical pioneers shunted towards the dural sinuses, taking advantage of the physiological anti-siphoning effect of the IJVs. Despite several promising reports, the ventriculosinus shunts did not yet become standard neurosurgical practice. In this mono-centric prospective clinical study, we implanted the retrograde ventriculosinus shunt, as advocated by El-Shafei, in 10 patients. This article reports on our operation technique and longterm outcome, including 4 extra patients in whom this shunt was implanted as a rescue, where all other options failed. Only in 3 patients, functionality of the retrograde ventriculosinus shunt was maintained with more than 6 years follow-up. We remain convinced that ventriculosinus shunting may be a safe technique which warrants physiological drainage of CSF. In our opinion, these

shunts fail because present venous access devices are difficult to implant correctly and are too easily obstructed. After discussing possible causes of the frequent obstruction of present ventriculosinus shunts, a new dural venous access device is presented. An easy to implant and thrombogenic-resistant dural venous access device needs to be developed before ventriculosinus shunting can become general practice.

Introduction

In hydrocephalus (HC) the physiological evacuation of the CSF towards the dural venous sinuses is inhibited, either because of obstruction of its outflow from the cerebral ventricles towards the subarachnoid space ('obstructive' HC), or by limitation of its absorption at the level of the arachnoid villi into the blood stream of the dural venous sinuses ('communicating' HC) (1-5).

The standard treatment of HC with ventriculoperitoneal or ventriculoatrial (VA) shunts has a failure rate of about 50% in the first two years after implantation (6-10). A major cause of shunt failure is over-drainage due to the siphoning effect of the CSF column in the vertically orientated catheter when a patient is in a sitting or standing position. By gravity, this CSF column creates aspiration like a piston falling in a cylinder. This siphoning leads to shunt-related intracranial hypotension and aspiration of the choroid plexus into the ventricular catheter. Intracranial hypotension causes headaches, nausea, vomiting, malaise and may lead to slit-ventricle syndrome and even subdural haematoma. Aspiration of the choroid plexus is a main cause of shunt obstruction. In response, more sophisticated valves were developed, such as valves with programmable resistance, flow-regulating valves and anti-siphon devices. In spite of these, non-physiological CSF drainage and therefore non-physiological ICPs continue to be an issue in 5-10% of the shunted patients.
Moreover, these devices increase the financial cost, technical complexity and vulnerability of CSF shunts.

A ventriculosinus shunt drains CSF to its natural absorption site, the superior sagittal sinus (SSS). Theoretically it reduces the risk of shunt failure in several ways (11, 12). First, excessive drainage is prevented by preservation of the natural, self-regulating anti-siphon effect of the IJV (11). Therefore, there is no need for sophisticated valves or anti-siphon devices. Second, the shunt system is short, less complex and confined to the skull, which minimizes the risk of mechanical failure and infection. Although a promising technique, early attempts were not successful due to thrombotic obstruction of the distal catheter positioned in the dural venous sinus (Gartner (13), Payr (14) and Dandy (1-3) at beginning of 20th century and Sharkey (15), Hash (16) and Wen (17) from 1960's till 1980's). I. El-Shafei claimed that implanting the distal catheter with the tip directed against the blood flow ('retrograde') solves the thrombotic obstruction issue. Subtle hydrodynamic related advantages would prevent regurgitation of blood in the distal catheter and preserve the delicate pressure gradient between the dural venous sinus and the ventricles (12). After extensive experimental and clinical work, El-Shafei evolved from the retrograde ventriculo-jugular to the RVS shunt and reported excellent results in retrospective clinical studies, up to a shunt survival rate of 95% after a mean follow up of over 6 years (18). In collaboration with the department of Hydraulics of Ghent University Civil Engineering, we implemented both a physical and numerical (computerized fluids dynamic) model of the RVS shunt (19). These models supported El-Shafei's experimental work on the hydrodynamic principles of the RVS shunt. Similar efforts were realised by S.E. Børgesen, F. Gjerris and A. Eklund leading to the development of the

SinuShunt[®], with an anterograde orientated dural venous sinus catheter (20-23).

Although inspired by the RVS shunt and the SinuShunt[®], we wondered why, despite the potential advantages and the promising published clinical results, the RVS shunt nor the SinuShunt[®] are implanted on a regular base worldwide. We realized that many neurosurgeons are reluctant to operate on the dural sinus, due to the risk of major haemorrhage, air embolism (AE) or sagittal sinus thrombosis (SST). Interestingly, none of the published clinical reports mentions these complications.

Therefore, we evaluated the RVS shunt in a mono-centric prospective clinical study for the treatment of communicating HC. This report summarizes the operation details and the follow-up of all 10 patients included in the study as well as of the 4 extra patients in whom the RVS shunt was used as a rescue operation.

Materials and methods

Inclusion/exclusion criteria

Approval of Ghent University Hospital's Ethical Committee was obtained to include 'communicating' HC patients during the year 2011 (using an extensive informed consent and a no-fault insurance). Every patient was eligible to be included, without restriction concerning age. Exclusion criteria included: 1) pregnancy, 2) infectious, cardiovascular, haemostatic or severe internal diseases. Inclusion was on voluntary basis.

Surgical technique and materials

Every included patient had a pre-operative computed tomography (CT) and/or magnetic resonance imaging (MRI) of the brain. In some cases,

neuronavigation (NN) was applied (Medtronic, StealthStation[®] Treon[™] AxiEM, Minneapolis, MN, USA). Standard preoperative clinical and serological/clotting examinations were performed.

Surgery was performed under general anaesthesia with tracheal intubation. The semi-sitting supine positioning was used, to retain the venous Psss slightly positive. After shaving, washing and disinfection of the surgical region, proper sterile draping of the operating field and Tegaderm[®] (3M, 2510 Conway Ave, St. Paul, MN, USA) on the scalp were applied to avoid cutaneous contact.

Two semicircular scalp incisions and underlying burr holes were made: 1) a right or left parabregmatic and 2) a midline incision across the sagittal suture in the vertex region (about 10 cm posterior to bregma or about 3 cm anterior to lambda). In most patients, the superior sagittal sinus (SSS) diameter starts to widen posterior to bregma and reaches a large and useful diameter halfway between bregma and lambda, with 3-5 mm width and 6-8 mm height internally. Through the parabregmatic burr hole a ventricular catheter (VC; anti-block right angle VC, Phoenix / Vygon S.A., 5 Rue Adeline, 95440 Ecouen, France), was positioned in the frontal horn of the lateral ventricles. Specific care was taken to minimize CSF spilling:

The dura was perforated with a 2.0-2.5 mm wide round opening, applying monopolar coagulation on the VC's stylet (without the VC); during introduction, the 3 mm diameter VC was stretched on its stylet, narrowing it; once its position in the frontal horn reached, the stretching was released and the catheter re-expanded to its original diameter, creating a 'watertight' joint. If the closure seemed not watertight, a small amount of human fibrin glue was applied.

 The VC was kept blocked once positioned in a frontal horn of the ventricles. Any loss of CSF was compensated by intraventricular injection of an equivalent amount of physiological saline.

A unidirectional valve with 10 mm H₂O resistance (Codman precision Hakim valve, J&J, 325 Paramount Drive, Raynham, MA 02767, USA) was flushed, connected with its proximal end to the VC and positioned between the two incisions in the subgaleal layer. At the bottom of the sagittal suture's burr hole, the roof of the SSS was identified; if necessary the burr hole was widened laterally to have it in its centre. Then, a 3 mm wide and 1 cm long bevelled groove was punched out at the posterior border of the burr hole, in line with the trajectory of the SSS. This groove guided the catheter in the longitudinal direction of the SSS and prevented kinking. At the lateral border of this guiding groove, a 1 mm wide drill hole was made to apply a stabilising polyfilament polyester wire around the sagittal sinus catheter (SSC, Phoenix / Vygon atrial catheter ref A03, pliant tip of 3.0 cm length and 1.3 mm outer diameter). In neonates, infants and toddlers, the skull bone was too thin to create this groove and the SSC was stabilised with stitches through the periosteal layer. Once these steps taken, a longitudinal 4 mm slit incision was made in the roof of the SSS. With a venous hook, the slit incision was opened and lifted to introduce the tip of the SSC into the lumen of the sinus. If no resistance was felt, the pliant tip was fully introduced until the thicker catheter part (outer diameter of 2.5 mm) fitted into the slit incision of the sinus roof. If resistance was experienced (septa within the sinus (16, 24, 25)) the catheter was retracted and reintroduced. In case of persistent resistance, the burr hole was extended and the catheter introduced through a new slit incision in the sinus roof. Catheter patency was checked firstly by aspiration of blood and secondly by infiltration of saline without resistance. A small patch of absorbable

gelatine sponge was applied on top of the catheter's passage through the sinus roof to control possible bleeding. Repetitive flushing of the SSC with saline was performed to prevent blood regurgitation. After having replenished the ventricular volume with saline through the VC, SSC and valve were connected. Wounds were rinsed with 1/10 Isobetadine Dermicum[®]/water solution and closed in separate layers. In all patients the SSC could be properly positioned with an SSS length of about 3 cm, in a retrograde direction.

Postoperative follow up

The postoperative follow up was based both on clinical and radiological examinations:

- For children under the age of 2 years, the clinical examination included head circumference, frontal fontanel tension, eye movement examination, evaluation of factors of wellbeing (eating versus intake refusal or vomiting; active versus passive/apathetic behaviour; visual contact versus absence of visual contact; laughing versus irritability or crying). For older children and adults, complaints of headache, nausea/vomiting, malaise, fatigue were noted. Clinically the Glasgow coma scale, axial stability, visual functions/eye movements and orientation were observed.
- Radiological examinations included XR to control integrity of shunt trajectory and CT scan or MRI scan to control position of VC and SSC, to prove patency of the SSS and to evaluate the ventricular dimensions and signs of transependymal CSF drainage. All patients had pre- and postoperative MRI and/or CT scan. Three patients with obstructed SSC underwent digital subtraction angiography (DSA) of the cerebral veins or

iodine contrast injection through the obstructed SSC under fluoroscopy, to investigate the mechanism of its occlusion.

Results

Table 1: patients included in prospective group (1-10) and in rescue group(11-14)

Age represents the age at the moment of the first RVS shunt operation [abbreviations used: patient (P), sex (S), female (F), male (M), (Hydrocephalus etiology (HC E), myelomeningocele (MMC), complications (C), neonatal sepsis (NNS), congenital (CON), chronic subdural hematoma (CSH), traumatic brain injury (TBI), tumor resection (TR), aneurysmal subarachnoid hemorrhage (ASAH), normal pressure hydrocephalus (NPH), tumor (T), Guidance (Guid) electromagnetic neuronavigation (EM NN), Doppler (Doppl), survival time (ST), retrograde ventriculosinus shunt (RVSS); ventriculoperitoneal shunt (VPS); ventriculoatrial shunt (VAS); obstruction (obstr), reoperation (R)]

Р	S	age	HC E	С	Guid	ST	Failure	R	result
1	F	6d	MMC	-	-	21d / 85d	SSC obstr	Y	VPS
2	F	52d	NNS	-	EM NN	46d	SSC obstr	Ν	VPS
3	Μ	84d	CSH	-	Doppl.	бу+	-	Ν	RVSS
4	F	293d	CON	-	EM NN	бу+	-	Ν	RVSS
5	Μ	16y	TBI	AE	EM NN	21d	SSC obstr	Ν	VAS
6	Μ	36y	TR	-	EM NN	100d	SSC obstr	Ν	VPS
7	F	55y	ASAH	-	EM NN	7d / 7d	SSC obstr	Y	VAS
8	F	60y	ASAH	-	EM NN	12d / 7d	SSC obstr	Y	VPS
9	Μ	63y	ASAH	-	EM NN	4d	SSC obstr	Ν	VPS
10	Μ	86y	NPH	-	-	112d	SSC obstr	Ν	VPS
11	F	Зу	MMC	-	-	12y+	-	Ν	RVSS
12	F	15y	Т	-	-	(68d)	T growth	Ν	death
13	F	16y	TR	-	Doppl	14d	SSC obstr	Ν	VAS
14	F	42y	TR	-	Doppl	105d	SSC obstr	Ν	VPS

In the prospective group, only 2 out of 10 patients benefited from a long lasting RVS shunt ST (Table 1). Both were young children and in both cases, the RVS shunt was successful without the need of reoperation (figure 1).



Figure 1. profile skull X-ray of patient 4 at 5 months postop (A) and 4 years 11 months postop (B); black asterisk indicates the tip of the VC, white asterisk the shunt valve and black arrow the tip of the SSC

In the RVS shunt failure group (in all cases because of an obstructed SSC), 3 out of 8 patients underwent an operative revision of the obstructed SSC (Figure 2). None of the re-operated RVS shunts were lasting and all patients of the failure group were converted to a VP- or VA shunt.

During surgery of a blocked SSC, visualisation of the catheter's tip inside de SSS was technically impossible. Prior to removal of a blocked SSC, we remarked that pre-operative contrast injection demonstrated a sleeve around the catheter's tip; limited amount of contrast fluid was leaking into the SSS, the rest oozed at the catheter's SSS introduction point, from between the SSC and its surrounding sleeve. This sleeve could be a thrombotic or an endothelial one, or a combination of both. We considered it medico-ethically unacceptable to open the SSS roof widely or to introduce a Fogarty balloon catheter in order to remove the obstructed SSC together with its surrounding sleeve. Hence, the SSC was simply retracted out of the SSS and seemed – at close inspection – immaculate. In all 3 occasions of introduction of a new SSC through a slit incision at about 1 cm anterior to the former, the procedure remained uneventful.



Figure 2 Kaplan-Meier graph, displaying the survival time (time to clinical proof of block/obstruction in weeks) in 17 SSC implantations, on 14 patients

In the rescue group, only in 1 out of 4 patients the RVS shunt remained undeniably functional. Perhaps one could include patient 12 in the successful group, as her HC control lasted until she died because of progressive malignant brainstem glioma. However, we considered a control period of 68 days to be too short to conclude. Patient 14 provided information concerning the physiological CSF drainage effect of the RVS shunt. 4 days before her RVS shunt surgery, she had an intraparenchymal ICP sensor implanted, being the bearer of a functional VA shunt with Integra OSV II valve but with ongoing intracranial hypotension in upright position. Her VA shunt was ligated 1 day before the RVS shunt surgery. Before ligation, her ICP ranged between 0 mm Hg in supine position to -15 mm Hg sitting or standing. After ligation, the ICP raised progressively up to 30 mm Hg. During the RVS shunt implant, the ICP dropped from 20 mm Hg to 11 mm Hg as the RVS shunt became functional. 2 days later, her ICP ranged from 0 mm Hg in supine position to -7 sitting or standing and the clinical signs of intracranial hypotension disappeared. It is to note that none of the patients received anti-thrombotic drugs, except for patient 10. This patient was on prophylactic warfarin because of cardiac atrial fibrillation.

Discussion

Despite being modest, this study provided answers to questions about technical feasibility, operative safety, physiological CSF drainage, and longterm effectiveness of the RVS shunt.

The implantation of the ventriculosinus shunt was technical feasible. A watertight closure of the dura around the ventricular catheter was obtained in all patients. The postoperative imaging confirmed that the sinus catheter was positioned inside the SSS as intended. It however was not always evident

to exactly locate the midline of the SSS through a standard burr hole. In some cases the burr hole needed to be extended; NN and US Doppler were helpful.

In accordance with previous research (18, 22, 26), we consider the RVS shunt implantation a safe procedure. Only in 1 out of 17 procedures an onset of AE was noticed by an acute drop in the end tidal PCO2. Application of fibrin glue, combined with mild Trendelenburg table tilting, immediately solved the problem. In none of the patients an SST occurred, in the short nor in the long term follow up (Figure 2). All bleedings were controllable with gentle compression with some gelatine sponge and – if necessary – extra anti-Trendelenburg tilt of the operation table. We encountered no wound healing problems, infections and operation related morbidity nor mortality. No shunt related problems other than obstruction of the SSC have occurred. In line with previous reports (18, 22, 26, 27), we found that the RVS shunt restored a physiological ICP, as was noted above concerning patient 14. In the 3 patients with already more than 6 years lasting patency of the RVS shunt, absence of anamnestic, clinical and radiological signs of intracranial hypo- or hypertension was noted. In the infants, head circumference evolution stabilised on its percentile.



Figure 3 axial (A) and sagittal (B) T1 with IV gadolinium cerebral MRI of patient 4, 1 month postop; the open arrow indicates the tip of the SSC centrally in the SSS; the white arrow indicates the passage of the SSC through the roof of the SSS; the homogeneous contrast enhancement of the SSS excludes SST.

However, rapid and frequent obstruction of the SSC proved to be a major issue leading to the interruption of the study after the inclusion of 10 patients. DSA examination of 3 patients with an obstructed shunt, revealed an impeding sleeve around the distal catheter's tip (Figure 3).



Figure 4 (A) instantaneous and (B) few seconds later contrast enhancement of SSC and SSS during venogram (iodine contrast injection through the SSC), 4 months postop; (C) T1 with IV gadolinium cerebral MRI 2 months after removal of SSC; the open white arrow indicates the tip of the SSC, the white star the SSS, the white arrow the passage of the SSC through the roof of the SSS, the black asterisk the transverse-sigmoid sinuses and the white triangle the burr hole above the SSS; note the homogeneous contrast enhancement of the sinuses.

Although we were not able to harvest this sleeve for investigation, we suppose that it consisted of thrombus and/or of endothelial overgrowth.

These results contradict the hypothesis of El-Shafei that implanting the SSC with its tip directed against the blood flow ('retrograde') solves the issue of thrombotic obstruction. According to El-Shafei, the beneficial effect of the retrograde position relies on two advantages. Firstly, the blood flow 'hits' the draining CSF column and stagnates at the shunt tip. According to Bernoulli's principle, kinetic energy is converted to potential energy and the static

pressure in the shunt rises by the amount of the dynamic Psss. In other words, the ICP is kept above the static Psss. This effect is called the 'impact effect' by El-Shafei (12, 19). This impact effect should preserve the delicate pressure gradient between the ventricles and the SSS, creating a continuous CSF outflow. Secondly, when the venous catheter is directed against the blood flow, CSF will be deflected and flow over the shunt surface. According to El-Shafei, the resulting 'CSF sleeve' protects against clot formation (12) (Figure 4).



Figure 5 Drawing of retrograde orientated catheter in a vessel with laminar blood flow (big black arrows); the CSF continuously streaming out of the catheter (small black arrow) creates a molecular CSF layer on the outside surface of the catheter (transparent grey zone) and gets accumulated in the blood turbulences at the wake zone (WZ) of the intravascular part of the catheter (spirals); the pressure at the impact zone (IZ, P_{IZ}) is the venous pressure (P_V) augmented by the dynamic pressure of the impact effect (P_{IE}) and equals the pressure inside the SSC

The rapid and frequent obstruction in the failure group urged us to critically revise the hypothesis of El-Shafei. We identified two factors that may promote clot formation and shunt obstruction:

- Decentralised position of the SSC tip In the failure group, we noticed on the postoperative CT-scan imaging that the tip of the SSC was not "centrally" positioned in the SSS, but rather 'laterally', with its tip against the vessel's wall (Figure 5). Despite our drilling of a guiding groove for the SSC, in accordance to the recommendations of Børgesen (1), this decentralised position of the SSC tip occurred in the majority of patients. We suspected that the lateral position of the SSC tip plays a major role in the frequent and rapid obstructions, as it has many disadvantages:
 - The velocity of the blood stream close to the wall of a blood vessel is very low. The velocity is at its maximum in the centre of the vessel. Therefore a tip against a vessel wall cannot benefit of the impact effect created by the retrograde orientation (19, 27).
 - In a blood vessel, the concentration of red blood cells is at its highest in the centre of the vessel and at its lowest at the border. The opposite is true as to the clot forming factors of blood, plasma and platelets, which are at their highest concentration against the vessel wall (28).
 - A device in contact with the endothelial wall, stimulates both the endothelial growth and the clot forming cascade (29, 30).

Possible causes of the lateral position:

- As SSS septa might block the passage of the SSC, they might also deviate the catheter's tip from its straight and central trajectory.
- Both the RVS shunt and the SinuShunt[®] require a long distance
 SSC in the SSS. It is technically impossible to make sure that the
 tip of a long and flexible catheter is centrally positioned.



Figure 6. (A) coronal and (B) sagittal iodine IV cerebral CT-scan of patient 8, 14 days after the first SSC implantation, just before the RVS shunt revision operation; the open white arrow indicates the tip of the SSC, the white triangle the subgaleal trajectory of the RVS shunt, the white arrow the passage of the SSC towards the SSS through the burr hole, the white asterisk the tip of the VC just passing through the foramen of Monro; note the eccentric position of the tip of the SSC against the sinus wall and the homogeneous contrast enhancement of the sinuses.

CSF inducing blood clotting – We suspected and proved in vitro, that CSF induces blood clotting (31). In clinical practice, this can be observed by the rapid formation of membranes around the CSF collection of a CSF leak, trying to encapsulate and stop the leakage. CSF should reach a minimal

concentration of about 5-9% to have a thrombogenic effect. Physiological concentrations of CSF in the SSS are far below 5%, as CSF inflow is approximately 0.35 ml/min for a blood flow of more than 200 ml/min (18, 22, 32). However, in specific circumstances the coagulation enhancing effect of CSF could be problematic. Typical situations are contact between CSF and foreign material (molecular layer of continuous CSF outflow around tip of SSC) and accumulation of CSF in 'wake' zones (in blood turbulences at the wake zone of the SSC). Consequently the 'protective' CSF sleeve around the tip of the SSC might have turned out to be thrombogenic.

To address the issues mentioned above, we proposed a novel 'dural venous sinus access device' (DVSAD – Figure 6), designed to secure the catheter's tip in the centre of the sinus and to be more easily implantable.



Figure 7. Drawing of the DVSAD with its intravascular tip (1), epidural base plate (2) and connecting catheter (3), inside the SSS (4) and compared with the standard SSC (5). Note the significant difference in intravascular volume.

The device consists of a short intravascular tip with adaptable length, to determine the tip's depth in the SSS centre. Its perpendicular introduction makes it easier to implant and reduces significantly the intravascular volume and surface. The stabilizing epidural base plate secures its position. The proximal extravascular catheter allows connection with the shunt's valve. The distal opening of the intravascular catheter is oriented neutrally, perpendicular to the direction of the blood flow. In this position, CSF will immediately be carried away by the blood flow maintaining the contact surface between CSF and the intravascular tip minimal. Also, in the neutral position, the shunt tip will be minimally subjected to unfavourable flow conditions.

The potential benefits of this novel DVSAD in the surgical-technical domain and for the prevention of thrombosis is currently being evaluated by in vitro and in vivo animal models. In case of positive results we will proceed with a human prospective clinical study.

Conclusion

The prospective clinical trial with the RVS shunt as described by El-Shafei was interrupted because of high failure rate due to blockage of the SSC. Nevertheless, operative feasibility and safety were proven, as was physiological drainage of CSF. Our goal to create a long-lasting and easily implantable RVS shunt remains. Therefore, the data obtained here formed the basis for a subsequent research project aiming at developing a new DVSAD, easily implantable and with its tip stabilized in the centre of the SSS, to be tested both in vitro and in vivo (animal model).

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Disclosures

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predispose to thrombotic

Introduction

complications

Chapter 5. Factors that

Experimental non-hydrocephalic goat model

After the - unexplained - disappointing results of the clinical study with the retrograde VS shunt we decided to take a step back and to evaluate the VS shunt in a suitable animal model.

A large animal model is more suitable than the previously described canine models because the dimensions of the larger brain ventricles and SSS allow the usage of shunt systems that are comparable in size and design to their counterparts for human applications (1).

We searched the anatomical literature and performed dissections on animal cadaver heads to identify a proper animal model. Dogs, pigs and cattle were excluded due to far backwards extending frontal sinuses that may impede frontal ventricular access. Remaining possible models were sheep, goats and horses or ponies.

The SSS in goats has a triangular cross section. The base and height measure around 3 mm (Figure 1). In horses/ponies the SSS is significantly larger. The base of the triangular section, assessed 1 cm cranially of the confluens, measures about 6-8 mm and is more than 10 mm in height (Figure 1). These

dimensions correspond to those of the human SSS. Also, the dimensions and morphology of the lateral ventricles resemble these of humans.



Figure 1. Dimensions of the caprine (upper) and equine (lower) SSS

We concluded that horses or ponies are anatomically best suited to evaluate the ventriculosinus shunt. However, we anticipated some practical and safety issues. Unique anatomical and physiological characteristics make horses more vulnerable during general anesthesia than other species (2). This results in a higher morbidity and mortality but also limits the duration of the anesthesia, to be considered as a major drawback in a research setting. Also, the large dimensions of horses are an issue for several reasons. First, obtaining brain imaging would be cumbersome. Second, animals may become aggressive when anxious or in pain (2). In such situations, horses may impose a risk to themselves and their care givers.

Based on these practical and safety issues we finally decided to use goats (Saanen breed), which are friendly and easy to manage.

Manuscript 2 presents a non-hydrocephalic goat model that was developed to clarify factors that may predispose VV shunts to thrombotic complications. It may also be used to evaluate whether a new technique is feasible, safe and well tolerated. As explained in the manuscript, the induction of hydrocephalus is not required for the evaluation of these factors. The manuscript describes the anatomy and coagulation properties of the caprine model as well as the surgical technique and the results of the implantation of an El-Shafei shunt in 3 goats.

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Manuscript 2. A non-hydrocephalic goat experimental model to evaluate the

ventriculosinus shunt

J. Vandersteene¹, E. Baert¹, S. Schauvliege², K. Vandevelde², F. Dewaele¹, F.

Desomer³, D. Van Roost¹

Laboratory Animals, accepted

- 1 Department of Neurosurgery, Ghent University Hospital, Belgium
- 2 Faculty of Veterinary Medicine, Ghent University, Belgium
- 3 Department of Cardiac Surgery, Ghent University Hospital, Belgium

Abstract

The ventriculosinus shunt is a promising treatment for hydrocephalus. Currently, different shunt techniques exist, and it is not clear whether one is preferable. This pilot study reports on a non-hydrocephalic goat model (Saanen breed) that provides opportunities to evaluate and optimize several aspects of the ventriculosinus shunt technique. Analysis of the coagulation properties of 14 goats by a viscoelastic coagulation monitor showed that goats have a hypercoagulable state compared to humans. This property can be partially counteracted by antiplatelet drugs. During implantation of a ventriculosinus shunt, a pulsatile reflux of blood was observed. After implantation, the animals recovered to their preoperative state, and none of them developed a superior sagittal sinus thrombosis. Evaluation of the shunts after 16 days showed an obstructing luminal clot. Several model-related factors may have promoted this obstruction: the absence of hydrocephalus, the hypercoagulability of caprine blood and the smaller dimensions of the caprine superior sagittal sinus. However, the pulsatile reflux of blood, which is caused by the compliance of the shunt system distal to the valve, may have

been an important factor as well. In conclusion, the non-hydrocephalic goat model limits animal suffering and simplifies the study protocol. This model allows researchers to evaluate their implantation technique and shunt hardware but not the efficacy of the treatment or shunt survival.

Introduction

Hydrocephalus, or the accumulation of CSF in the brain, is treated with ventriculo-peritoneal or ventriculo-atrial shunts. An important drawback of these techniques is siphoning, in which the CSF column within the catheter exerts suction through gravity when the patient is in a sitting or standing position. This effect leads to shunt-related intracranial hypotension and aspiration of the choroid plexus into the proximal catheter (1). Intracranial hypotension causes headaches, nausea, vomiting and even subdural haematomas, while aspiration of the choroid plexus is a major cause of shunt obstruction (2). Despite the usage of expensive resistance valves and antisiphon devices, the rate of shunt failure—which requires surgical revision—remains as high as 50% in the first 2 years (3).

A more physiological, but still experimental, technique is the ventriculosinus shunt. This shunt drains CSF (CSF) to a natural resorption site, such as the superior sagittal sinus, and theoretically reduces the risk of shunt failure in several ways (4, 5). First, excessive drainage of CSF is prevented by the natural, self-regulating anti-siphon effect of the IJV. Second, the shunt system is shorter, less complex and confined to the skull, which minimizes the risk of mechanical failure and infection (6).

The efficacy of the ventriculosinus shunt was evaluated in a few clinical studies (7-10). Although the technique has proven to be safe and effective, (7-11)

several issues and uncertainties persist (11). First, authors do not agree on whether the tip of the shunt should be directed towards or against the direction of the blood flow (11). Second, problems with the implantation of the shunt system exceed 10% in most of the available studies (9, 11). A technical advance using the Seldinger technique was published, but this method was evaluated in only 1 patient (12). Third, when the shunt system is correctly implanted, obstruction of the intravascular catheter remains an issue (7, 9, 10). Based on their experience, different authors have proposed several prototypes of the ventriculosinus shunt with distinct features (13-15). It is not clear which of these shunt systems would be preferable (11).

To optimize the implantation technique and to evaluate the different prototypes of the ventriculosinus shunt, an animal model would be an indispensable tool (16).

The only model described to date to evaluate a ventriculosinus shunt is a hydrocephalic dog model that used only two animals, and has substantial shortcomings: the induction of hydrocephalus was not well-tolerated, and the implantation of the ventriculosinus shunt resulted in a thrombosis of the superior sagittal sinus (16). The only way to prevent venous congestion and sinus thrombosis in a canine model is an extended miniaturization of the intravascular catheter to fit the small size of the superior sagittal sinus (16). To facilitate the use of shunt systems that are similar in size and design to their human counterparts, a large animal model must be created (17). A hydrocephalic sheep model to evaluate ventriculoperitoneal shunts has been described in a previous study (17).

The purpose of this pilot study is to assess the suitability and feasibility of a goat model (specifically 'Saanen breed' goats, which are very similar to sheep) for evaluating the implantation technique and design of the ventriculosinus shunt. Since hydrocephalus is not required for addressing the research question, a non-hydrocephalic model was chosen.

The study consists of a cadaver anatomical study, an in vitro coagulation assay (Sonoclot Analyzer ©) and an in vivo study. The cadaver anatomical study describes the relevant surgical anatomy of the caprine brain ventricles and superior sagittal sinus. The in vitro coagulation assay analyses the coagulability of the caprine blood. The in vivo study assesses the feasibility of the in vivo implantation of a ventriculosinus shunt.

Materials and methods

Animals

The species was selected based on anatomical characteristics. In pigs and cattle, frontal access to the ventricles and superior sagittal sinus may be impeded by the pronounced caudal extension of the frontal sinuses. The remaining possible models included sheep, goats and horses or ponies. Ultimately, domestic dairy goats (Saanen breed) were chosen because of their manageability and short hair. All goats were purchased from dairy goat farms. The goats were 1 to 2 years old and weighed less than 65 kg. Only female goats were included because the more pronounced cornual processes of bucks could impede frontal ventricular access.

Since the investigation was a pilot study, small sample sizes were chosen. The study consisted of a cadaver study (9 goats), an in vitro coagulation assay (14 goats) and an in vivo study (3 goats). Three of the 14 goats included in the in

vitro coagulation assay were also used for the in vivo study; thus, 23 goats were used in total. The studies were conducted serially, and the goats were allocated to the experiments in order of acquirement.

All experiments in this study were approved by the Ethics Committee of the Faculty of Veterinary Medicine of Ghent University (EC2012/187, EC2013/66, EC2013/129). The care and use of animals were in full compliance with the most recent national legislation (Belgian Royal Decree of 29 May 2013) (18) and the relevant European Directive (2010/63/EU) (19).

For the cadaver anatomical study, the goats were euthanized directly after arrival at the research facility. The remaining goats were admitted to the animal facility at least 10 days prior to the start of the study for acclimatization and health checks (including clinical investigation, ultrasonographic examination of the abdomen and thorax, and blood and faeces analyses). The animals were housed in small groups (3-4 animals per cage). The cages measured 3 x 4 m. The bedding consisted of straw, and cage enrichment (an elevated platform) was provided in all cages. Natural light was provided by translucent windows, and the cage temperature was maintained between 15 and 20 °C. The animals were fed hay and water ad libitum and supplemented with 450 g of nutritional pellets daily.

Clinical evaluation of the animals was performed twice daily using a clinical scoring system. This scoring system was developed by the authors in cooperation with the Department of Internal Medicine of the Faculty of Veterinary Medicine of Ghent University. The score consists of objective (e.g., vital parameters, weight, and food intake) and subjective (e.g., general impression and posturing) parameters, and it is based on existing pain scores

(20, 21). A perfectly healthy animal without signs of distress will score 0, while a very ill animal with signs of unbearable suffering will score 21. A total score of 6, or a maximum score for one of the parameters, was the threshold for therapeutic action to alleviate suffering.

All animals fasted for 24 h before surgery and received an intramuscular injection of 2.5 mg trimethoprim and 12.5 mg sulfadiazine/kg body weight (Borgal® 24%, Virbac, Barneveld, The Netherlands) starting one day prior to surgery and daily until 4 days after surgery. If needed, postoperative pain and fever were treated with 48 mg meloxicam subcutaneously (Metacam, Boehringer Ingelheim, Germany).

Euthanasia was performed by intravenous administration of 50 mg/kg sodium pentobarbital (20%) (Pentobarbital, Kela, Hoogstraten, Belgium) after intravenous premedication with 0.3 mg/kg midazolam (Dormicum, Roche Pharma, Brussels, Belgium) and 0.1 mg/kg morphine (Morphine HCL Sterop, Brussels, Belgium). The anaesthesia was intravenous propofol 2-4 mg/kg (Propovet, Parsippany-Troy Hills, New Jersey, United States).

Cadaver anatomical study

After euthanasia, the goats were frozen at –20 °C and decapitated. The heads were sawed in coronal slices of approximately 1 cm thickness. The superior sagittal sinus was inspected for septa or trabeculae and measured at the confluens sinuum and 1 cm rostral to the confluence. The rostral horns of the lateral ventricles were measured at the level of the coronal suture. A point on the coronal suture was determined where a catheter, which is inserted perpendicularly to the skull in the coronal plane, would enter the ipsilateral

ventricle. The length of the intraventricular trajectory of a shunt placed in that manner was measured.

In vitro coagulation assay

The goats were anaesthetized on the morning of the operation in the operation theatre. Eight animals received 75 mg clopidogrel (Plavix, Sanofi, Machelen, Belgium) and 80 mg acetylsalicylic acid (Asaflow, Takeda, Sint-Jans-Molenbeek, Belgium) perorally starting the day before the procedure. Six goats did not receive any antiplatelet drugs. Three millilitres of CSF and 15 ml of venous blood (citrated with 0.129 mole Na3-Citrate/I, Terumo, Heverlee, Belgium) were obtained by a sub-occipital puncture and a venipuncture, respectively. The samples were stored at room temperature and processed within 60 min. Because tissue factor is a potent activator of the extrinsic coagulation pathway, the first 1 ml of CSF and 3 ml of blood were not used for analysis.

To assess the impact of CSF on coagulation, different concentrations of CSF were added to the blood samples (0 μ l CSF/ml blood and 100 μ l CSF/ml blood). Subsequently, the mixture was recalcified with 40 μ l of 0.25 mol/l CaCl₂ and analysed by a Sonoclot Coagulation Analyzer © (Sienco, Arvada, CO, USA).

The Sonoclot Analyzer © is an in vitro method for the analysis of the coagulation process from the start of fibrin formation through polymerization of the fibrin monomer and platelet interaction and eventually to clot retraction and lysis. The system consists of an open-ended plastic probe, which vibrates vertically while immersed in a cuvette containing a 0.33-ml sample of whole blood, and the probe measures changes in the viscoelastic properties of whole blood during the clotting process. The curve or signature

reflects the changes in viscoelasticity from a liquid to a solid state (22). Three parameters are defined: the activated clotting time (ACT), clot rate (CR) and platelet function (PF). The ACT is an expression of how long the sample remains completely in the liquid phase and corresponds to the time necessary for fibrinogen to be converted to fibrin monomers. The CR is the slope of the second peak/plateau of the curve, which corresponds to the polymerization of fibrin monomers; a faster fibrin polymerization will be reflected by a steeper slope. The PF represents the attachment of platelets to fibrin and the retraction of the clot (22).

Statistical analysis was performed using SPSS Statistics[®] 22 (IBM Corp., Released 2013, IBM SPSS Statistics for Windows, Version 22.0, Armonk, New York, USA).

The distribution of the Sonoclot parameters was evaluated using QQ-plots and a Shapiro–Wilk test

To evaluate the effect of CSF on blood coagulation, the goats were considered one group independent of antiplatelet drug administration. Each of the Sonoclot parameters of pure blood was compared to the blood-CSF mixture using a paired-sample T test.

The effects of antiplatelet drug administration on the Sonoclot parameters were evaluated by comparing the Sonoclot parameters of the goats that received antiplatelet drugs with the parameters of the goats that did not receive antiplatelet drugs. An independent sample T test was used.

Statistical significance was set at 5%.

In vivo study

Shunt implantation. A ventriculosinus shunt was implanted in 3 goats under general anaesthesia. The procedure started in the morning and was performed in the operation theatre. The animals received 75 mg clopidogrel (Plavix, Sanofi, Machelen, Belgium), 80 mg acetylsalicylic acid (Asaflow, Takeda, Sint-Jans-Molenbeek, Belgium) and 40 mg pantoprazole (Pantomed, Takeda, Sint-Jans-Molenbeek, Belgium) perorally starting 24 h before surgery until the end of the study.



Figure 1. Positioning and incision

Left: the goats were positioned prone with the head slightly elevated and fixated in a custom-built head

clamp. Right: a linear incision was made, starting 2 cm rostral to the coronal suture and ending 2 cm caudal to the lambdoidal suture. The foramen magnum and the arch of the atlas were also marked as these are the anatomical references for a suboccipital puncture.

C: coronal suture; L: lambdoid suture; FM: foramen magnum; C1: atlas

A surgical plan was made based on a contrast-enhanced brain CT scan the day before surgery. As shown in Figure 1, the head of the animal was secured in a custom-built frame. Under sterile surgical conditions, a 10 cm midline skin incision was made that reached from 2 cm rostral to the coronal suture to 2 cm caudal to the lambdoidal suture.

A hole was drilled approximately 18 mm to the right of the midline on the coronal suture, and another hole was drilled on the midline just rostral to the lambdoidal suture. To introduce the ventricular catheter, an aiming device was used, which was similar to a device described in the literature (23).

This device was placed over the burr hole parallel to the sagittal plane and perpendicularly to the surface of the skull in the coronal plane. In the sagittal plane, the appropriate angle was set, and the ventricular catheter (Codman Hakim Ventricular Catheter, inner diameter (ID) 1.4 mm and outer diameter (OD) 2.7 mm) was inserted into the rostral horn of the right lateral ventricle. The correct position was confirmed by the outflow of CSF. The catheter was connected to a Codman Hakim very low pressure valve[®] (Depuy Synthes - Codman Neuro, Raynham, Massachusetts) and obstructed by a clamp.

The superior sagittal sinus was then identified. The roof of the sinus was punctured with an 18 G needle and/or incised with a surgical blade (n° 11). A peritoneal catheter (Codman Hakim Peritoneal Catheter, ID 1 mm and OD 2.2 mm) was introduced over a length of 3 cm in the superior sagittal sinus against the direction of the blood flow.

The correct position of the sinus shunt was confirmed both by injection of a 0.9% sodium chloride solution and by aspiration of blood. The intravascular catheter was then connected to the valve after flushing the catheter with a 0.9% sodium chloride solution. The clamp was removed from the ventricular
catheter, and the system was inspected for drainage of CSF to the sinus or reflux of blood to the catheter system.

In one goat, a spinal epidural catheter (Portex, Smiths-Medical, Hythe, United Kingdom, ID 0.55 mm and OD 1.03 mm), which was obliterated at its proximal end, was inserted in the superior sagittal sinus before implantation of the final catheter. After being inspected for blood reflux, the spinal epidural catheter was replaced by the final Codman Hakim peritoneal catheter.

Postoperative evaluation. Postoperatively, head computed tomography was acquired to verify the correct position of the shunt components and the patency of the superior sagittal sinus. The animals were evaluated daily until two weeks after the implantation. This follow-up period was chosen because full recovery or major complications, such as a superior sagittal sinus thrombosis or infection, are expected to manifest within this period. For clinical evaluation, the scoring system described above was used.

At the end of the follow-up period, the animals were anaesthetized, and the patency of the ventricular and intravascular catheters was assessed using water columns. At the end of this procedure, the animals were euthanized, and the superior sagittal sinus containing the intravascular catheter was explanted with the catheter left in place. The lateral wall of the superior sagittal sinus was opened to visualize the intravascular catheter. The correct position was verified, and the presence of clots was evaluated using a stereomicroscope. Subsequently, the catheters were removed along with the surrounding sinus wall, and the catheters were transversely cut in two equal parts and fixed in a HEPES buffer containing 2.5% glutaraldehyde solution (Sigma Aldrich, Steinheim, Germany). After fixation, the samples were rinsed

with a 0.9% sodium chloride solution, air-dried, mounted on aluminium pin mounts and sputtered with platinum particles.

The samples were then observed with a JEOL JSM-5600 LV scanning electron microscope (SEM) with the lumen facing the camera and evaluated at different magnifications.

Results

Cadaver anatomical study

The mean weight of the animals was 45.3 kg (range 40-62 kg).

Table 1 shows the dimensions of the superior sagittal sinus and the lateral ventricles.

Table 1.

Dimensions (mean values and 95% confidence intervals) of the superior sagittal sinus (SSS) and lateral ventricles. The dimensions of the superior sagittal sinus are expressed as latero-lateral x dorso-ventral distances. The dimensions of the ventricles are measured at the level of the coronal suture.

Variable	Dimension (mm)
SSS at confluence of sinuses	5.5 (4.0-7.0) x 6.0 (4.7-6.8)
SSS 10 mm rostral to confluence of	2.8 (2.3-3.3) x 3.3 (2.6-4)
sinuses	
Ventricle height	3.5 (2.6-4.4)
Bifrontal ventricular diameter	16.6 (14.4-18.9)
Intraventricular shunt trajectory	5.8 (4.6-7.0)
Centre of burr hole to midline	12.0 (11.0-13.0)
Dura to ependyma	18.9 (17.0-20.7)

The confluence had variable dimensions. The mean latero-lateral diameter was 5.5 mm, and the dorso-ventral diameter was 6 mm. As seen in Figure 2A, the confluence frequently contains septa and trabeculae.

Ten millimetres rostral to the confluence, the cross section of the superior sagittal sinus has a triangular shape (Figure 2B). The mean <u>latero-lateral</u> diameter (base) was 2.8 mm, and the dorso-ventral diameter (height) was 3.3 mm on average. A septum was observed in only a few goats.

The mean height of the lateral ventricles at the level of the coronal suture was 3.5 mm. The mean bifrontal diameter at the same slice was 16.6 mm.

A burr hole at the coronal suture should be placed 12.0 mm lateral to the midline to ensure that a catheter inserted perpendicularly to the tabula externa of the skull will enter the rostral horn of the ipsilateral ventricle. Following this trajectory, the distance between the internal tabula of the skull and the dorsal ependyma of the rostral horn was 18.9 mm, and the intraventricular trajectory was 5.8 mm (Figures 2C and 2D).



Figure 2. Anatomy of the caprine superior sagittal sinus and lateral ventricles.

Figure 2a: septa in the confluence of sinuses. Figure 2b: cross section of the superior sagittal sinus 1 cm

rostral of the confluence of sinuses in the same animal.

Figure 2c: a catheter, inserted 12 mm lateral to the midline perpendicular to the tabula externa of the skull, will enter the ipsilateral rostral horn of the lateral ventricle. Figure 2d: the tip of the ventricle catheter is inserted in the rostral horn of the right lateral ventricle (arrow).

In vitro coagulation assay

A normal distribution was assumed because the Shapiro–Wilk test was not statistically significant for any Sonoclot parameter. The influence of the in vitro

addition of CSF to pure blood and the oral administration of antiplatelet drugs on the ACT, CR and PF are shown in Table 2.

Table 2. Coagulation properties of goat blood.

The influence of in vitro addition of CSF to pure blood and oral administration of antiplatelet drugs on the ACT, CR and PF are shown (mean value and 95% confidence interval).

Variable	ACT	CR	PF				
CSF							
0 μl CSF/ ml blood	130.4 (113.2-	53.9 (44.7-63.1)	3.3 (2.7-3.8)				
	147.7)						
100 μl CSF/ ml	114.3 (103.9-	65.5 (56.0-74.9)	3.3 (2.8-3.9)				
blood	124.8)						
P-value	0.006	0.009	0.734				
Antiplatelet drugs							
No antiplatelet	108.8 (88.2-129.3)	66.4 (54.3-78.6)	3.5 (2.4-4.7)				
drugs							
ASA + clopidogrel	146.7 (124.9-	44.5 (34.7-54.4)	3.0 (2.2-3.9)				
	168.4)						
P-value	0.009	0.005	0.405				

After the addition of 100 μ l of CSF per millilitre of blood, the ACT shortened from 130 seconds to 114 seconds, and the CR increased from 54 units/min to 66 units/min. There was no significant impact on the PF.

After oral administration of antiplatelet drugs, the ACT increased from 109 seconds to 147 seconds, and the CR decreased from 66 units/min to 45 units/min. There was no significant impact on the PF.

In vivo study

Shunt implantation. No specific obstacles were encountered during implantation of the shunt. When the transparent part of the Codman Hakim low pressure valve was inspected, spontaneous drainage of CSF to the superior sagittal sinus was observed directly after implantation of the shunt. Through the wall of the distal segment of the silicone catheter, a pulsatile reflux of blood to the shunt system was observed. This reflux disappeared after obliterating the catheter 1 cm proximally to its entrance in the superior sagittal sinus. No reflux was observed after introduction of a more rigid catheter with a smaller inner diameter.

Clinical score. The average clinical score of the 3 animals during the last 5 days before surgery was 1.5. The clinical score increased to 3.2 immediately after surgery and to 3.5 on the first postoperative day. The average clinical score normalized starting on the second postoperative day (average score between day 2 and 5 after surgery: 1.33).

CT imaging. CT imaging after surgery showed a correct position of the ventricle catheter in 2 animals. In the third animal, the ventricle catheter was positioned too deep. This suboptimal position had no clinical consequences. The intravascular catheter was correctly positioned in all animals. The distal part was always located in the ventral angle of the triangular section of the sinus (Figure 3). Clinically and radiographically (contrast-enhanced CT), there were no indications of thrombosis of the superior sagittal sinus.



Figure 3. Position of the intravascular catheter in the superior sagittal sinus. Coronal (left) and sagittal (right) computed tomography imaging of the caprine head showing the

position of the intravascular catheter and the ventricular catheter. The intravascular catheter was always positioned in the ventral tip (just above the falx) of the superior sagittal sinus. In this position the catheter touches the lateral walls of the sinus. The ventricular catheter was positioned too deep in this animal. A: intravascular catheter; B: ventricular catheter.

Assessment of shunt patency. The assessment of the shunt system after 16 days showed a patent ventricle catheter, but there was an obstructed intravascular catheter in all animals.

Autopsy. Stereomicroscopic evaluation showed a correct position of the intravascular catheter in the three animals. However, the presence of a clot was visualized around all three catheters. This clot was situated at the site were the catheter enters the sinus, extending downstream (i.e., caudally) along the sinus roof (Figure 4a). The SEM evaluation of the lumen of the intravascular catheter showed the presence of an intraluminal clot in all catheters (Figure 4b).



Figure 4. Microscopic evaluation of the intravascular catheter.

Figure 4a: evaluation with a stereomicroscope showed the presence of a clot (arrow) originating at the entry site of the catheters and extending downstream (i.e. caudally) along the sinus roof

Figure 4b: scanning electron microscopic (SEM) views of the obstructed intravascular catheter.

Left: SEM evaluation of a transverse section of the intravascular catheter showing the obstructing

clot. Right: Higher magnification of the intraluminal clot showing fibrin network with red blood cells and

platelets. A: fibrin network; B: red blood cell; C and white arrow: platelets

Discussion

Shunting CSF to its natural resorption site—the superior sagittal sinus—with a ventriculosinus shunt is a promising treatment for hydrocephalus (7, 8, 11). Different authors have evaluated this shunt in clinical series (7-9). Based on their experience, the authors have modified the technique and developed designated shunt hardware (12-15). Currently, it remains unclear which technique or shunt system is ideal (11). To maximize the chance of success, the ventriculosinus shunt should be optimized by evaluating and combining the most valuable characteristics of the available techniques. This process requires a suitable animal model (16).

This pilot study reports on the characteristics and feasibility of a nonhydrocephalic goat model. The purpose of this model is to enable the evaluation and optimization of different implantation techniques and prototypes of the ventriculosinus shunt.

Strengths and limitations of the non-hydrocephalic caprine model

The implantation of a ventriculosinus shunt in goats has been found to be feasible and safe. The anatomy and dimensions of the caprine brain ventricles and superior sagittal sinus allow for the implantation of ventriculosinus shunts that are closer in design and dimensions to shunts for human use (8). These characteristics are in contrast to the previously described canine model, in which the implantation of a distal catheter with a comparable outer diameter resulted in venous congestion and sinus thrombosis (16).

Although the goat model resembles human anatomy, the dimensions of the caprine superior sagittal sinus are significantly smaller (24). Depending on the prototype that will be tested, miniaturization of the shunt material might yet

be necessary. The smaller superior sagittal sinus may also promote distal shunt obstruction, as the proximity of the sinus walls to the catheter tip may cause endothelial irritation and blood stasis, which are both known to enhance coagulation (25).

In contrast to previously described animal models, (16, 17) hydrocephalus was not induced in this study. Injection of Kaolin by a sub-occipital puncture, which is the best documented method for the induction of hydrocephalus, causes chemical meningitis (26). This technique is associated with a high morbidity and mortality (17, 26-28). However, hydrocephaly is not required for the evaluation of the implantation technique and the design, dimensions and tolerance of current and potential new prototypes of the ventriculosinus shunt. The clinical impact of meningitis itself may even cloud the assessment of the tolerance for the shunt system. Thus, the use of a non-hydrocephalic model is an important refinement because it simplifies the study protocol and drastically reduces animal suffering.

A major limitation of the non-hydrocephalic model is the impossibility to evaluate the efficacy and survival of the shunt system. The preserved physiological drainage of CSF causes the flow through the shunt system to be at least limited and inconsistent. This inconsistency leads to impaired clearing of fibrin deposits, which are known to result in catheter obstruction (29). This phenomenon partially explains why all implanted shunts were found to be obstructed after two weeks.

In addition to the absence of hydrocephaly, the coagulation properties of the caprine model may promote shunt obstruction. Sonoclot analysis showed that goats have a hypercoagulable compared to humans. Compared to normal human values(30), the ACT is 34% shorter, and the CR is 127% higher. This difference in coagulability was partly counteracted by administration of antiplatelet drugs, which reduced the relative difference in ACT to 11% and CR to 52%. The addition of CSF to blood enhances coagulation in humans (30). This effect appears to be more pronounced in goats, which may further increase the risk of shunt obstruction.

Intra-operative evaluation of the ventriculosinus shunt

The current study shows that an intra-operative evaluation of the shunt system may be useful for clarifying the causes of shunt failure, even in the absence of hydrocephalus. One could observe a pulsatile reflux of blood to the shunt system despite the use of a competent one-way valve and a retrograde position of the shunt. This reflux is probably caused by a combination of the compliance of the silicone shunt system distal to the valve, the pressure pulsations in the superior sagittal sinus and the inertia of blood corpuscles that hit the CSF column at the distal shunt tip.

Pulsatile reflux of blood results in the development of a relatively static blood-CSF mixture in the distal shunt system. Both stasis of blood and the interaction with CSF promote clot formation, which finally results in shunt obstruction (30).

The reflux could be prevented by clamping the distal catheter close to its entrance in the superior sagittal sinus. In addition, reflux was not observed when a more rigid catheter with a smaller inner diameter was inserted in the sinus. Both manoeuvres reduce the compliance of the shunt system distal to the valve. These findings suggest that using a more rigid distal catheter with a smaller internal diameter may help prevent distal shunt obstruction. In conclusion, the implantation of ventriculosinus shunts is feasible and safe in a non-hydrocephalic goat model. This model facilitates the intra-operative evaluation of the implantation technique, hardware and functions of the ventriculosinus shunt. The tolerance for the shunt system and possible postoperative complications can be monitored without interference of sequelae from the induction of hydrocephalus. However, in the absence of hydrocephalus, it is impossible to evaluate shunt efficacy and shunt survival. The development of a hydrocephalic goat model for this purpose may be used in future research.

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Chapter 6. Pulsatile backflow of blood into the shunt

Dynamic experimental model

Introduction

A potential risk of VV shunts is backflow of blood into the distal (intravascular) catheter which results in a relatively static blood-CSF mixture that predisposes to thrombotic complications (obstructions or emboli).

To prevent backflow of blood into a VA shunt, one-way valves are being used. For a VS shunt, blood backflow may be prevented by implanting the shunt in a 'retrograde' position according to El-Shafei (Figure 3, chapter 4) (1). In this position the blood flow 'hits' the draining CSF column and stagnates at the shunt tip. According to Bernoulli's principle, kinetic energy is converted to potential energy and the static pressure in the shunt rises by the amount of the dynamic Psss. In other words, the ICP is kept above the static Psss. This effect is called the 'impact effect' by El-Shafei (1, 2).

In the anterograde position, it can theoretically be expected that the ICP becomes lower than the static Psss. El-Shafei describes this as the 'wake effect' (1). Bernoulli's principle cannot be used to calculate this effect, as the blood flow might not be laminar in the wake zone (2).

El-Shafei claims that the impact effect protects against the development of intracranial hypotension and assures a constant drainage of CSF through the catheter, regardless of postural changes (1). The assumption is based on his early experimental work about the ventriculo-jugular shunt. The experimental pressure evolution when a patient changes his posture from supine to sitting/standing and back to supine (1) is illustrated in Figure 1. When the catheter is implanted anterograde (Figure 1, left) and the patient is in the supine position, the steady state ICP is slightly lower than the static Psss due to the wake effect. When the patient changes to the sitting or standing position, the Psss drops and the flow increases. The wake effect remains constant when the flow in the sinus doubles, as shown by numerical modeling (2). By consequence, CSF will be suctioned to the SSS and the ICP will drop. When the patient changes back to the supine position, the Psss increases again and becomes higher than the ICP. In this situation, blood will reflow into a valveless shunt system or if a valve is present, no drainage of CSF will occur until – due to the production of CSF – the ICP increases beyond the Psss again (1).

When the catheter is implanted retrograde (Figure 1, right), the ICP is kept slightly higher than the static Psss due to the impact effect. When the patient verticalizes, the decrease in the sinus pressure is compensated by the increase of the flow and thus the increase of the impact effect. By consequence, no excessive drainage of CSF will occur and the ICP will remain higher than the Psss regardless of the variation of the patient's position (1).

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	Anterograde		Retrograde	
Situation/pressure (mmHg)	Psss	ICP	Psss	ICP
1	3.2	1.8	3.1	3.2
2	- 15.3	- 28,1	- 18.1	- 18
3	Backflow	observed	No backflow	observed

Figure 1. Protective role of the impact effect in postural changes

The SSS is represented by a cylinder. The sinus catheter penetrates the roof and ends with the tip in the center of the SSS. The catheter is inserted in the direction 'anterograde' (left) or against the direction 'retrograde' (right) of the blood flow. The pressure evolutions due to changing the patient's position from supine [1] to sitting/standing [2] and back to supine [3] are represented by color codes. The direction of the flow is indicated by an arrow. The flow rate is represented by the magnitude of the arrow. The experimental values/observations on which El-Shafei based his theory are shown in the table (1). El-Shafei substantiated his theory also with intra-operative measurements in the IJV (45 patients) (3). When the shunt was implanted retrogradely, the ICP measuring 9 mmHg in the supine position, dropped to 3 mmHg when the patient was brought in a sitting position. Fifteen patients were kept in the sitting position during 30 minutes. The ICP remained stable. When the patients were switched back to the supine position, the ICP increased to 9 mmHg again.

Experimental and numerical models endorse that the impact effect protects against backflow of blood due to positional changes and Valsalva maneuvers (1, 2). However, the protective effect was only partial and reflux of blood still occurred during provocation maneuvers (2). Also, the clinical superiority of the retrograde position remains unproven (4) and, although El-Shafei advocates that the impact effect prevents reflux of blood in all situations (1), he started adding a one-way valve to the shunt system himself (5).

In the animal model (Chapter 5), pulsatile reflux of blood occurred regardless of the orientation of the distal catheter (anterograde or retrograde) and despite the presence of a competent one-way valve. A potential cause of this reflux is the interaction of pressure waves in the brain ventricles (proximal end of the shunt) and in the SSS or the right atrium (distal end of the shunt).

Up to now, these pressure waves, originating from different events during the heart cycle, were neglected in experimental and numerical models (1, 2).

This chapter discusses the methodology and results of a dynamic experimental model to evaluate whether the intracranial and venous pressure waves can cause backflow of blood to VV shunts. It also highlights remaining uncertainties that are currently addressed in the context of a master thesis (ongoing master thesis: Cranial and venous pressure waves cause backflow in ventriculovenous shunts in a numerical model; T. Billiet, J. Vandersteene, D. Van Roost, P. Segers).

Materials and methods

Assumptions

To develop an experimental model some assumptions/simplifications were made.

- Modelling of the brain and ventricular system as water
 The brain and CSF are mainly composed of water and can be considered
 incompressible. Brain and CSF can adequately be modelled by water (2).
- The spinal compartment is not included in the model
 With regard to the research question, only the compliance added by this compartment is of importance (2). This was modeled by a windkessel.
- Only the distal venous system (cortical veins and SSS) is included in the model

The rest of the cerebral vascular system is only relevant to the research question as far as the ICP pulsations are concerned. These were modeled by a pump, connected to the intracranial compartment.

As the shunt will be implanted in the SSS, only the flow conditions in this SSS are relevant to the research question. The downstream venous system can be left out as long as the flow rate and the downstream pressure in the SSS are modelled correctly.

- No production of CSF in the model

The physiological CSF production rate is 0.35 ml/min. The difference between the pressure in the SSS at the position of the shunt tip and the pressure inside the shunt tip will be approximately the same when CSF

production is taken into account as without CSF production. Due to the very low CSF flowrates, the changes in terms of impact or wake effect are negligible. However, the difference between the pressure in the CSF reservoir (ICP) and the pressure in the SSS at the shunt tip is increased by the pressure loss in the shunt. According to Poiseuille's law, this pressure drop will be < 1mmHg. In accordance with previous literature (2), we decided not to include CSF production in the model.

Experimental model

The experimental set-up is shown in Figure 2.

Figure 2. Experimental set-up to evaluate the impact of intracranial and venous pressure waves

a: schematic drawing. The model consists of a venous compartment [D-E-F-G-H-I] that is partially submerged in the cranial compartment [A-B-C]. The cranial compartment is formed by a rigid container [A], the compliance is set by a windkessel [B] and pulsations are applied by a computer-controlled pump [C]. A volumetric pump [E] generates a constant flow in the venous compartment. The glycerin-water mixture circulates from the blood reservoir [D] through a needle valve [F] and the distribution tubes to the cerebral veins [G] and the SSS [H]. From the SSS the mixture flows to the adjustable-pressure reservoir [I] and back to the glycerin-water mixture reservoir. The ventriculosinus shunt [J] connects the intracranial compartment and the superior sagittal sinus. The pressure is measured by pressure sensors [P or pattern filled rectangle in panel a], connected to the intracranial compartment and to the SSS. b: Schematic drawing of the venous system that is submerged in the cranial container (frontal view). The cerebral veins run upwards from the distribution tubes, cross the midline and are connected through a right-angle connector to the plexiglass block containing the SSS, which is mounted above the cranial container. C: Schematic drawing of the SSS. From the right-angle connector, the veins (dashed lines) run within the plexiglass to join the SSS at the appropriate distance from the origin and at an appropriate angle with the longitudinal axis of the SSS. The dimensions of the SSS progressively increase from proximal to distal. In between the origin (a point) and the marked sections [1 and 2] the dimensions of the SSS increase linearly. Distal to section 2, these dimensions stay the same. d: schematic drawing of sections 1 and 2.

Page 147 shows the actual set-up in three pictures (upper: overview; lower left: lateral view; lower right: top view).







The model consists of two separate compartments. The first [A in Figure 2], a rigid container filled with water, models the brain tissue and CSF in the ventricles and subarachnoid space. These structures are incompressible and can adequately be modelled using water (2). A windkessel [B in Figure 2] was used to set the total compliance of the CSF reservoir to 0,008 ml/Pa (6). The windkessel accounts for the compliance of the spinal dura mater.

The second compartment, the venous system [D-E-F-G-H-I in Figure 2], consists of the cerebral veins [G in Figure 2] and the superior sagittal sinus [H in Figure 2]. The SSS [Figure 2, c and d] was milled out of plexiglass. The dimensions are based on anatomical data found in literature. The total length is 252 mm (weighted average based on the number of patients in references (2, 7)). The triangularly shaped cross-section increases from proximal to distal. The dimensions of the section at the origin of the sinus, end of the sinus and in two specific places were based on reference (8), and between these sections a linear gradient was chosen. Twenty-two cerebral veins, 11 on each side of the SSS (weighted average based on the number of patients in references (7-9)), are embedded in the first container and join the superior sagittal sinus each at a specific place and individual angle (weighted average based on the number of patients in references (7, 10)).

The pliant cerebral veins are modeled by a polyethylene shrink-film that was welded in a cylinder and shrunken to the right diameter (2.5 mm). To obtain a physiological venous volume, the length of the veins was chosen to be 74 mm. This volume was calculated based on the percentage of the cerebral blood flow that drains to the superior sagittal sinus and the total blood volume in the cerebral veins (11). Blood was modeled by a 40% glycerin and 60% water solution with a mass density of 1103 kg/m3 and a dynamic viscosity of 3.75

mPa s at 25 °C (2). A volumetric pump [E in Figure 2] brings the mixture into two distributors, from where it is divided over the 22 cortical veins. The downstream Psss is set to 7.5 mmHg by an adjustable-pressure reservoir [I in Figure 2] which captures the glycerin-water mixture. A silicone shunt [J in Figure 2] that is commonly used in clinical practice (Codman Hakim atrial catheter; internal diameter 1.0 mm and external diameter 2.2 mm; Johnson & Johnson Medical; Diegem, Belgium) connects the intracranial compartment with the superior sagittal sinus. Experiments were done with and without interposition of a one-way valve (Codman Hakim programmable valve; programmed on 2.2 mmHg; Johnson & Johnson Medical; Diegem, Belgium). Three luer lock connectors are mounted on the roof of the SSS making angles of 45, 90 and 135 degrees with the direction of the blood flow respectively. These luer lock connectors converged to a common entrance in the SSS, 190 mm distal to its origin. The silicone shunt was then mounted on an 18 G needle (BD Microlance 3; 18G, 11/2", 1.2x40mm; Erembodegem, Belgium) that was brought into the center of the SSS through each of the luer lock connectors sequentially. As such the needle opening was oriented retrograde, neutral or anterograde. The Psss was measured in each position.

A pressure transducer was connected to the intracranial compartment and to the distal shunt (at the entrance into the SSS) using a 3-way luer lock valve (Discofix C; B Braun; Diegem, Belgium). Pressure curves where recorded with ViVitro QCTest software (ViVitro Labs; Victoria, Canada). The pressures were corrected for height differences between the sensors. To simulate hydrocephalus, the ICP was brought to 22.5 mmHg or 3000 Pa by adding water to the intracranial compartment with a syringe. A computer-controlled pump (ViVitro SuperPump; ViVitro Labs; Victoria, Canada [C in Figure 2]) is connected to the cerebral compartment. The pressure measurements were performed under static (no pulsations applied by the computer-controlled pump) and dynamic conditions.

In the dynamic set up the computer controlled pump was programmed to generate pressure waves with an amplitude of 3-4 mmHg (12) and a frequency of 70 pulsations per minute (Figure 3).

To simulate a person changing from upright to supine position, the pressure in the superior sagittal sinus was suddenly increased by 0.75 mmHg (100Pa) (13). To simulate a lumbar puncture the ICP was lowered by 0.75 mmHg (100Pa)(2).

Results

Constant flow experiments

When, in the static situation, drainage is permitted through the ventriculosinus shunt, CSF flows from the reservoir to the SSS. CSF drainage stops when the ICP equalizes to the total Psss. With the shunt in the retrograde position, the stabilization pressure is 0.51 +- 0.1 mmHg higher than when the shunt is implanted in the anterograde position.

Dynamic experiments

In the dynamic situation, the pump generates pressure waves with a frequency of 70 pulses per minute and an amplitude of 3.3 +- 0.2 mmHg in the cranial compartment. These pulsations are effectively transferred through the cerebral veins to the SSS. The amplitude of the resulting pressure waves in the SSS was 1.8 +- 0.1 mmHg.





The pressure waves within the cranial compartiment and the SSS are shown (upper boxes: 4 cycli - 3.4s). The detailed views (lower boxes) show clearly that both curves cross at several points.

After opening of the shunt, CSF drains to the SSS. The steady state situation is reached when the mean ICP equalizes the mean pressure in the SSS at the shunt tip. In the dynamic situation no difference was observed between the anterograde and retrograde position, in terms of mean pressure differences. The pressure at the shunt tip equals the static + dynamic (impact or wake) pressure in the SSS. However, in the steady state situation, the maximal ICP is higher than the maximal Psss, and the minimal ICP is lower than the minimal Psss (Table 4). Also, the pressure waves in the cranial and venous compartments are not identical in morphology nor in phase. By consequence the curves of the ICP wave and the pressure wave in the SSS (Psss) cross at

several points (Figure ...). The above relations between the ICP an Psss were identical in the retrograde and the anterograde position.

Table 4. Difference between ICP and Psss at the shunt tip (minimum, mean and maximum) after reaching the steady state in the dynamic situation

The mean difference and the 95% confidence interval are shown. Note that the 95% confidence interval of the mean difference in ICP and Psss encompasses 0.

	Difference in ICP and Psss (ICP – Psss) [mmHg]			
	Minimum	Mean	Maximum	
Retrograde	-0.4 (-0.6; -0.2)	0.1 (-0.2; 0.5)	1.2 (1.0; 1.4)	
Anterograde	-0.6 (-0.7; -0.5)	0.1 (0; 0.3)	1.0 (0.8; 1.2)	

Provocation maneuvers

Regurgitation of blood to the shunt system was observed in response to the provocation maneuvers (sudden increase in SSS pressure by 0.75 mmHg or 100 Pa and sudden decrease in ICP by 0.75 mmHg or 100Pa). The backflow stopped when the Psss equalized the ICP.

Influence of a one-way valve

When a one-way valve with minimal differential pressure (+- 2.2 mmHg) was added to the shunt system, the ICP decreased faster and more pronounced as compared to a valveless system. The mean stabilization pressure after implanting a retrograde VS shunt measured 13.7 mmHg without valve versus 7.9 mmHg after adding a one-way valve (Figure 4).





The steady state ICP is lower after implanting an RVS shunt with a one-way valve compared to the same system without a valve.

Discussion

Backflow of blood to the shunt system is a potential risk to VV shunting that may cause shunt obstruction. The phenomenon is believed to be prevented by adding a one-way valve and by implanting the shunt with the tip directed against the blood flow ('retrograde') (1). However, thrombotic shunt complications remain the main reason that most neurosurgeons reserve VV shunts to patients in whom VP shunts are contra-indicated or not successful (14). The impact effect has proven to be only partially protective against backflow of blood, provoked by Valsalva maneuvers or changes in position of the patient (2). In a recent animal model, pulsatile reflow of blood to a VS shunt was observed, regardless of the orientation (anterograde or retrograde) of the shunt and despite the presence of a competent one-way valve (15).

Causes of pulsatile backflow

The results of the present dynamical experimental model identify the pulsatility of the intracranial and venous pressure waves as the source of this reflux. In the experimental set-up, the mean intracranial steady state pressure equalizes the mean venous pressure after implanting a VV shunt. However, the maximal ICP is higher than the maximal venous pressure while the minimal ICP is lower than the minimal venous pressure. The intracranial and venous pressure wave curves, that differ in morphology and phase, do cross during the heart cycle which may result in an inversion of the flow in the VV shunt. This flow is suspected to be positive (this is from the ventricles to the venous system) in the beginning of the heart cycle but negative at the end. It is plausible that, as observed in the experimental model after the in vivo implantation of a VS shunt, CSF will drain to the venous system until the mean pressures at the proximal (ventricular) and distal (venous) end of the shunt are equal.

The experimental finding that the intracranial and venous pressure waves differ in amplitude, morphology and phase, is in line with observations on patients in the intensive care unit for whom the intracranial, arterial and central venous (atrial) pressure waves are recorded simultaneously. The latter observations can be explained by the physiology of the intracranial and venous pressure waves:

- The ICP waves reflect variations of the cerebral blood volume during the hart cycle (6, 16). The contraction of the left ventricle of the heart causes

an arterial pulse wave that propagates to the cranial compartment. The suddenly increased cerebral arterial inflow is not immediately compensated by the venous outflow: due to the vascular resistance and the arterial compliance, the arteries dilate. The added intracranial arterial blood volume, increases the pressure due to the rigidity of the intracranial compartment (6, 16).

- The pressure waves in the SSS are caused by the pulsatile cerebral venous drainage. This drainage becomes pulsatile due to the transmittance of the cerebral arterial pulse wave through the incompressible brain and CSF to the thin-walled cortical veins. These veins are compressed and blood is periodically 'squeezed' into the SSS (17).
- The atrial pressure wave reflects atrial contraction, ventricular contraction and atrial filling driven by systemic venous return (18). These events are represented by 3 atrial pressure peaks.

As, after the implantation of a VV shunt, the intracranial and venous pressure waves will have the same mean but will differ in amplitude, morphology and phase, the curves will cross. When the ICP drops long enough beneath the venous pressure, the flow in the shunt may inverse which causes blood and recently drained CSF to enter the shunt system and form a relatively static blood-CSF mixture. Both stasis of blood and the interaction with CSF, known to promote coagulation, will finally result in clot formation and shunt obstruction (19).

Measures taken so far to prevent backflow of blood to the shunt system implanting the shunt with the tip directed against the blood flow ('retrograde') and incorporating a one-way valve - are insufficient. The impact effect, that was observed in the static experiment, disappeared in the dynamic situation. This may indicate that the pulsatile drainage of the cerebral veins into the SSS disturbs the linear laminar flow in the SSS, while the impact effect does rely on laminar flow conform the law of Bernoulli. 4D flow MRI imaging has shown that the flow is unidirectional laminar in the proximal part of the SSS (laminar flow in the SSS is supported by longitudinal ridges on the luminal surface of the dural venous sinuses called chordae Willisii (20)), but non-laminar from the distal part of the SSS onwards (21). Ultrasound imaging of the proximal SSS of neonates also indicates multi-directional flow (personal communication with professor Paul Govaert, neonatologist).

Also a one-way valve may not be sufficient to prevent pulsatile reflux of blood into the shunt caused by the intracranial and venous pressure waves (15). The combination of the intracranial and venous pressure waves causes variations of total pressure in the shunt. An important part of the shunt system is located outside the intracranial and venous compartment. This part is thus subjected to varying transmural pressure. The compliant silicone shunt system distal to the valve might distend and permit reflux of blood when the venous pressure becomes maximal.

Cause of backflow to a ventriculosinus shunt during provocation manoeuvres As described in previous static experiments (1, 2), the impact effect only partially protects against reflux of blood when the steady state is disturbed by physiological changes in venous pressure (changing position, Valsalva maneuver) (2). Also, in our dynamic set-up, regurgitation of blood to the shunt system was observed during all provocation maneuvers. We identified two possible causes. First, although an impact effect was observed during the constant flow measurements, it was not measurable when intracranial pulsations were applied. The pulsatile drainage of the cortical veins into the SSS might cause a non-laminar flow, which may result in a diminution of the impact effect.

Second, reflux might be caused by the loss of the normal, fixed relation between the central venous pressure and the ICP (see chapter 2, section on intracranial pressure). This relation is maintained by the adaptation of the diameter and thus the volume of the cerebral veins in function of the transmural pressure (22, 23). The transmural pressure is negative in the distal segment because the Psss is lower than the ICP in physiological situations (22). The radius of the distal segment will decrease, causing an increase in the resistance to flow and thus an increase in the pressure difference over the segment (24). The pressure proximal to the collapsed segment will thus be equalized to the ICP (25). When the Psss increases, the cerebral veins will open, adding volume to the intracranial compartment and thus increasing the ICP (22).

Why the natural coupling between the ICP and the Psss was lost in the current and previous experimental models was not yet investigated. One can expect however that in case of a ventriculosinus shunt, the ICP will always be approximately equal to the Psss, resulting in the cerebral veins to be fully open at all times. As, in this situation, the cerebral veins cannot expand in response to an increase in Psss, the normal link between intravenous pressure and ICP will be lost. In this situation every increase in central venous pressure will result in reflux of blood to the shunt system (Figure 5).

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Figure 5. Relation between the Psss and the ICP

In physiological conditions (no ventriculosinus shunt present) the Psss is lower than the ICP and the cerebral veins (CV) are partially collapsed at their distal end. When the Psss increases (e.g. Valsalva maneuver) the distal part of the CV will open a bit more, increasing the intracranial volume and thus the ICP.

When a ventriculosinus shunt is present the ICP almost equalizes the Psss and the CV are fully open. When the Psss increases, the CV cannot distend anymore, causing the Psss to rise above the ICP.

This hypothesis suggests that, to prevent the ICP to drop below the pressure in the sinus and to maintain the physiological coupling between the intracranial and the venous pressure, one should use a valve with a certain opening pressure and not a very low pressure valve as advocated by El-Shafei (5). At present too much uncertainties persist to be able to calculate what the ideal opening pressure would be.
6

Pulsatile backflow of blood into the shunt

Result of using a one-way valve

As the impact effect is only partially protective and as the intracranial - and venous pressure wave curves cross, a one-way valve is always necessary to prevent blood from entering the shunt system. However, we found that a one-way valve has an influence on the functioning of the shunt and on the pressures in the different compartments. In the presence of a one-way valve, the ICP dropped more rapidly and more profoundly than observed without a valve. Despite the valve's openings pressure of 2.2 mmHg, the ICP dropped even significantly below the Psss. As we did not find a sufficient explanation for this observation we repeated the measurements several times, but the results proved to be consistent. No issues with the test set-up were encountered, especially no leakage at the connection between the silicone catheter and the valve.

The observation concerning the dropping ICP may be explained partially by the following factors:

- 1) Is has been proven in previous literature (26) that intracranial pulsations cause the opening pressure of a valve to be lower than when constant pressure is applied. The inertia of the valve causes the closing pressure to be lower than the opening pressure. Thus, the valve opens when the ICP is maximal and permits drainage of CSF until the (lower) closing pressure is reached. Due to the inertia of the valve and the high frequency of the pulsations, the valve, once open, might not be allowed the time to close until the ICP is lower than the opening pressure during the whole heart cycle.
- When the ICP exceeds the venous pressure, CSF will drain to the SSS.
 However, when later in the hart cycle the pressure gradient is

reversed, blood will be prevented to flow back to the shunt system. In this way CSF is 'pumped' to the SSS until the ICP is equal or lower than the Psss at every point of the pressure curve (Figure 6).



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Figure 6. Theoretical effect of adding a one-way valve

In the above figure two pressure curves are represented. The dotted line represents the ICP-curve and the full-line the venous pressure curve. The time is on the x-axis and the pressure on the y-axis.

In the absence of a valve, blood will move in and out of the distal catheter as the pressure curves cross (upper graph). When a one-way valve is added, CSF will drain whenever the ICP exceeds the venous pressure. However, no blood can enter the shunt

when the ICP drops under the venous pressure. By consequence, CSF will be 'pumped' to the venous system until the ICP is lower than the venous pressure at every point of the pressure cycle (lower graph).

However, these factors cannot explain the full magnitude of the pressure drop that was provoked by the valve. The influence of a one-way valve on the function of a VV shunt and the pressures in the different compartments is currently the subject of a master thesis (ongoing master thesis; Cranial and venous pressure waves cause backflow in ventriculovenous shunts in a numerical model; T. Billiet, J. Vandersteene, D. Van Roost, P. Segers; see below).

Strengths and weaknesses

To our knowledge we are the first to evaluate the VV shunt under dynamical pressure conditions. The experimental set-up simulates the complex interaction between the ICP and the Psss. The anatomy of the cerebral veins, their entrance (location and angle) in the SSS and the dimensions of the SSS are modeled conform the available literature describing the in vivo situation. The results of the experimental set-up are somehow validated by the fact that these are in line with the observations during the animal experiment. However, at present, several weaknesses persist:

1) In accordance with previous literature (2), no CSF infusion was applied to the model. Constant CSF production would result in a pressure loss over the shunt of about 0.4 – 0.8 mmHg. This is of the same magnitude as the differences in ICP and venous pressure that were observed during the heart cycle. CSF production might thus play a significant role in preventing backflow due to crossing of the venous and cranial pressure curves in vivo. However, CSF production will not protect against backflow due to alterations in transmural pressure affecting the shunt system distal to the valve.

- 2) The waveform of the pulsations in the cranial compartment is only a rough approximation of the in vivo situation. Although the ViVitro SuperPump is especially dedicated to the simulation of physiological cardiac flows, better suited waveforms could not be obtained.
- 3) It was not verified whether the magnitude and the duration of the negative differential pressure (ICP < Psss) at the end of the hart cycle are sufficient to cause an inversion of the flow.
- 4) It was not assessed whether using a valve with a certain differential pressure actually preserves the natural regulation mechanisms that maintain a physiological fixed relation between the intracranial and venous pressures. Likewise, it was not assessed what the ideal opening pressure of such a valve would be.

Ongoing research

The above weaknesses are currently being addressed in the context of a master thesis (ongoing master thesis; Cranial and venous pressure waves cause backflow in ventriculovenous shunts in a numerical model; T. Billiet, J. Vandersteene, D. Van Roost, P. Segers). The aim is to supplement the experimental set-up with a numerical model. Such a numerical model allows to apply pressure curves that are a far better approximation of the physiological situation. It also allows to further explore certain findings by manipulating the boundary conditions. The simulations are solved with the software package Fluent (Ansys Fluent Inc., Sheffield, UK).



Figure 7. Constant flow simulations in the numerical model

Upper left and right: three-dimensional geometry with a mesh applied. Middle left: flow velocity vectors in the SSS with a shunt in the anterograde position. Middle right: flow velocity vectors in the SSS with a shunt the retrograde position. Lower Left: pressure fields the SSS with a shunt in the anterograde position. Lower Left: pressure fields the SSS with a shunt in the retrograde position. 1, SSS; 2, cortical vein; 3, shunt; 4, wake zone with low pressure, non-laminar flow and lower velocity; 5, impact zone with higher pressure, laminar flow and higher velocity; 6, entrance of blood into the shunt. In the numerical model, the inlet veins, the SSS and the shunt are constructed three-dimensionally with exactly the same geometry as the experimental model (Figure 7).

To validate the model, it is solved with the same boundary conditions that were imposed on the experimental model. These results are compared to those obtained from the in vitro set-up.

We already obtained results for the static situation. The constant flow simulations show that the pressure in the ventriculosinus shunt equalizes the total Psss, being 0.35 +/- 0.1 mmHg higher in the retrograde position compared to the anterograde position, which is comparable to the results of the in vitro model.

Conclusion

When a VV is implanted, CSF will drain to the venous system until the mean ICP equals the mean venous pressure. This steady state condition is in contradiction with the physiological situation were the ICP stays above the venous pressure at all times, and this causes backflow to a valveless shunt system during the steady state condition as well as during provocation maneuvers.

Backflow during the steady state condition occurs because, although the ICP and the venous curves have the same mean value, they differ in amplitude, morphology and phase, causing alternating pressure differences over the shunt. Backflow during provocation maneuvers occurs because the normal adaptation mechanisms that ensure a fixed relation between the ICP and the SSS rely on the ICP to be always higher than the venous pressure. The impact effect does not prevent backflow due to the intracranial and venous pressure waves and only partly protects against backflow during provocation maneuvers. Backflow to a valveless shunt system thus occurs regardless of the shunt's orientation.

A one-way valve does protect against backflow of blood due to alternating pressure differences over the shunt both during steady state conditions and provocation maneuvers. However, if the shunt system distal to the valve is sufficient compliant, it may still allow backflow due to alterations in transmural pressure. This kind of reflux can be prevented by reducing the compliance of the shunt system distal to the valve. The compliance of a catheter can be kept minimal by reducing the inner diameter, increasing the wall thickness and using a less compliant material.

After incorporation of a one-way valve with a minimal opening pressure, CSF will be 'pumped' to the venous system until the ICP is lower than the total venous pressure at every point of the heart cycle. This unphysiological situation can be prevented by using a differential pressure valve.

To render the experimental findings more robust they will have to be confirmed in a numerical experimental model (computerized fluid dynamics).

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Chapter 7. Procoagulant effect of CSF

Static coagulation assay and dynamic roller pump model

Introduction

Draining CSF to the venous system causes blood-CSF-foreign material interactions. The influence of CSF on blood coagulation in general is not well established. Some authors suggest that CSF may enhance hemostasis as it contains proteins such as fibrinogen and tissue factor that may activate the clotting cascade (1-3). Consequently, the protective effect of the 'constantly renewing CSF sleeve', which has never been substantiated, was put in doubt. Therefore, in the experimental goat model, we evaluated the effect of adding CSF to blood on blood coagulation and found that CSF has a procoagulant effect.

In this chapter we explore whether CSF also has a procoagulant effect in humans and if the blood-CSF-foreign material interaction prevents or promotes clot formation. These questions are addressed in 3 consecutive manuscripts.

The first manuscript presents a suitable setup to evaluate the research question. In theory, animal- or in vitro models can been used (4). However, in vitro models that use human fresh blood are preferred over animal models, as the clotting and platelet function of animals and humans are essentially different (4-6). A suitable in vitro model should allow to infuse fluids, to implant the shunt in a correct position and to generate realistic flow

conditions. Such a model was not found in previous literature. In the manuscript we present a new non-occlusive roller pump model that allows to adequately simulate the in vivo situation to which the distal (intravascular) part of the ventriculosinus shunt is subjected.

The second manuscript addresses the quantitative assessment of clot formation on the shunt's surface. These tiny clots are evaluated on SEM images which are 2D projections of the 3D objects. Due to projection effects, the cylindrical shunt surface and the covering clots will be represented distorted and scaled (7, 8). If not corrected, these projection effects will bias the quantitative assessment of the clots. The manuscript explores this problem and presents a Matlab Simulink[®] script to correct the projected SEM images in order to enable an accurate quantitative assessment.

The third manuscript uses the new in vitro model and the Matlab Simulink[®] script, to evaluate the effect of CSF infusion on clot formation on the surface of retrograde implanted shunts. CSF infused shunts are compared to Ringer's Lactate (RL) infused shunts and controls (no infusion fluid). The strong point of this dynamic experiment is the approximation of the in vivo situation. However, the set-up contains possible sources of bias: blood and CSF are not from the same donor, which may cause immunological reactions due to incompatibility, and the coagulation tests may be disturbed because of the need for heparinization. To address these weaknesses the manuscript combines the dynamic experiment with a static in vitro coagulation assay. This static setup evaluates if adding CSF to blood of the same donor enhances coagulation.

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7 Procoagulant effect of CSF

Manuscript 3. A new non-occlusive roller pump model for in vitro evaluation

of intravascular devices

E. Baert¹, <u>J. Vandersteene¹</u>, F. Dewaele¹, F. Desomer², A. Van Tilborg³, D. Van Roost¹

Artificial Organs, to be submitted

1 Department of Neurosurgery, Ghent University Hospital, Belgium

2 Department of Cardiac Surgery, Ghent University Hospital, Belgium

3 Department of Haematology, Ghent University Hospital, Belgium

Abstract

Introduction: we present an experimental model to evaluate thrombus formation on catheters. The model allows infusion of fluids, correct positioning of the catheter and generation of realistic flow conditions. These factors may impact on the amount of clot formation. The model was applied on the intravascular catheter of the ventriculosinus shunt, an experimental treatment for hydrocephalus.

Methods: a cerebrospinal fluid (CSF), Ringer's Lactate (RL) or no fluid (control) infused catheter was inserted through the wall into a tubing. The tubing was filled with donor blood, circulated by a semi-occlusive roller-pump. The sixteen loops (6 CSF, 6 RL, 4 control) ran for 60 minutes each. We assessed the thromboelastogram of pure blood at the beginning to that of the infusion fluid - blood mixture at the end of the loops. Clot formation was assessed quantitatively on scanning electrode microscopy images, corrected for projection effects.

Results: the flow was 141 +/- 7.5 ml/min, the pressure wave had a maximum of 15 mmHg and a minimum of 5 mmHg. At the end of the experiment, the concentration of the infusion fluid in the tubing was 5.82%. In the control loops, the thromboelastogram was not significantly different before and after running the control loops, but RL and CSF infusion provoked an activation of coagulation, which was more pronounced in the latter. Compared to the control loops, there was more clot formation on the catheters in the CSF loops and less in the RL loops. There was less clot formation on the side of the catheters facing the blood flow than on the side that was hidden from the blood flow.

Discussion: the significant differences, depending on infusion fluid and side of the catheter relatively to the blood flow, indicate that infusion fluid, flow conditions and position of the catheter in the vessel are worth modeling.

Introduction

Catheters are widely used to gain vascular access. Examples are central venous catheters, atrial lines and ventriculovenous shunts. These devices may suffer from thrombotic complications, making thrombogenicity testing essential in their preclinical evaluation trajectory.

The Chandler Loop, a reference in vitro model to evaluate hemocompatibility and clot formation on intravascular devices (1), consists of a circular closed tubing filled with blood and a small amount of air. When the loop is rotated at a constant speed, the air bubble - which remains at the highest point generates a 'blood flow' (2). The set-up allows to evaluate catheter related factors such as biomaterial and design but does not allow to mimic several relevant in vivo conditions that may impact on thrombotic reactions. A first

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enduring a high flow rate. However, in the Chandler loop the flow rate is limited, because at higher rotation speeds, the air bubble starts to rotate together with the tubing (2). A second example is the infusion of fluids through the catheter. This is only possible when the catheter is inserted through the tubing wall. Although theoretically possible, a major disadvantage of this approach would be the exposure of the catheter to an air-blood interface while rotating together with the tubing (2). This causes mechanical hemolysis, leucocyte induction, platelet activation and non-physiological shear forces that will bias the results (2-4).

example is the flow rate. Catheters are often inserted in major vessels

Animal models do allow to evaluate relevant in vivo conditions. However, the clotting and platelet function of animals and humans are essentially different which may influence the tests results, especially when evaluating the hemocompatibility of small bore catheters (2, 5, 6). As such more reliable results are obtained using fresh human blood for the evaluation of thrombogenicity of medical devices (2, 5, 6).

In this manuscript we present a new non-occlusive roller pump model that allows fluid infusion through the catheter and generation of a full range of flow conditions. The model was applied to the ventriculosinus shunt, an experimental treatment for hydrocephalus (7, 8). This shunt, that drains CSF from the brain's ventricles towards a dural venous sinus, consists of 3 components. Its proximal ventricular catheter and its unidirectional valve are generally accepted and routinely used components of CSF shunts, but its distal venous catheter still requires research concerning thrombogenicity before implementing it on a regular base in human medicine. We wanted to assess whether, besides the biomaterial, also the draining CSF and the (local) flow characteristics could have an impact on the amount of thrombus formation on the shunt.

Materials and methods

Experimental set-up

The experimental set-up is shown in figure 1.



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Figure 1. Set-up of the roller pump model

A syringe pump [1] injects the infusion fluid through a catheter [2] into the tubing [3] reflecting the blood vessel. The tube is closed by a T-formed connector [4] linked to a pressure transducer and an overflow line [5]. The overflow line compensates for the injected volume by draining an equal amount of the infusion fluid-blood mixture to a dripping chamber. Blood flow is generated by a semi-occlusive roller-pump [6]. Depending on the orientation of the roller pump [round arrows] the blood flow [straight arrows] will be directed with or against the direction of the flow in the catheter (in the drawing the blood flow and the flow in the catheter have opposite directions). The silicone tube is partially submerged in a bath containing water [7] that is temperature controlled by a heater [8].

This set-up was used to evaluate the intravascular catheter of a ventriculosinus shunt. Specific characteristics of the in vivo situation are the infusion of CSF through the shunt, the high flow in the SSS (150 ml/min) and the position of the shunt, directed against the blood flow ('retrograde') (9).

A syringe pump (Ohmeda 9000; GE Healthcare, Madison, USA) injected CSF through the catheter ('shunt') at a rate of 2 ml/h. To evaluate the influence of CSF infusion on thrombus formation, two other groups were defined: Ringer's lactate (RL) infusion and no infusion ('controls', CTRL). The CSF used in the CSF group was obtained from a patient with a ventriculo-external drainage and had a total protein concentration of 25.7 mg/dl. In the control group the shunt was purged with RL and subsequently closed at the extravascular end to prevent blood from entering the lumen of the catheter. The shunt, made of Tecothane (Lubrizol; TT-1074 A; 1.3 mm inner diameter × 1.9 mm outer diameter, 30 mm length) was inserted through the tubing wall and advanced for 25mm into the tubing lumen. The tubing consisted of phosphorylcholinecoated silicon (length: 1 meter, inner diameter: 6.35 mm, outer diameter: 9.52 mm; PHISIO coating, LivaNova, Mirandola, Italy). Fresh blood was collected by standard venipuncture from two healthy donors and immediately heparinized with 0.7 IU/ml. After rinsing the tube with RL, it was filled with donor blood and closed by connecting both ends with a polycarbonate connector with a luer lock. An overflow line, connected to the luer lock, allowed to compensate for the injected infusion fluid volume by draining an equal amount of the blood-infusion fluid mixture to a dripping chamber. The chamber is positioned 14 cm above the tubing which results in a pressure of 140 mm H_2O (10.3 mm Hg or 1373 Pa) equal to the physiological pressure in the superior sagittal sinus in supine position (10). In one loop, a pressure transducer (DTXPlus; Argon; Bornem Belgium) was connected to the luer lock. A roller-pump (LivaNova, Mirandola, Italy) is set at 15 rotations per minute (RPM). A dynamic occlusion setting was used to obtain a blood flow of 150 mL/min at 15 RPM or 75% occlusion. The accuracy of the occlusion was validated by a calibrated cylinder. This non occlusive setting is non traumatic to blood (11).

The blood flow is opposite to the outlet of the shunt. The shunt outlet is thus positioned 'retrograde' (Figure 3). All tubing outside the pump housing is submerged in a water bath to maintain blood temperature at 37 °C.

The concentration of the infusion fluid in the loop depends on the infusion rate (Q), the outflow of the blood-infusion fluid mixture and the total intravascular volume (V_{tot}) (Figure 2). The volume percentage of the infusion fluid (V%_{inf}) at a given time (t) is obtained by the following formula:

$$V\%_{inf} = t^{*}Q/(V_{tot} + t^{*}Q)^{*}100\%$$

The infusion rate was 2 ml/h or 0.033 ml/min, the total intravascular volume 32 ml (volume tubing = $\pi r^2 x l = \pi x (0.635 \text{ cm} / 2)^2 x 100 \text{ cm}$) and the duration of the test 60 minutes. Thus, at the end of the experiment the volume percent of the infusion fluid was 60 min*0.033 ml/min/(32 ml+60 min*0.033 ml/min)*100% = 5.82%. Sixteen experiments were performed (6 with CSF, 6 with RL, 4 CTRL) and lasted 60 minutes each. The experiments were performed in separate runs of 4. Each run contained blood from the same donor and at least one experiment of each group (CSF, RL and CTRL).



Figure 2: Calculation of the volume percent of the infusion fluid at a given duration of the experiment.

After infusion of the infusion fluid [1] it circulates through the tubing [2] were it is mixed with blood [curved arrows]. The blood – infusion fluid mixture is drained to the dripping chamber [3]. The intravascular blood-infusion mixture is identical to the mixture that is drained to the dripping chamber. By consequence draining to the dripping chamber does not change the ratio between blood and CSF in the intravascular compartment.

 V_{inf} : infused volume (ml); t: duration of the experiment (min); Q: infusion rate (ml/min); C_{inf} : concentration of the infusion fluid in the tubing; V_{tot} : total volume in the tubing; V_{out} : volume of the blood-infusion fluid that is drained to the dripping chamber.

A Sonoclot[®] Coagulation Analyzer was used to evaluate changes in blood coagulation between the start and the end of the experiment. This apparatus gives three values, activated clotting time (ACT), clot rate (CR, conversion of fibrinogen to fibrin) and platelet function (PF).



Figure 3. Retrograde position of the shunt in the vessel.

The shunts are implanted against the blood flow. Two sides of the catheter are visualized: the impact side, defined as the flank facing the blood flow and the wake-side, defined as the 180 degrees opposite flank (away from the incoming blood flow).

After termination of the experiment, the catheter was cut out together with the surrounding tubing wall (to prevent abrasion of deposits) and prepared for SEM imaging. Two sides of the catheter are visualized: the impact side, defined as the flank facing the blood flow and the wake-side, defined as the 180 degrees opposite flank (away from the incoming blood flow) (Figure 3). The SEM images were corrected for projection effects by a script (MATLAB Simulink version 8.6) that applies the appropriate mathematical formulas to 'unroll' instead of project the cylinder onto a two-dimensional plane. This method is described in detail elsewhere (12). Next, at each side of the shunt, the surface covered with clots was delineated (ImageJ for Windows, Version 150, available for download at https://imagej.nih.gov/ij/index.html) and expressed as a percentage of the visualized total surface at the same side (Ratio_{impact} and Ratio_{wake} respectively). Based on these ratios, Ratio_{total} (Ratio_{impact} + Ratio_{wake}) was calculated.

Statistical analysis

Statistical analysis was performed using a commercial software package (SPSS Statistics® IBM Corp., Released 2013, IBM SPSS Statistics for Windows, Version 22.0, Armonk, New York, USA). Baseline Sonoclot® parameters were compared to those obtained at the end of the experiment by a non-parametric Mann-Whitney U test. The amount of visualized shunt surface covered with clots is compared between the different infusion fluids (CSF, RL or no infusion fluid) by a non-parametric Mann-Whitney U test. A one-sample t-test was used to evaluate differences in clot formation on the impact and wake sides of the shunt (Ratio_{impact} - Ratio_{wake}).

Statistical significance is set at 5%.

Results

Evaluation of the In vitro test-setup

The non-occlusive roller pumps generated an average blood flow of 141 +/-7.5 ml/min.

The pressure inside the tubing increased until draining to the spillover reservoir began after which the pressure remained stable throughout the experiments. The pressure wave had a maximum ('systolic' pressure) of 15

mmHg and a minimum ('diastolic' pressure) of 5 mmHg. At the end of the experiment 1.46 +/- 0.15 ml was collected in the spillover reservoir. No leakages were observed during the experiments.

Coagulation parameters

Sonoclot parameters are presented in table 1. No statistically significant differences were found for the control group. However, after infusion of both RL and CSF, the CR and PF increased significantly. There was a trend towards an increase in ACT in the control (p=0.285) and RL group (p=0.138), but this trend was absent in the CSF group (p=1).

Table 1. Comparison of the difference of ACT/CR/PF values before and after the experiments for CSF, RL and CTRL, grouped by infusion fluid.

ACT, activated clotting time; CR, clot rate; CSF, cerebrospinal fluid; CTRL, control (no infusion fluid); med., median; PF, platelet function; RL, Ringer's lactate solution; *, comparing the start and stop value (before and after the loop) yielded a p-value < 0.05.

	infusion fluid		
Parameter	CTRL	RL	CSF
[median]	0		
Δ ACT [s]	41.0	44.0	0.0
Δ CR [-]	3.5	4.2*	6.3*
Δ PF [-]	1.0	1.4*	2.3*

Evaluation of clot formation on the catheter surface

Clot formation, defined as red blood cells and platelets embedded in a fibrin network, was observed on the surface of all catheters. The amount of clot formation was evaluated by calculating the ratio between the surface of the shunt covered by debris and the total visualized surface (Ratio_{Clot}).

Parameter	Ratioclot [-]
Donor 1	0.45 +/- 0.11
Donor 2	0.53 +/- 0.14
CTRL	0.68 +/- 0.15
RL	0.63 +/- 0.14*
CSF	0.88 +/- 0.05*
Impact	0.42 +/- 0.08**
Wake	0.50 +/- 0.09**

Table 2: the ratio between the catheter surface covered with clots and the total catheter surface depending on blood donor, infusion fluid and catheter side.

Ratio_{clot}: ratio between the catheter surface covered with clots and the total catheter surface; CTRL: control, no infusion; RL: infusion of RL; CSF: infusion of CSF; Impact: side of the catheter facing the blood flow; Wake: side of the catheter away from the incoming blood flow. * and **: the difference between the marked parameters is statistically significant p < 0.05 We searched for differences in the amounts of clot formation depending on donor (donor 1 versus donor 2), infusion fluid (CRTL, RL versus CSF), or side of the catheter surface (impact- versus wake side). The values of Ratio_{Clot} for the different groups are shown in table 2.

Ratio_{Clot} did not differ between the two donors (P-value = 0.6). However, differences were found depending on the infusion fluid. The differences between RL and CSF are statistically significant (P-value = 0.009).

When the impact and the wake side of the catheters were evaluated separately, Ratio_{Clot} was higher on the wake side of the catheters (statistical significant, P-value = 0.008).

Discussion

To our knowledge this is the first in vitro experiment that allows to mimic the in vivo conditions to which intravascular catheters are subjected: the infusion of fluids through the catheter, the position of the catheter in the vessel and a realistic flow rate.

The set-up was applied to the venous catheter of a ventriculosinus shunt, an experimental treatment for hydrocephalus. An evaluation was performed to know whether the drainage of CSF and the local flow characteristics impact on the amount of thrombus formation on the shunt.

The infusion of fluids proved to have an influence. There was a trend towards less clot formation in the RL group compared to the CTRL group. Probably early deposits on the shunt's surface are 'washed away' by the infused fluid. However, we found significantly more clot formation in the CSF group compared to the RL group. This is in line with previous literature showing that CSF enhances coagulation (13).

Also, the position of the catheter in the vessel and the (local) flow conditions proved to be important. There was significantly less clot formation on the side of the shunt that faces the incoming blood flow compared to the 180 degrees opposite side that is 'hidden' from the flow. When the streamlines hit the shunt surface they deflect and cause shear forces that might clear clots in an early stage. Directly downstream from the shunt, some of the running fluid separates from the stream lines and is submitted to turbulences and stagnation (14). This slow, non-laminar flow promotes clot formation (9).

Strengths and weaknesses of the model

The usage of blood from different donors is a possible source of bias. This was attenuated by performing a control loop (without infusion of fluid) with each portion of donated blood and by distributing the different loops (RL; CSF and CTRL) equally between the donors.

The infusion of fluids results in hemodilution that may bias the results. In the experiment with the ventriculosinus shunt, hemodilution was controlled by limiting the duration of the loops to 60 minutes and the infused volume to 2ml.

Even after this relatively short experiment, impurities were observed on the surface of every shunt. This was satisfactory as early-stage reactions, that consist of the adherence of proteins and platelets, are known to mediate the further coagulation process (5).

The infusion rate of 2ml/h is significantly lower than the physiological drainage of CSF (21 ml/h). However, even with this small infusion rate, significant differences were found in the amount of clot formation between shunts infused with RL versus CSF.

By limiting the duration of the experiment and the infusion rate, the volume percentage of the infusion fluid was only 5,88% at the end of the experiment. This is significantly lower than 9 - 11%, the percentage known to be the threshold for infusion fluids like CSF and RL to affect coagulation (15). However, the coagulation properties changed during the experiment:

In case of RL or no infusion, the ACT and the CR both increased. ACT is a measure of initial fibrin formation and represents the intrinsic limb of the coagulation cascade. Higher post-test ACT values can be explained by deprivation of fibrinogen and consummation of clotting factors during the in vitro test. The CR value is a measure for the rate at which fibrin monomers are polymerized into fibrin strings. The CR value increases in al post-test blood samples. This can be explained by the activation of thrombin, due to the extra-corporal circulation of blood (16).

After the infusion of CSF, the ACT remains stable while the CR and PF both increase. This finding confirms the coagulation enhancing effect of CSF (13) which seems to be dominant over the roller pump effects.

The impact of CSF on overall coagulability may have reinforced the CSF-bloodforeign material interaction. However, the opposite is true for RL. Although CR and PF increased more in the RL group compared to control, less clot formation was observed on the shunts. Thus, the coagulability enhancing effect of RL did not mask the protective effect of the fluid sleeve.

Conclusion

We present an in vitro experiment that allows to model the in vivo conditions to which intravascular catheters are subjected. The set-up allows infusion of fluids, correct positioning of the catheter and generation of realistic flow conditions. Applying the model on the intravascular catheter of a ventriculosinus shunt proved that these factors may have an influence on the amount of clot formation on a catheter's surface.

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Manuscript 4. A method for improved quantitative evaluation of scanning electron microscope images of cylindrical surfaces

J. Vandersteene¹, T. Van Den Berghe², G. Planckaert², E. Baert¹, F. Dewaele¹, F.

De Somer³, D. Van Roost¹

Physiological measurement, submitted

1 Department of Neurosurgery, Ghent University Hospital, Belgium 2 Faculty of Medicine and Health Sciences, Ghent University, Belgium

3 Department of Cardiac Surgery, Ghent University Hospital, Belgium

Abstract

Surfaces of medical devices are typically evaluated by scanning electron microscopy (SEM) (1-13) (1-13), which generates 2D projections of 3D objects. The projected images of surfaces, not perpendicular to the direction of the projection, will be distorted and scaled. This impedes a quantitative assessment of surface irregularities (regions of interest, ROI). In this paper a Matlab Simulink[®] script is presented that corrects SEM images of cylindrical surfaces for the above projection effects. The accuracy of the script was verified by evaluating the same ROI in different locations on a cylindrical object. Any given projected ROI became progressively smaller when it was moved from the center to the periphery of the cylindrical surface. Thus, when expressed in relation to the total visualized surface, the ROI is overrated in the center and underrated in the periphery of the projected images. The relative difference, that was found to be as high as 60%, decreased to 10% after correcting the images. The script was then applied to an in vitro experiment. Analyzing the corrected images yielded results that were statistically strongly different from those based on the uncorrected images. Study of these differences between the uncorrected and corrected images supports the conclusion that ROI tend to be located in the periphery of the cylindrical surface.

Introduction

Surfaces of medical devices can be evaluated for "regions of interest" (ROI) (1-13). Specific examples of ROI are deposit formation in ventriculoperitoneal shunts, clot or biofilm formation on catheters and coating irregularities on coronary artery stents (1-13). This evaluation may be part of assessments of general biocompatibility and thrombogenicity, which are compulsory according to the relevant ISO standards (14).

Surfaces of medical devices are typically analyzed by scanning electron microscopy (SEM). The generated SEM images, which are 2D projections of 3D objects, allow a qualitative evaluation (1-13). However, quantitative evaluation will be biased due to deformation and scaling of surfaces that are not perpendicular to the direction of the projection (15, 16).

This paper investigates how projection affects evaluation of ROIs on cylindrical surfaces. It presents a Matlab Simulink[®] script that corrects the projected images to enable a more accurate quantitative assessment.

Materials and methods

Image correction

It is assumed that the cylindrical object is mounted with its longitudinal axis perpendicular to the SEM's direction of view. The generated image will be a projection of half of the cylinder. Surfaces situated away from the image center will have a smaller projection area then those close to the midline (Figure 1).



The aim is to correct the projected image in a way that it corresponds with the projection of a cylinder that has been 'unrolled' to adjust for the projection distortion. The concept is shown in Figure 2. A circle segment s (length = β R, β in radians) will have a projected length k; k has to be corrected to k', corresponding to the length of s. k' is a function of k and β , as expressed in equation 1. Half a cylinder (radius R) has a real length of π R, which should be the total length of the projected segment.

The length of k' is given by $k'(k, \beta) = \beta R = sin^{-1}(k/R)R$ [equation 1], which is not a linear function (15, 16). Thus, the correction, needed when the projected circle segment is further away from the image center, will be more important.

In computational terms the image transformation is implemented using matrices (Figure 3). Each element of the matrix corresponds to a pixel in the projected image. The number of rows correlates with the length of the longitudinal axis of the cylinder, while the number of columns correlates with the length of the projection of the half cylindrical arc. The value of the matrix

elements, an 8 bit integer between 0 and 255, represents the grey value of the corresponding pixel.



Figure 2. Correction of the projected image

A segment s of a circle is vertically projected to k. Due to the projection, the original length of s is downscaled to the length of k. The aim is to correct the image, so that in the corrected image the length of k' corresponds to the original length of the circular segment s

A script (Matlab Simulink[®] version 8.6, MathWorks Inc., Natick, Massachusetts, USA) was written to transform the matrix of the projected image into a matrix that represents the unrolled image (15, 16). The corrected matrix will have more columns than the original, because the visualized total surface - half a cylinder - has a projected length of 2R while the unrolled length equals π R (Figure 2) (15, 16).


Figure 3. Image transformation using matrices.

First, the projected image (not shown) is represented as a matrix (upper left) composed of 4 rows (longitudinal axis of the cylinder) and 23 columns (projection of the arc). The value of each of the resulting 92 pixels represents the grey value of the corresponding dot of the image. For visual reasons, only 0 and 1 are used. Second, the corrected matrix is generated (lower left). The corrected matrix has more columns than the original matrix and the original elements are progressively more spread out when going from the center to the periphery (principle of unrolling according to equation 1). The last row of the corrected matrix (letters a-k) at the bottom of the left image gives the column names. The empty columns in the matrix correspond to the black lines in the image (right, uncorrected side). Third, the value of the empty elements is calculated using a bilinear interpolation model that uses the average of the two adjacent translated pixel values. Finally, the corrected image is generated based on the corrected matrix (right, corrected side).

The value of the elements of the additional columns (which are empty and need to be calculated) is calculated using a bilinear interpolation model, for which the code block uses the average of two adjacent translated pixels (15, 16). Based on the corrected matrix, the unrolled image is generated.

Validation

A black dot is drawn on the surface of a cylinder (medical device) to determine a ROI using SketchUp[®] 2017 software (Trimble Inc., Sunnyvale, California, USA) (Figure 5). Starting with the circle in the center of the image, the cylinder is rotated counter clockwise in steps of 5° to move the ROI progressively to the periphery of the image. The maximal rotation angle is limited to 60° to prevent the circle from crossing the plane of view, which would bias the assessment. The surface areas of the projected cylinder and covering ROI are assessed using ImageJ[®] software (National Institutes of Health, 9000 Rockville Pike, Bethesda, Maryland 20892, USA) and the ratio between these surfaces is calculated. Both the uncorrected ('projected image') and corrected ('unrolled image') images are assessed and the difference between the obtained ratios is calculated. Likewise, the difference between the relative projected surface areas of the ROI in the center versus the periphery of the cylindrical surface is calculated.

Practical example - implementation

The setup of the in-vitro experiment is discussed in detail elsewhere (17). In summary, a roller-pump assures circulation of blood through a silicone tube, representing a blood vessel. A catheter, directed against the direction of the blood flow, was inserted through the tube wall (Figure 4). Two sides of the catheter are defined: the impact side, which is facing the incoming blood flow, and the wake side which is the 180° opposite flank (the side away from the incoming blood flow).



Figure 4. Position of the catheters in the in-vitro experiment

The catheter is inserted through the wall of a silicone tube that represents a blood vessel. The tip of the catheter is aimed against the direction of the blood flow (arrow). The impact side faces the blood flow. The wake side is the side away from the incoming blood flow.

After the experiment, both the impact and wake sides of the catheters were evaluated by SEM imaging. The total shunt surface and the ROI (here the covering debris on the shunt) were delineated using the ImageJ[®] software package. An assessment was made before and after correction of the images, by two different investigators. Interobserver variability was ruled out by interobserver control methods (agreements on which ROI to delineate and delineation done by two independent observers). No trends or statistically significant differences were found between the observers. The area of the ROI was expressed as a percentage of the catheter's total visualized surface resulting in "Ratio Impact" and "Ratio Wake". "Ratio Total" was defined as the total surface of the ROI (cell debris) at both sides of the shunt divided by the total shunt surface.

A statistical analysis was performed using SPSS Statistics[®] 22 (IBM Corp., Released 2013, IBM SPSS Statistics for Windows, Version 22.0, Armonk, New York, USA). The normal distribution of Ratio Impact, Ratio Wake and Ratio Total was objectified by one-sample Kolmogorov-Smirnov tests. A one-sample t-test was used to compare the ratios obtained before and after correction of the image. For all tests, statistical significance was set at 5% and strong statistical significance at 0.1%.

Results

Calculational example

When the circle put upon the cylinder is projected to a 2D plane, it is observed as an oval object. After correction with the Matlab Simulink[®] script it is observed as a circle again (Figure 5).

Starting with the circle in the center of the image, the cylinder is now rotated counterclockwise in steps of 5 degrees to see stepwise differences. The projected surface of the circle progressively decreases as it is displaced to the periphery of the image. This phenomenon is clearly less pronounced after correction of the images (Table 1 and Figure 6).



Figure 5. Schematic representation of the calculational experiment

Left: a cylindrical object, comprising a circular ROI, is turned to move the ROI from the image center (upper row) to the periphery (lower row). The degrees of rotation are limited to prevent the ROI to be rotated out of the field of view.

Middle: After SEM projection along the Z-axis, both the total visualized surface and the circular ROI are represented distorted due to scaling along the X-axis. The circular ROI is represented as an oval. The distortion of the ROI is far more pronounced when the ROI is located in the periphery (lower row) versus the center (upper row) of the image. Right: The Matlab Simulink script corrects the SEM images. The total visualized surface (represented as a rectangle) is wider along the X-axis in the corrected images. The ROI is correctly represented as a circle.

Please note that for visual reasons the ROI is represented larger than in the actual experiment.

Rotation	SEM	Matlab	Table
	Projection	Unrolled	periph
0	2.86619384	2.03183	 circula
5	2.84230138	2.048334	 projec
10	2.74130629	2.080918	 The p
15	2.70761053	2.025509	 circulai
20	2.56965804	2.057953	 percen
25	2.45784106	1.956758	 visualiz
30	2.291043	1.950369	_
35	2.11973143	1.938867	_
40	1.89857141	2.024634	_
45	1.71782113	1.941526	_
50	1.49548276	1.801682	_
55	1.31393807	1.828629	
60	1.07337045	1.829391	

Table 1: Influence of peripheral dislocation of the circular object on its projected surface.

The projected surface of the circular object is expressed as a percentage of the projected total visualized surface.

The projected relative surface of the circle is compared between the projected images and the unrolled images and expressed as a percentage of the total visualized surface. When the circle is in the central position, the relative surface is higher on the projected images. The opposite is true when the circle is located at the periphery of the projected surface. At 39.44° rotation, the relative surface area of the circle is equally observed on the projected and unrolled images. Results are illustrated in Figure 6.



Figure 6. Results of the calculational experiment

Left: Difference between the projected versus unrolled surface of the circular object, in function of the peripheral displacement. Right: The relative difference between the surface of the circular object in a given position (rotation angle X degrees) is compared to that in the central position (rotation angle = 0 degrees) for the projected images (solid dots and dashed line) and unrolled images (open dots and dashed line). This represents the scaling or error of the images and thus the opportunity for correction.

As it is known that the circle has in reality the same surface area in both positions, the difference between the central and peripheral measurements represents the error of the image that has been used. The relative error made after assessment of the projected surface of the circle relatively to the total visualized surface is shown in Figure 6 – right side. The error increase is not linear: it increases faster towards the periphery of the image. The maximal possible rotation that still allowed visualization of the total circle is 60 degrees. The relative error at this point is 60% for the projected images versus 10% for the corrected or unrolled images.

Practical example to prove applicability

The mean ratios obtained on the projected versus the unrolled images are shown in Table 2. The ratio was always higher when assessed on the unrolled images. The Ratio Difference (Ratio unrolled – Ratio projected) was clearly different from zero. This difference was strongly statistically significant (P < 0.001).

Table 2: The ratio of deposits expressed as a percentage of the totalvisualized surface as observed on the projected and unrolled images.

	Projected	Unrolled	Difference
Ratio _{Impact}	0.43	0.69	0.26*
Ratiowake	0.52	0.77	0.25*
Ratio _{Total}	0.48	0.74	0.26*

*P < 0.001

Discussion

Irregularities, deposits or ROIs in general on the surface of medical devices are typically evaluated by SEM (1-13), which generates 2D projections of 3D objects. Surfaces of the 3D object that are not perpendicular to the direction of the projection will be represented distorted and scaled on the final SEM image (15, 16). This phenomenon, if not corrected, impedes a quantitative assessment of the visualized irregularities. However, a quantitative assessment enables a more objective evaluation and statistical analysis. In the present paper, the effects of projection and the way to correct these are elaborated for cylindrical objects.

The effects of projection are assessed by analyzing a circle with a fixed surface area (representing an irregularity or deposit or ROI), wrapped around a

from a central to a peripheral position (along the X-axis) on the cylindrical surface (Figure 5). The projected surface area of the circle decreases in a guadratic relation with the peripheral dislocation. This finding is explained by the progressive increase in angle between the cylindrical surface and the direction of the projection. In the very center of the cylinder (X = 0) this angle equals 90° (Figure 7). By moving away from the center, the angle increases progressively until it equals 180° in the extreme periphery. On the projected images, the very center of the cylinder will thus be represented at its true size, while the periphery is progressively underrated (Figure 7). So, the central image will be relatively overrated in comparison to the periphery and vice

The cylinder was mounted with its longitudinal axis parallel to the Y-axis, perpendicular to the direction of the projection (Z-axis). By consequence, moving the circle along the Y-axis will not affect the projected surface area. The fact that scaling occurs along the X-axis but not along the Y-axis results in distortion of the ROI. In our theoretical example, the circle is projected as an oval with the long axis being the original length along the Y-axis and the short axis the underrated length along the X-axis (Figure 7).

versa.

cylinder (modeling the medical device). The circle is progressively displaced

When the angle between the surface of a medical device and the direction of the projection is fixed, the projection will affect both ROI and total visualized surface equally. In this case, a biased quantitative assessment can be prevented by expressing the surface of deposits relatively to the total visualized surface. However, in the experiment described above, the ratio between the surface area of the circle and the total visualized surface decreased in a quadratic relation with the peripheral dislocation. To

understand this phenomenon, one should study the absolute values that compose the ratio. The projection of the total visualized surface is a fixed value that equals 2R times the length of the cylinder. As described above, the projected surface of the circle (in Figure 5) and thus the ratio between the surface of the circle and the total visualized surface of the cylinder, decreases when the circle is moved towards the periphery of the cylinder.



Figure 7. Projection effects

Left: Scaling of a surface under a fixed angle with the direction of projection. The absolute values of a part of the surface and the total surface are altered equally by the projection. By consequence, the ratio between a part of the surface and the total surface is not altered by the projection.

Right: Scaling of a cylindrical surface. The angle between the surface and the direction of the projection plane increases progressively from central to peripheral. As the surface will be scaled in function of the angulation with the direction of the projection, scaling of central parts of the cylindrical surface will be less pronounced than scaling of peripheral parts. By consequence, the ratio between a part of the surface and the total surface decreases from central to peripheral.

It is important to note that when the circle is located in the center of the image, it will be less underestimated and when it is located peripherally it will be more underestimated than the total visualized surface. Consequently, the

ratio between the circle and the total visualized surface will be overrated when the circle is located in the image center and underrated when it is located at the periphery of the cylinder (Figure 7).

These projection effects cause an important bias in the quantitative assessment when performed on the projected images: the relative difference between the surface ratio of the same deposit in a central versus peripheral position is around 60% when analyzed in a classical way. To prevent this biased measurement, the projected images are corrected to correspond to half a cylinder that has been unrolled onto a plane. A Matlab Simulink® script was written to apply the appropriate formulas (see equation 1) (15, 16). After applying the script, the oval projection of the circle is corrected to represent a circle again and the relative difference between the surface ratio of the same ROI in a central versus peripheral position decreased to 10%, thus decreasing the error significantly. These findings proof both the accuracy of the script and the importance of the correction to obtain unbiased quantitative analyses.

The impact of the Matlab Simulink[®] correction is illustrated by applying the script to SEM images of catheters that have been in contact with blood during an in-vitro experiment. The amount of shunt surface covered with clots was statistically strongly different when assessed on the projected versus the unrolled images. Additional information about the distribution of the deposits was obtained by combining both results: the ratio between the total surface of the deposits and the total visualized surface is always significantly higher when assessed on the corrected images. As described above, central clots will be overrated while peripheral clots will be underrated when these are assessed on uncorrected images. Thus, the higher values after Matlab

Simulink[®] correction indicate that clot formation occurred predominantly on the peripheral parts of the catheters. This correlates with the influence of the blood flow that hits the very center of the shunt's impact side with maximal power, washing away adsorbed proteins and platelets. Further away from the midline, the blood will be diverted resulting in a slow non-laminar flow and even turbulence which predisposes to clot formation (18).

Conclusion

Quantitative assessment of irregularities, deposits and ROIs in general on a cylindrical surface are biased when performed on SEM images due to projection effects. This bias can be overcome by accurately calculated correction of the projected images. By comparing the uncorrected and corrected images, information about the distribution of ROIs can be obtained.

Disclosures

The authors report no conflicts of interest.

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Manuscript 5. The influence of cerebrospinal fluid on blood coagulation and the implications for ventriculovenous shunting

J. Vandersteene¹, E. Baert¹, G. Planckaert², T. Van Den Berghe², D. Van Roost¹,

F. Dewaele¹, M. Henrotte², F. De Somer³

Journal of Neurosurgery, accepted

1 Department of Neurosurgery, Ghent University Hospital, Belgium 2 Faculty of Medicine and Health Sciences, Ghent University, Belgium 3 Department of Cardiac Surgery, Ghent University Hospital, Belgium

Abstract

Object: The effect of CSF on blood coagulation is unknown. Enhanced coagulation by CSF may be an issue in thrombotic complications of ventriculoatrial and ventriculosinus shunts. This study aims to assess the effect of CSF on coagulation and its potential effect on thrombotic events affecting ventriculovenous shunts.

Methods: Two complementary experiments are performed. In a first static experiment, the effect on coagulation of different CSF mixtures is evaluated, using a viscoelastic coagulation monitor. A second dynamic experiment confirms the amount of clot formation on the shunt surface in a modified Chandler loop.

Results: CSF concentrations of 9% and higher significantly decrease the activated clotting time (ACT) (164.9 s at 0% CSF; 155.6 s at 9% CSF; 145.1 s at 32% CSF). Increased clot rates (CR) are observed starting at a concentration of 5% (29.3 at 0% CSF, 31.6 at 5% CSF; 35.3 at 32% CSF). The modified Chandler loop shows a significantly higher percentage of shunt surface covered with

deposits when the shunts are infused with CSF instead of Ringer's lactate solution (90% versus 63%). The amount of clot formation at the side facing the blood flow or 'impact side', tends to be lower than at the side facing away from the blood flow or 'wake side' (71% versus 86%).

Conclusion: Addition of CSF to blood accelerates coagulation. The interaction CSF-blood-foreign material promotes clot formation which may result in thrombotic shunt complications. Further development of the ventriculovenous shunt technique should focus on preventing CSF-blood-foreign material interaction and stagnation of CSF in wake-zones.

Introduction

The effect of CSF on blood coagulation is not well established. Some authors suggest that CSF may enhance hemostasis as it contains proteins such as fibrinogen and tissue factor that may activate the clotting cascade (1-3). This prothrombotic status is an advantage in case of brain injury or subarachnoid hemorrhage but could be potentially harmful when CSF is shunted to the venous system as happens for the treatment of hydrocephalus (4).

Ventriculoatrial shunts have a similar effectiveness and complication rate as ventriculoperitoneal shunts (5-8). However, thromboembolic complications are one of the reasons that most neurosurgeons reserve the former technique to patients in whom ventriculoperitoneal shunts are contra-indicated or not successful (4).

Ventriculosinus shunts have several advantages over the classical ventriculoperitoneal or ventriculoatrial shunts. First, overdrainage is prevented by maintaining the natural, self-regulating anti-siphon effect of the IJV (9). Second, the shunt system is shorter in length, less complex and

confined to the skull, which minimizes the risk of mechanical failure and infection⁴. While some authors describe excellent long term results, others report that obstruction due to clot formation in and around the distal shunt tip remains an issue (10, 11).

The impact of the CSF-blood-shunt interaction on this kind of thrombotic complications is still under debate. CSF, due to its composition, may enhance clot formation (1-3). To attenuate clot formation, some authors recommend to implant the ventriculosinus shunts with the tip opening directed against the blood flow ('retrograde') in order to deviate the CSF flow around the distal shunt tip. The resulting 'constantly renewing CSF sleeve' is believed to be protective against clot formation (10).

The present study assesses the impact of CSF on blood coagulation and the impact of CSF-blood-foreign material interaction on thrombotic shunt complications.

Materials and Methods

Two complementary experiments are performed: a static experiment to evaluate the impact of CSF on the coagulability of blood and a dynamic experiment to assess the impact of CSF on clot formation on an intravascular shunt.

Static experiment

The study protocol is approved by the independent ethics committee of the Ghent University Hospital (registration number EC/2016/0560). Participation in the study is proposed to every patient – not threated with anticoagulants or antiplatelet drugs – undergoing a lumbar puncture (LP) or ventriculoexternal drainage. CSF and citrated venous blood (0.109 mol

trisodium citrate/L, Terumo, Heverlee, Belgium) are collected from each patient. As the puncture itself may contaminate the first sample of each patient, these first samples are never used for the study. Immediately after the collection of at least a second sample from any selected patient, CSF is added to blood from the same patient in increasing concentrations (Table 1).

Mixture no.	1	2	3	4	5
Blood (µL)	900	900	900	900	900
Buffered Trisodiumcitrate	100 100	100	100	100	100
0.109 mole/L (μL)	100	100	100	100	100
Calcium solution (µL)	40	40	40	40	40
CSF (μL)	0	10	50	100	500
V% CSF (= V _{CSF} /V _{Total} x 100%)	0	0.952	4.587	8.772	32.468
V CSF / V blood (%)	0	1.111	5.556	11.111	55.555

Table 1. Preparation of the 5 different blood-CSF mixtures.

The different blood-CSF mixtures are recalcified (40 µL of 0.25 mol/L CaCl2 solution) and analyzed by a Sonoclot[®] Coagulation Analyzer (Sienco[®], Arvada, CO, USA). The Sonoclot[®] signature reflects the viscoelastic changes during the transition from liquid whole blood to a solid blood clot (Figure 1). It consists of the activated clotting time (ACT), the clot rate (CR) and the platelet function (PF).

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Figure 1. Sonoclot signature.

The activated clotting time (ACT) is how long the sample completely stays in the liquid phase and corresponds to the time necessary for fibrinogen to be conversed to fibrin monomers. The clot rate (CR) is the slope of the second peak/plateau of the curve which corresponds to the polymerization of fibrin monomers: the faster the fibrin polymerization, the steeper the slope. The platelet function (PF) is determined by the time to the peak (TP), to which it corresponds inversely proportionally, and by the peak amplitude (PA) of the curve, to which it corresponds proportionally. It represents the attachment of platelets to fibrin and the retraction of the clot

Dynamic in vitro experiment

The experimental setup, that is described in detail elsewhere (12), is shown in figure 2.



Figure 2. Setup of the dynamic experiment.

A silicone tube filled with blood simulates a blood vessel. Circulation of blood is achieved by a roller-pump. The tubing is partly submerged in a warm water bath to maintain a blood temperature of 37 °C. A catheter ('shunt') is inserted through the wall of the tubing and connected to a syringe pump. This pump simulates the hydrocephalic lateral ventricle and ensures infusion of CSF or RL. To compensate for the infused volume, an overflow tank is connected. 1 syringe and syringe pump, 2 shunt catheter, 3 silicone tubing filled with blood, 4 T-shaped connector, 5 dripping chamber, 6 rollerpump. A roller-pump, set in non-occlusive modus, circulates heparinized whole blood (collected from two healthy donors) through a phosphorylcholine-coated silicon tubing (LivaNova, Mirandola, Italy) that is partly submerged in warm (37°C) water. A syringe pump infuses a Ringer's lactate (RL) solution or CSF (collected from a patient with a ventriculoexternal drainage) through a Tecothane (Lubrizol, Ohio, USA) catheter ('shunt') that is inserted through the wall of the tubing. The control shunts (no infusion) are purged with RL and subsequently closed at the extravascular end to prevent blood from entering the lumen of the shunt. The infused volume is compensated by an overflow tank. The blood flow goes against the direction of the shunt insertion, the shunts are thus oriented 'retrograde' (Figure 3).



Figure 3. Shunt insertion in tubing and definition of impact and wake side. The tip of the shunt is directed against the blood flow or 'retrograde'. The solid black arrows represent the direction of the blood flow in the tubing, whereas the white arrows represent the direction of the infusion of CSF or RL. The impact and wake sides of the shunt are defined relatively to the direction of the blood flow.

Each Chandler loop runs for 60 minutes. A total of 13 loops are performed (5 with CSF infusion, 5 with RL solution infusion, 3 without infusion).

The coagulability of the pure blood at the beginning of the experiment is compared to that of the infusion fluid - blood mixture at the end of the experiment by a Sonoclot[®] Coagulation Analyzer.

At the end of the experiment, the shunts are removed together with the surrounding tubing wall and prepared for scanning electron microscopic (SEM) evaluation. The samples are mounted in a horizontal position and analyzed with an 18-fold magnification. Two sides of the shunt are visualized: the impact side, defined as the flank facing the blood flow and the wake-side, defined as the 180 degrees opposite flank (away from the incoming blood flow).

SEM images are 2D projections of 3D cylindrical objects. As can be seen in figure 4, debris more distant from the image center present a smaller projection surface than debris closer to the midline section, although in reality both can have the same surface area.

To correct for this bias, a specific script, written in MATLAB Simulink version 8.6 is executed. This script applies, to the projected surface areas, the appropriate mathematical formulas to simulate to 'unroll' the cylinder instead of 'project' it onto a two-dimensional plane.



Figure 4. Bias due to 2D projection of a cylindrical object.

Two depositions that cover an equal true surface of the shunt are shown (black and light grey surface). On the projected scanning electron microscopic image, the outlined surface resembles only half as big as the solid surface due to 2D projection of the cylindrically shaped surface

At each side, the surface covered with clots is delineated (ImageJ for Windows, Version 150, available for download at <u>https://imagej.nih.gov/ij/index.html</u>) and expressed as a percentage of the visualized surface at the same side (Ratio_{impact} = $A_{clot impact}/A_{impact} \times 100\%$; Ratio_{wake} = $A_{clot wake}/A_{wake} \times 100\%$). Next, the total surface of the clots (impact side + wake side) is expressed as a percentage of the visualized total surface (Ratio_{total} = ($A_{clot impact} + A_{clot wake}$) /($A_{impact} + A_{wake}$) $\times 100\%$)

Statistical analysis

Statistical analyses are performed in IBM® SPSS® Statistics 22.0 for Windows.

In the static experiment, a parametric paired two-sample t-test is used - after objectifying normality - to compare each of the Sonoclot parameters (ACT, CR and PF) of pure blood (0% CSF) with those of the different blood-CSF mixtures (1%, 5%, 9% and 32% CSF).

In the dynamic experiment, the Sonoclot parameters of the donor blood before the start of the experiment are compared to those of the blood-infusion fluid mixture after the experiment by a non-parametric Mann-Whitney U test. The amount of visualized shunt surface covered with clots is compared between the different infusion fluids (CSF, RL or no infusion fluid) by a non-parametric Mann-Whitney U test. A one-sample t-test is used – after objectifying normality – to evaluate if there is a difference between clot formation on the impact and the wake sides of the shunt (Ratio_{impact} - Ratio_{wake}).

Statistical significance is set at 5%.

Results

Static study

The characteristics of the study population are shown in Table 2.

Table 2. Study population characteristics

AD, Alzheimer's disease; APTT, activated partial thromboplastin time; CD, cognitive dysfunction; CP, cerebral palsy; CSF, cerebrospinal fluid; CVA, cerebrovascular accident; ELD, external lumbar drainage; FTD, frontotemporal dementia; INR, international normalized ratio; LP, lumbar puncture; MS, multiple sclerosis; N/A, information not available; NOSD, neuromyelitis optica spectrum disorder; PTT, prothrombin time; SAH, subarachnoid hemorrhage; VED, ventriculoexternal drainage; WM, white matter lesions.

pat	age	CSF	diagnosis	platelets	Protein	Coagulation
	(y)			(10³/µL)	(mg/L)	(INR, APTT, PTT)
1	59	LP	FTD	201	38.6	Normal
2	59	LP	СР	201	50.0	Normal
3	43	LP	WM	227	25.2	Normal
4	29	ELD	rhinoliquorrhea	N/A	71.5	N/A
5	68	LP	NOSD	307	151.9	N/A
6	47	LP	CD	637	40.5	N/A
7	48	LP	Vasculitis	253	115.2	Normal
8	50	LP	CVA	183	58.1	Normal
9	61	VED	SAH	394	N/A	Normal
10	70	VED	SAH	413	N/A	Normal
11	68	LP	Neurosyphilis	178	41.4	Normal
12	70	LP	AD	105	N/A	Normal
13	39	LP	Narcolepsy	235	18.6	Normal
14	58	LP	AD	180	N/A	Normal
15	19	LP	MS	260	17.5	Normal

The results of the Sonoclot[®] coagulation analysis of the different blood-CSF mixtures are shown in Table 3.

Table 3. Results of the patient study and comparison of ACT/CR/PF values fordifferent CSF concentrations in the blood-CSF mixtures.

ACT, activated clotting time; CR, clot rate; CSF, cerebrospinal fluid; PF, platelet function. *P < 0.05.

	% of CSF				
Parameter	0.0	1.0	5.0	9.0	32.0
ACT (mean)	164.9	160.4	158.9	155.6*	145.1*
CR (mean)	29.3	30.9	31.6*	31.3*	35.3*
PF (mean)	3.7	3.8	3.3	3.5	4.1

CSF concentrations of 9% and higher significantly decrease the ACT and CSF concentrations of 5% and higher significantly increase the CR. No significant effect on the PF is found.

Dynamic in vitro experiment (modified Chandler loop)

Hemodilution. The concentration of the infusion fluid increases during the experiment and depends on the infusion rate trough the shunt and the evacuation of the infusion fluid-blood mixture by the overflow tank. The calculated concentration of the infusion fluid at the end of the experiment equals 5.88%, as each loop runs for 60 minutes, the total blood volume is 32 ml and the infusion rate is set at 2 mL/h (12).

Sonoclot[®] coagulation analyzer. The differences of the Sonoclot parameters after and before the experiment, grouped by infusion fluid, are shown in Table 4.

Table 4. Comparison of the difference of ACT/CR/PF values before and afterthe experiments for CSF, RL and CTRL, grouped by infusion fluid.

ACT, activated clotting time; CR, clot rate; CSF, cerebrospinal fluid; CTRL, control (no infusion fluid); med., median; PF, platelet function; RL, Ringer's lactate solution. *P < 0.05.

	Infusion fluid		
Parameter	CSF	RL	CTRL
ACT _{difference} (med.)	0.0	44.0	41.0
CR _{difference} (med.)	6.3	4.2*	3.5
PF _{difference} (med.)	2.3	1.4	1.0

The ACT is higher after the experiment in the RL and CTRL group. In the CSF group there is no difference (before - after) for the ACT. Both the CR and the PF increase during the experiment and this increase is more pronounced in the CSF group.

Differences in clot formation in function of infusion fluid. RL-infused shunts show less clots and CSF-infused shunts show more clots than control shunts. Table 5 shows the medians of the three ratios.

Table 5. Impact of the infusion fluid on the amount of clot formation on the different shunt surfaces (Ratio_{impact}, Ratio_{wake} or Ratio_{total}).

The amount of clot formation tends to decrease when shunts are perfused with RL but tends to increase when shunts are perfused with CSF. Clot formation on CSF-perfused shunts is significantly higher than on RL-perfused shunts (marked with an asterisk). Statistical significance was also reached when the Ratio_{wake} of CTRL shunts was compared to that of CSF-perfused shunts (marked with a double asterisk).

CSF, cerebrospinal fluid perfused shunts; CTRL, control (no infusion fluid); med., median; RL, Ringer's lactate perfused shunts; Ratio_{impact}, total surface of clots on the impact side divided by the total visualized surface of the impact side of the shunt; Ratio_{wake}, total surface of clots on the wake side divided by the total visualized surface of the wake side of the shunt; Ratio_{total}, total surface of clots on the impact + wake side divided by the total visualized surface of the impact + wake side

	Infusion fluid		
Parameter	RL	CTR	CSF
Ratio _{impact} (med.)	0.59	0.62	0.89*
Ratio _{wake} (med.)	0.71	0.75	0.93**
Ratio _{total} (med.)	0.68	0.73	0.90*

Figure 5 shows the differences between the ratios, depending on the infusion fluid.



Figure 5. Boxplot of different ratios separated for infusion fluid.

For each infusion fluid the different ratios are displayed as a boxplot. Ratio_{impact}, total surface of clots on the impact side divided by the total visualized surface of the impact side of the shunt; Ratio_{wake}, total surface of clots on the wake side divided by the total visualized surface of the wake side of the shunt; Ratio_{total}, total surface of clots on the impact + wake side divided by the total visualized surface of the wake side of the total visualized surface of the impact + wake side divided by the total visualized surface of the impact + wake side of the shunt); CSF, cerebrospinal fluid; RL, Ringer's lactate solution; CTRL, control group (no infusion fluid).

Ratio_{impact}, Ratio_{wake} and Ratio_{total} are significantly higher for CSF shunts in comparison with RL shunts. Ratio_{wake} is significantly higher for CSF shunts in comparison to control shunts.

Orientation. Considering CSF and RL shunts to be one group, Ratio_{impact} (med. = 0.71) tends to be lower than Ratio_{wake} (med. = 0.86). The difference is statistically not significant (borderline: P = 0.067).

Discussion

The effect of CSF on blood coagulation may be an issue in thrombotic complications of ventriculoatrial and ventriculosinus shunts (4).

Ventriculoatrial shunts have a similar effectiveness and complication rate as ventriculoperitoneal shunts (5-7, 13). However, thromboembolic complications are one of the reasons that most neurosurgeons reserve the former technique for patients in whom ventriculoperitoneal shunts are contraindicated or not successful(4). The ventriculosinus shunt is a promising new treatment for hydrocephalus. However, obstruction due to clot formation in and around the distal shunt tip remains an issue (10, 11).

To assess the effect of CSF on blood coagulation and the role of the CSF-bloodshunt interaction in distal shunt obstruction, two complementary experiments are performed.

The first experiment evaluates the effect of CSF on the thromboelastogram by analyzing different blood-CSF mixtures. The second, a modified Chandler loop, assesses the amount of clot formation on the shunt surface in more realistic conditions.

Influence of CSF on hemostasis

The first experiment shows that adding CSF to blood makes blood hypercoagulable. This is demonstrated by accelerated conversion from fibrinogen to fibrin after CSF addition and gradual shortening of the ACT. These effects become statistically significant at CSF concentrations of at least 5-9%. Interestingly the same critical concentration is found in the modified Chandler loop. The increase in CR and the higher platelet activation are most likely due to thrombin formation on the surface of the activated platelets (14) and is only found in the group where CSF was infused.

It is unclear which factors contribute to the influence of CSF on hemostasis. CSF contains coagulation proteins and tissue factor, a potent activator of the extrinsic coagulation pathway (15). In healthy individuals, there is an imbalance between the CSF concentration of tissue factor and that of tissue factor pathway inhibitor, making CSF procoagulant. Apart from these clotting factors, immunoglobulins and other immunological factors like C3 can cause neuro-inflammation leading to a procoagulant state (1). In pathological conditions, the concentration of coagulation proteins and the imbalance between tissue factor and tissue factor pathway inhibitor even increase, resulting in a more pronounced procoagulant effect of CSF (16). Apparently, further research is necessary to elucidate this mechanism.

Based on our results we can endorse the finding of clinical series that under normal circumstances shunting CSF to the dural venous sinuses or superior vena cava will not lead to sinus or caval thrombosis (17, 18). Concentrations of CSF in the superior sagittal sinus and superior caval vein are below 5%, as CSF inflow is approximately 0.35 mL/min for a blood flow of more than 200 mL/min (10, 13, 19). However, in specific circumstances the coagulation enhancing effect of CSF can be problematic. Typical situations are contact between CSF and foreign material, accumulation of CSF in 'wake' zones and formation of a CSF-blood mixture in the distal shunt tip at higher than physiologically harmless concentrations.

Foreign material

Some authors implant the ventriculosinus shunt against the direction of the blood flow. CSF drained by a shunt in this position will flow along the shunt's surface resulting in a 'constantly renewing CSF sleeve' (Figure 6). This CSF sleeve is believed to protect against clot formation by preventing adherence of proteins and platelets to the foreign material's surface (10, 20).



Figure 6. CSF sleeve effect.

The white arrows represent the CSF 'sleeve'. This sleeve is formed by CSF draining along the shunt surface due to the blood flow that is oriented in the opposite direction. The solid black arrows represent the direction of the blood flow in the blood vessel.

The protective effect of a constantly renewing 'fluid sleeve' is confirmed by the reduced clot formation on RL-infused shunts compared to controls. However increased clot formation was observed on CSF-infused shunts. So, a CSF fluid sleeve is – contradictory to the protective effect of a fluid sleeve in general – harmful. The CSF sleeve may promote adherence of thrombogenic proteins such as fibrinogen, fibronectin and globulins. Once adhered, these will attach platelets through the GPIIb/IIIa platelet receptor which mediates the further coagulation process (14, 21).

Wake zones

A wake zone, characterized by a slow and non-laminar flow, develops directly distally to an object placed in the bloodstream (Figure 7) (20).



Figure 7. Hydrodynamic principles of flow past a cylindrical object.

When a cylindrical object is placed in the blood flow, blood will wrap around the object. When it reaches the broadest point of the object, blood will detach from the surface. At this point it will be dragged towards the wake side which causes a slow and nonlaminar flow.

The current study endorses the hypothesis of previous literature that, due to the characteristic flow conditions, more clot formation occurs on the 'wake side' of a shunt (4, 19). This procoagulant effect may be reinforced when CSF is drained to a wake zone. The local slow and non-laminar flow may result in accumulation of CSF which promotes hemostasis.

Distal shunt tip

When blood regurgitates into the shunt system, it will become stagnant and the risk of intraluminal clot formation will be high (20). The development of a blood-CSF mixture in the distal shunt system may even increase this risk further.

In the absence of a one-way valve, regurgitation of blood may occur due to a sudden increase of the pressure in the superior sagittal sinus or a decrease of the ICP (Valsalva maneuver or lumbar puncture respectively) (22, 23).

Shunt material and design

Several shunt related factors, such as material and design, may have an influence on clot formation.

The shunt material should be bio- and hemocompatible. Silicone and polyurethanes are typical materials with a suitable profile (24). In this study, Tecothane, a non-coated aromatic polyether urethane, is used. Although Tecothane is known to have a superior hemocompatibility (25), clot formation was visualized on the surface of all shunts. Different coatings may be used to further reduce the thrombogenicity of biomaterials (26). Typical examples are phosphorylcholine and heparin (26, 27). Phosphorylcholine may counteract the procoagulant effect of CSF by preventing protein adhesion to the foreign material's surface (27, 28). Heparin eluting and non-eluting coatings exist(26). Heparin eluting coatings have a limited duration of action and are developed to reduce clot formation in the acute setting (26). There is good quality evidence that a heparin eluting coating - which has mainly been evaluated on central venous catheters in children - has no beneficial effect on catheter patency (29, 30). Heparin non-eluting coatings have theoretically a permanent antithrombotic effect and are known to reduce thrombus formation on vascular grafts and vascular stents (26). In conclusion, both а phosphorylcholine and a heparin non-eluting coating may be useful to reduce
the general thrombogenicity of venous shunts and may also counteract the procoagulant effect of CSF.

Besides the material, also the shunt design might affect the amount of clot formation. The results of this study indicate that wake zones should be held as small as possible, contact between CSF and shunt material should be minimized and CSF should be prevented from entering the distal shunt tip. Wake zones can be reduced by reducing the volume of the intravascular catheter. Contact between CSF and shunt material can be minimized by not implanting the shunt retrograde. Ideally the distal shunt tip should be oriented perpendicular to the blood flow (neutral position). In this way CSF will not drain along the shunt surface nor will it drain to wake zones. CSF can be prevented from entering the distal shunt tip by using a one-way valve and keeping the compliance of the shunt system distal to the valve minimal.

Strengths and limitations of the study

To our knowledge this is the first study to address the question as to how the interaction between CSF, blood and foreign material affects clot formation.

Especially the combination of a static and a dynamic experiment is a strong point of this study.

The static experiment is designed to minimize confounding factors. The blood and CSF come from the same donor to exclude possible immunological reactions due to incompatibility. The coagulation tests are not disturbed because there is no need for heparinization. The dynamic experiment is designed to approximate the in vivo situation. Special attention is paid to the flow conditions, the position of the shunt in the vessel and the infusion of CSF through the shunts.

However, not all the aspects of the in vivo situation are modeled. The influence of the endothelium covering the wall of the blood vessel is maybe the most important factor that is not addressed. An intact endothelium counteracts coagulation, but when the endothelium is damaged or irritated, it releases thrombogenic factors(4, 31). Endothelial damage is unavoidable when the shunt is implanted. Irritation may occur at the insertion site of the shunt and at the shunt tip when positioned against the vessel wall.

Although the duration of the dynamic experiment is limited by the progressive dilution and degradation of blood products, clot formation is visualized on all shunts. This early-stage reaction consists of the adherence of proteins and platelets and is known to mediate the further coagulation process (14).

Over-dilution is avoided by maintaining the concentration of the infusion fluid beneath 6%, which is well below the concentration of 11% that is known to have an influence on hemostasis(32).

Conclusions

Adding CSF to blood enhances coagulability starting from a concentration of 5-9%. When CSF is shunted to the venous system, concentrations are generally below this critical threshold. However, in some specific situations CSF may concentrate, resulting in accelerated clot formation and shunt obstruction.

To prevent clot formation around the shunt tip (external shunt obstruction), contact of CSF with the outer shunt surface and accumulation of CSF in wakezones should be avoided.

To prevent luminal clot formation (internal shunt obstruction), blood should be prevented from entering the shunt tip using an appropriate one-way valve.

Disclosures

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Chapter 8. Evaluation of the efficacy of novel hydrocephalus treatments

Hydrocephalic experimental animal model

Introduction

This thesis is a first step in a larger research project aiming at the development of a new, long-lasting VS shunt. New prototypes can be evaluated, with regard to dimensions, implantation technique, safety and tolerance, in the nonhydrocephalic experimental goat model presented in Chapter 5. However, in order to be able to evaluate the (long term) efficacy of new prototypes to treat hydrocephalus, a hydrocephalic model will be necessary.

Manuscript 6 presents a hydrocephalic goat model to evaluate the short- and long-term efficacy of a new VS shunt. To approximate the treatment conditions in humans, a model of non-obstructive hydrocephalus is preferable.

At present, the most frequently used technique to induce hydrocephalus is a cisternal injection of kaolin (1, 2). The technique is generally referred to as being simple, reproducible and inexpensive (1, 2). It was recently used in various species, including rats (3), dogs (4) and sheep (5). Based on the above we decided to apply this technique to the goat model. Two different injection sites were evaluated: the interpeduncular cistern (6) and the cisterna magna (7-9). As described in the manuscript, the technique effectively produced hydrocephalus in almost 90% of the animals. However, the clinical impact of

the chemical meningitis, caused by kaolin to provoke hydrocephalus, was considered unacceptably high. This issue is seldom reported as a major finding in previous literature. In fact, the issue was 'extracted' from previous literature by a post hoc review of the experimental data. In this way we also found that small animals like mice and rats seem to tolerate the kaolin injection better than larger animals like dogs and sheep. To our knowledge, this finding was not published before.

Manuscript 6 thus not only reports on the details of the kaolin injection technique and the character of the resulting hydrocephalus, it also addresses the high clinical impact, that we experienced to be unacceptable.

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Manuscript 6. A hydrocephalic goat experimental model to evaluate the efficacy of hydrocephalus treatments

E. Baert¹, S. Schauvliege², <u>J. Vandersteene¹</u>, K. Vandevelde², F. Dewaele¹, F. Desomer³, D. Van Roost¹

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1 Department of Neurosurgery, Ghent University Hospital, Belgium

- 2 Faculty of Veterinary Medicine, Ghent University, Belgium
- 3 Department of Cardiac Surgery, Ghent University Hospital, Belgium

Abstract

Hydrocephalus is treated with ventriculo-peritoneal or ventriculo-atrial shunts, which have a failure rate of 50% in the first two years. A hydrocephalic large animal model is presented that allows evaluation of novel treatments. Hydrocephalus was induced in 9 female domestic dairy goats (Saanen breed) by injection of a 25% kaolin/sodium chloride solution into the interpeduncular cistern (IC) (n=3) or into the cisterna magna (CM) (n=6). The animals developed a severe aseptic meningitis that was expressed clinically by reduced food intake, refusing to stand, spasticity of the legs, pressing of the head and for some animals even seizures. Two out of 9 animals (22 %) died before hydrocephalus could be diagnosed. Six of the remaining 7 animals (86 %) developed hydrocephalus. The increase in intracranial pressure was comparable between the two groups (9.3 mmHg to 15.1 mmHg). Two of the 3 animals of the IC group and none of the animals of the CM group developed ventricular dilatation. In contrast with other species, an outflow channel between the spinal central channel and the lumbo-sacral subarachnoid space persists in goats. This channel prevents complete obliteration of the fourth

ventricular outflow and thus the development of obstructive hydrocephalus. This anatomical characteristic makes goats especially suited for the development of a model of non-obstructive hydrocephalus. However, the kaolin injection provoked a pronounced aseptic meningitis that had an unacceptable high clinical impact and clearly overshadowed the resulting hydrocephalus symptoms. The development of better tolerated techniques may be the subject of further research.

Introduction

Hydrocephalus, the accumulation of CSF in the brain, can be caused by obstruction of the CSF flow within the ventricular system (obstructive hydrocephalus), by an impeded CSF flow through the distal arachnoid spaces or by damage to the normal resorption capacity (the two latter being nonobstructive, communicating or malresorptive hydrocephalus) (1). Obstructive hydrocephalus is treated by endoscopic third ventriculostomy, while the current treatment of non-obstructive hydrocephalus consists of drainage of CSF to the peritoneal cavity or to the right atrium of the heart by a ventriculoperitoneal or ventriculo-atrial shunt (2). An important drawback of such shunts is siphoning: in a sitting or standing position of the patient, the CSF column within the catheter - through gravity - exerts suction, leading to shunt-related intracranial hypotension and aspiration of choroid plexus into the proximal catheter (3). Intracranial hypotension causes headaches, nausea, vomiting and even subdural hematomas while aspiration of choroid plexus is a major cause of shunt obstruction (2). The rate of shunt failure - necessitating surgical revision - remains as high as 50% in the first 2 years, despite the usage of expensive resistance valves and anti-siphon devices (4). As shunt failure is an important burden for patients and has a high economic impact, it is clear

that there remains a rationale for ongoing hydrocephalus research (5). To evaluate current and novel treatment techniques a suitable animal model will be indispensable (6). A large animal model is more suitable than canine models described in earlier studies as the dimensions of larger brain ventricles allow the usage of shunt systems that are similar in size and design to their counterparts for human use (7). A non-hydrocephalic goat model, allowing to evaluate whether a new technique for hydrocephalus treatment is feasible, safe and well tolerated, has been described in previous literature (6). However, to evaluate the long term efficacy of any new solution, a hydrocephalic model will be unavoidable (6). To approximate human treatment conditions, a model of non-obstructive hydrocephalus is preferable.

This paper reports on the technique and results of the induction of hydrocephalus in goats by kaolin injection. Two different injection sites were evaluated: the interpeduncular cistern (8) and the cisterna magna (9-11).

Materials and methods

Animals

The study was designed as a pilot study to identify a suitable hydrocephalic large animal model to evaluate hydrocephalus treatments. The species was selected based on anatomical characteristics. In pigs and cattle, a frontal access to the ventricles and superior sagittal sinus may be impeded by the pronounced caudal extension of the frontal sinuses. Remaining possible models were sheep, goats and horses or ponies. Finally, domestic dairy goats (Saanen breed) were chosen because of their manageability and short hair. All goats were bought from dairy goat farms. They were 1 to 2 years old and weighted less than 60 kg. Only female goats were included to be able to house the animals together.

Since the investigation was a pilot study, small sample sizes were chosen. The study consisted of a cadaver study (6 goats) and an in vivo study (9 goats). The studies were conducted serially and the goats were allocated to the different experiments in order of acquirement.

All experiments in this study were approved by the local Ethics Committee of the Faculty of Veterinary Medicine of the Ghent University (EC2012/187, EC2013/66). Care and use of animals were in full compliance with the most recent national legislation (Belgian Royal Decree of 29 May 2013) (12) and European Directive (2010/63/EU) (13).

For the cadaver anatomical study, the goats were euthanized directly after arrival at the research facility. The remaining goats were admitted to the animal facility at least 10 days prior to the start of the study for acclimatization and health checks (clinical investigation, ultrasonographic examination of abdomen and thorax, blood and feces analysis). These animals were housed in little groups (3-4 animals per cage). The cage measured 3 m x 4 m. The bedding consisted of straw and cage enrichment (an elevated platform) was present in all cages. Natural light was provided by translucent windows, and the cage temperature was kept between 15 and 20 °C. The animals were fed hay and water ad libitum, supplemented with 450 g nutritional pellets a day.

Clinical evaluation of the animals was performed twice daily. The evaluation consisted of objective (e.g. vital parameters, weight, food intake) and subjective (e.g. general impression, posturing) parameters.

All animals were fasted 24 h before surgery and received an intramuscular injection of 2.5 mg trimethoprim and 12.5 mg sulfadiazine/kg body weight (Borgal® 24%, Virbac, Barneveld, The Netherlands) starting one day prior to surgery and daily until 4 days after surgery. If needed, postoperative pain and fever were treated with 48 mg meloxicam subcutaneously (Metacam, Boehringer Ingelheim, Germany).

Euthanasia was performed by intravenous administration of 50 mg/kg sodium pentobarbital 20% (Pentobarbital, Kela, Hoogstraten, Belgium) after intravenous premedication with 0.3 mg/kg midazolam (Dormicum, Roche Pharma, Brussels, Belgium) and morphine 0.1 mg/kg (Morphine HCL Sterop, Brussels, Belgium) intravenously (IV) and induction of anesthesia with IV propofol 2-4 mg/kg (Propovet, Parsippany-Troy Hills, New Jersey, United States).

Anatomical cadaver study

After euthanasia, the goats were frozen to -20 °C and decapitated. The heads were sawn in coronal slices of about 1 cm thickness. The slices were photographed with and without a scale bar. The contours of the ventricles and the brain were delineated at the level of the coronal suture and the ratio between the ventricular surface and the total brain surface was calculated using ImageJ software (ImageJ for Windows; National Institutes of Health, 9000 Rockville Pike, Bethesda, Maryland 20892, USA; Version 150, available for download at https://imagej.nih.gov/ij/index.html). ImageJ provides a tool to measure surface areas of a plain image in two dimensions. By delineating the periphery, ImageJ calculates the surface area as measured by the number of pixels of the selected surface.

In vivo study

The day before the suboccipital puncture, the first three goats were anesthetized and a head computed tomography (CT) scan was performed. This was not the case for the subsequent 6 goats.

For the suboccipital puncture, the goats were anesthetized and correctly positioned. To reach the interpeduncular cistern (interpeduncular cistern group, n = 3), the goats were positioned with the neck in a neutral position (Figure 1).

To reach the cisterna magna (cisterna magna group, n = 6), the goats were positioned with the neck in maximal flexion. A sterile surgical skin incision was made in the neck 3 cm caudal to the external occipital protuberance. Under radioscopic guidance a spinal needle (15 G) was advanced into the cisterna magna. A pressure transducer (DTXPlus; Argon; Bornem Belgium) was connected and the ICP was measured. In the last 6 goats, the ICP was measured simultaneously with the Central Venous Pressure (CVP) within the superior caval vein and the arterial Partial Pressure of Carbon Dioxide (PaCO₂) within the auricular artery using an anesthesia monitor (Datex Ohmeda S/5) and a blood gas analyzer (Radiometer ABL 5). A PaCO₂ of 40-45 mmHg and a central venous pressure of 5-10 mmHg were targeted.



Figure 1. Suboccipital puncture to reach the interpeduncular cistern

Upper left: The goats were positioned prone with the neck in a neutral position, supported on a towel roll. A needle was inserted through a small skin incision 3 cm caudal to the occipital protuberance and advanced under radioscopic guidance into the cisterna magna. Through this needle a catheter was inserted and advanced, still under radioscopic guidance, around the brainstem to reach the interpeduncular cistern. Upper right: Sagittal slice through the cranio-cervical junction in the same goat. A white silicone catheter was inserted through the needle and left in place to mark the entry point into the cisterna magna (arrow). Lower left: fluoroscopic image showing the catheter curving around the brainstem (arrows) to end into to the interpeduncular cistern (circle). Lower right: image after injection of contrast agent. S, silicone catheter; B, brain stem; C, cerebellum; O, occipital cerebral lobe.

After completion of the ICP measurement a catheter was advanced through the spinal needle to reach the interpeduncular cistern (IC) in the first three goats (IC group). In these goats a spinal needle with a lateral opening (Tuohy needle, Ascenda intrathecal catheter spinal revision kit; Medtronic; Brussels Belgium) was used for the suboccipital puncture. The opening was turned to the right lateral side of the goat and, still under radioscopic guidance, a spinal catheter (Ascenda intrathecal catheter; Medtronic; Brussels Belgium) was inserted through the needle and advanced around the brain stem to end into the interpeduncular cistern (Figure 1). In the 6 subsequent goats (CM group) the procedure below was performed directly through the spinal needle (with the tip in the cisterna magna). Thus in this group no catheter was inserted through the needle.

Once the final position was reached 3-4 ml CSF was evacuated and 1-3 ml of lodine contrast (Omnipaque, GE Healthcare, Diegem, Belgium) was injected under fluoroscopic monitoring to verify the correct position of the catheter or needle respectively. Subsequently, 4ml (interpeduncular cistern group) or 3ml (cisterna magna group) of a 250 mg/ml kaolin (Sigma Aldrich, Overijse, Belgium)/Sodium Chloride solution was slowly injected.

All 9 goats were scheduled for ICP measurement conform the protocol described above on day 7. The 3 goats of the 4 ml kaolin group were scheduled for a head CT after the ICP measurement and were to be euthanized afterwards. The 6 subsequent goats (interpeduncular cistern group) were split into two groups: 3 goats were to be euthanized directly after the measurement, while the remaining 3 goats were to be followed for 21 days to observe the natural history of the hydrocephalus. The latter 3 goats were scheduled for ICP measurement on day 21 and were to be euthanized

afterwards. Euthanasia was performed earlier when necessary due to the animal's condition.

Statistics

The normal distribution of the parameters was assessed using QQ-plots and a Shapiro-Wilk test. An independent T-test was used to compare the increase in ICP between the IC and CM group. A paired T-test was used to analyze the increase in ICP (IC and CM group considered as one), and the ratio between the surface of the ventricles and the surface of the brain as measured on CT imaging. An independent sample T-test was used to evaluate whether there was a difference between the ratio of the ventricle to brain surface as measured during autopsy of non-hydrocephalic and hydrocephalic goats.

Results

Anatomical cadaver study

The ratio between the ventricular surface and the total brain surface at the level of the coronal suture amounted to 0.026 (0.13-0.040).

Interpeduncular cistern group

In this group (n=3) 4ml of the kaolin solution was injected into the interpeduncular cistern. No specific problems were encountered during the procedure. In the first days after the injection, the goats were periodically paddling and experienced seizures. In between these episodes and after the first days, the main symptoms were a lowered head, head pressing, refusing to stand, fore leg stiffening and weakness, decreased reactivity and reduced food intake.

The ICP and the ventricular size before and 7 days after the injection of kaolin are shown in table 1.

The mean baseline ICP was 3.33 (0-7.13) mmHg. The ICP increased only in one goat above the 95% confidence interval of the baseline values. The ratio between the ventricular and brain surface increased from 0.030 (0.018-0.040) to 0.085 (0.00-0.29). This increase was statistically not significant (P-value 0.338). In two goats, the ventricular size increased above the 95% confidence interval of the baseline values.

The CT-scan 7 days after the kaolin injection and the autopsy showed deposits of kaolin predominantly anteriorly of the pons and medulla oblongata but also in the cisterna magna in two goats (Figure 2).



Figure 2. Kaolin distribution 7 days after injection into the prepontine cistern

A: Axial head-CT showing the hyperdense kaolin around the medulla spinalis [*]. S, skull; C1, atlas; C2, dens axis.

B: Transverse section through the upper medulla spinalis and meninges in the same animal. The kaolin deposition around the medulla can be seen [*]. Note the canalis centralis of the medulla spinalis [O]. One animal developed obstructive hydrocephalus with marked ventricular dilatation (Figure 3).



Figure 3. Obstructive hydrocephalus

Coronal slices showing different parts of the ventricular system of the developed that qoat obstructive pronounced hydrocephalus. Top: rostral horns, Lower left: temporal horns. Lower right: aqueduct.

In this animal kaolin was not predominantly observed anteriorly of the brain stem but in the fourth ventricle, along the olfactory nerve and in the olfactory bulb (Figure 4). The ICP did not increase to a value above the upper limit of the 95% confidence interval of the baseline values in this goat.



Figure 4. Axial CT images showing the distribution of kaolin

Axial CT images showing the distribution of kaolin (white spots indicated by the white arrows) in the animal that developed obstructive (upper row) versus non-obstructive (lower row) hydrocephalus. From left to right: level of the foramen magnum, level of the caudal fourth ventricle, level of the olfactory nerve, level of the olfactory bulb.

Cisterna magna group

In this group (n=6) 3ml of the kaolin solution was injected into the cisterna magna. No specific surgical problems were encountered during the procedure. During orotracheal intubation, one goat experienced massive aspiration of gastric reflux and died shortly after the induction due to asphyxia.

In the 5 goats that survived, the ICP was measured by suboccipital puncture 7 days after the injection of kaolin. In one goat, the suboccipital puncture was cumbersome and no ICP measurement could be obtained. After the puncture the goat was tetraplegic and had to be euthanized. The autopsy showed subarachnoidal and brainstem bleeding. By consequence ICP measurements were obtained in 4 of the 6 animals of the second group.

The ICP before and 7 days after the kaolin injection is shown in table 1.

Table 1: ICP and brain morphometric measurements

The ICP and ventricular size before and after the development of hydrocephalus are shown. IC: interpeduncular cistern; CM, cisterna magna; ICP before: ICP before the induction of hydrocephalus; ICP after: ICP at least 7 days after the induction of hydrocephalus; CT: computed tomography; Ventricles before: ratio between ventricle surface and brain surface as assessed on a coronal slice at the level of the foramen of Monro before the induction of hydrocephalus; Ventricles after: ratio between ventricle surface and brain surface as assessed on a coronal slice at the level of the foramen of Monro at least 7 days after the induction of hydrocephalus; Asterisk: values that increased above the upper limit of the 95% confidence interval of the baseline values; x: missing value; /: value cannot be assessed.

ID	Group	ICP	ICP-a	Mod	Ventricles-b	Ventricles-a
1	IC	2	2	СТ	0,032	0,177*
2	IC	3	18*	СТ	0,024	0,024
3	IC	5	7	СТ	0,031	0,055*
4	CM	16	х	Autopsy	/	Х
5	СМ	12	20*	Autopsy	/	0,030
6	СМ	12	21*	Autopsy	/	0,043*
7	СМ	14	х	Autopsy	/	0,018
8	СМ	15	14	Autopsy	/	0,017
9	СМ	16	24*	Autopsy	/	0,024

The mean baseline ICP increased from 13.8 (10.5-17.0) mmHg to 19.8 (13.0-26.4) mmHg. The ICP increased to a value above the upper limit of the 95% confidence interval of the baseline values in 3 of the 4 animals.

The increase in ICP in the interpeduncular cistern group was almost equal to that of the CM group (6.0 mmHg and 5.7 mmHg respectively; P-value 0.95).

When all animals were considered as one group, the ICP increased from 9.3 mm Hg to 15.1 mm Hg. The increase in ICP was statistically significant (P-value 0.036).

The goat that died due to gastric reflux aspiration and the goat that became tetraplegic after the ICP measurement (see above) were part of the group that was planned to survive for 21 days. Consequently, only in one goat the ICP could be measured 21 days after the kaolin injection. In this goat the ICP before the injection was 16 mm Hg. It increased to 24 mm Hg on day 7 and decreased subsequently to 18 mm Hg on day 21.

The ratio between the ventricular and brain surfaces was assessed during autopsy. This ratio did not differ between the 9 animals that were injected with kaolin and the 6 non-hydrocephalic animals of the cadaver study (0.027 (0.015-0.040) and 0.026 (0.13-0.040) respectively).

Histology

A histological sample of the dura adjacent to the kaolin deposits showed aseptic meningitis with granuloma formation. The granulomas consisted of kaolin containing macrophages (Figure 5).



Figure 5. Histology of the dura after 7 days

A: Histological sample of normal dura; B: Sagittal section through the craniocervical junction showing the kaolin deposition and a thickened hyperemic aspect of the dura mater; C and D: Histological samples of the dura adjacent to the kaolin deposits showing aseptic meningitis with granulomas that consist of kaolin containing macrophages. M, medulla oblongata; *, inflamed dura mater; x, granulomas

The kaolin itself was observed in the subarachnoid space where it provoked perivascular inflammation. At the surface of the brain parenchyma, focal perivascular inflammatory infiltrates were observed (cuffing).

In the goats that developed increased ICP, the ependymal layer of the ventricles was flattened and denuded in some areas. Leukomalacia, focal hemorrhages and hyaline fluid were observed around the ventricular system.

This is consistent with transependymal resorption of CSF. The choroid plexus of the fourth ventricle was edematous.

Discussion

Non-obstructive hydrocephalus is treated with ventriculo-peritoneal or –atrial shunts, which have a failure rate that is as high as 50% in the first 2 years (4). The aim of this study was to present a hydrocephalic goat model to endorse the development of novel techniques that may lower this unacceptably high failure rate. To approximate human treatment conditions, a model of non-obstructive hydrocephalus was preferred. Two different techniques were evaluated: in the first animals (interpeduncular cistern group, n=3), 4ml of a 25% kaolin solution was injected into the interpeduncular cistern - anteriorly to the brain stem - to prevent occlusion of the fourth ventricles' outflow ('first group') (14). In the subsequent animals (cisterna magna group, n=6) 3ml of a 25% kaolin solution was injected into the cisterna magna, which is a more standard and well-documented technique to induce hydrocephalus in small domestic animals such as rats and dogs (9-11).

Two animals died during the experiment. One goat due to asphyxia after massive aspiration of gastric reflux during orotracheal intubation. A second goat due to brainstem bleed after a cumbersome suboccipital puncture.

In the remaining goats (n=7), the kaolin injection provoked pronounced aseptic meningitis that caused hydrocephalus in 6/7 (86%) of the goats.

Hydrocephalus

The hydrocephalus was characterized by ventricular dilatation (2/6 hydrocephalic goats – both belonging to group 1) *or* an increased ICP (the remaining 4/6 hydrocephalic goats).

Such a variable degree of ventricular dilatation within the same species and also in between species was described in previous literature and probably relates to the pathophysiology of a kaolin induced hydrocephalus: kaolin provokes aseptic meningitis that causes meningeal thickening and arachnoid adhesions that impede the normal CSF flow (9). This may lead to acute obstructive or latent non-obstructive hydrocephalus, depending on the location of the CSF-flow obstruction (9). Acute or obstructive hydrocephalus is due to obliteration of the fourth ventricle's outflow and is characterized by a steep rise in ICP and a marked ventricular dilatation (9, 15). Latent or non-obstructive hydrocephalus is caused by a more downstream obstruction of the subarachnoid space or damage to the normal absorption capacity. It is characterized by a more gradual increase in ICP and less pronounced ventricular enlargement. (9, 10, 15) Injection of kaolin into the basal cisterns probably causes a variable combination of both types.

The variability of the ventricular dilatation within species can be explained by the variable obstruction of the fourth ventricular outflow, which was more pronounced in the animals that did develop ventricular dilatation in the current study.

There is also variability of the ventricular dilatation in between species. The ventricular dilatation in goats and sheep is less pronounced than described in other species (7, 9, 16). Why a kaolin injection into the basal cisterns in goats and sheep produces such mild ventricular dilatation was not investigated. However, a similar issue was encountered in rabbits (17). In contrast with most other species, goats and rabbits have in common a persisting open outflow channel between the spinal central canal and the lumbosacral subarachnoid space (17-20). This channel enables CSF to bypass the (partially) obstructed

foramina of Luschka (a median foramen of Magendie does not exist in goats), thus eliminating the factor that contributes the most to the ventricular dilatation (17).

The persisting open outflow channel between the spinal central canal and the lumbosacral subarachnoid space makes goats very suitable as a model of latent non-obstructive hydrocephalus as it helps to prevent the obstruction of the fourth ventricular outflow.

The injection in the interpeduncular cistern, which is more complicated to reach, does not present an advantage over the injection into the cisterna magna to prevent an obstructive hydrocephalus. It is striking that ventricular dilatation was only seen in the animals of the interpeduncular cistern group, as kaolin was deliberately injected anteriorly of the brainstem to prevent obstruction of the fourth ventricular outflow. The ventricular dilatation was very pronounced (to >300% of the original volume) in one animal. The distribution of kaolin in this goat suggests intraventricular injection, which is possible if the caudal medullary velum was perforated by the suboccipital puncture. Only in this goat, a kaolin plug was observed in the fourth ventricle (Figure 4). This plug obstructed not only the lateral foramina of Luschka, but also the origin of the central canal at the obex. Interestingly in this goat, kaolin was also observed along the olfactory nerves and even in the olfactory bulb (Figure 4). In earlier studies, the nerve sheet of the olfactory nerve was found to drain up to 30% of the CSF towards the extracranial lymphatic system in sheep (which are very similar to goats) (21, 22). The kaolin around the olfactory nerve may have obstructed the latter absorption pathway.

The fact that no increased ICP was measured in the animals that developed ventricular dilatation may be explained by the location of the ICP measurement. When the outflow of the fourth ventricle is obstructed, a gradient may develop between the intraventricular and extraventricular CSF compartments, causing the ventricles to dilate. Although such a pressure gradient was not observed in kaolin induced hydrocephalic dogs (9), it was found in sheep (7), which are very similar to goats. By consequence the ICP measurements in the cisterna magna in this study may have led to underestimation of the intraventricular pressure in the goats that developed ventricular dilatation.

The natural evolution of the induced hydrocephalus is unclear as only one animal was followed for an extended period (21 days). In this goat the ICP initially increased but spontaneously decreased again to nearly normal values. The reason for this finding, that was also described in previous literature, is not clear (9). Possibly the arachnoidal adhesions (generated due to the aseptic meningitis) partially disappear or compensating mechanisms develop spontaneously.

Aseptic meningitis

The injection of 4ml kaolin in the interpeduncular cistern (n=3) provoked pronounced aseptic meningitis, which had an unacceptably high impact on the animals' clinical status. The main symptoms included head pressing, spastic paresis of the four legs, paddling and convulsions. In order to reduce animal suffering, the dose was lowered and in the subsequent animals (n=6) only 3ml of the kaolin solution was injected into the cisterna magna. The latter protocol (dose and injection site) was based on previous literature on sheep (7).

The lower dose of kaolin provoked a milder, but still unacceptable clinical picture. In both groups, the important discrepancy between the severity of the meningitis and the mildness of the hydrocephalus made it difficult, if not impossible to adequately monitor the developing hydrocephalus clinically.

The pronounced clinical impact of the aseptic meningitis was also a major issue in previous studies. Although kaolin injection into the cisterna magna seems to be relatively well tolerated by mice and rats (23, 24), this is not the case for larger animals like dogs, ferrets and sheep (7, 9, 16). In the latter species the clinical signs were comparable to those observed in the current study and the mortality rate - typically 30-40% - was even higher (9, 16, 25).

The very pronounced clinical impact of suboccipital kaolin injection in the current and previous studies should urge the development of techniques that do not rely on meningitis to produce hydrocephalus. The injection of a silicone elastomer into the interpeduncular cistern seems an interesting option (8).

Conclusion

In contrast to other species, an outflow channel between the spinal central channel and the lumbo-sacral subarachnoid space persists in goats. This anatomical characteristic may be especially convenient for the development of a model of induction of non-obstructive hydrocephalus because it protects against the development of obstructive hydrocephalus.

Although the suboccipital injection of kaolin was effective in producing nonobstructive hydrocephalus, it provoked a pronounced aseptic meningitis that had an unacceptable clinical impact and clearly overshadowed the resulting hydrocephalus. The development of better tolerated techniques that do not depend on meningitis to induce hydrocephalus may be the subject of further research.

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Declaration of Conflicting Interests

The Authors declare that there are no conflicts of interest

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Chapter 9. Discussion

At present, the mainstay treatment for hydrocephalus is draining CSF to the peritoneal cavity with a VP shunt. Alternatively, liquor may be drained to the venous system by a VA shunt or a VS shunt.

The VA shunt, a classical treatment of hydrocephalus besides the VP shunt, has some advantages over the latter (1). First, confirmation of the correct placement of the distal catheter is possible intraoperatively. Second, the right atrium provides a consistent low pressure outlet: an advantage gaining progressively more importance, as obesity, that may cause high abdominal pressure and therefore dysfunction of VP shunts, becomes a global epidemic (2).

The VS shunt, an experimental treatment of hydrocephalus, preserves the natural anti-siphon effect of the IJV and restores a physiological ICP (3-6). As this technique may prevent the most important causes of failure of VP- and VA shunts, it has theoretically the potential to become the new standard of care.

However, VV shunts suffer from thrombotic complications, which is the main reason why most neurosurgeons reserve VA shunts only for patients for whom VP shunts are contra-indicated or not successful and why they are even more reluctant to start using VS shunts (7-9). The high incidence of thrombotic complications cannot be explained on the basis of a foreign body in the venous system alone, as patients with for example pacemaker leads do not suffer equivalent rates of thromboembolism (10). Up to now, it remains uncertain which characteristics predispose VV shunts to thrombotic complications. To clarify this issue, we performed in vivo and in vitro evaluations of VV shunts.

In the experimental non-hydrocephalic goat model we identified two characteristics, specific to VV shunts, that predispose to thrombotic complications:

- During the implantation of VS shunts we observed a pulsatile reflux of blood to the shunt system regardless of its orientation (anterograde or retrograde) and despite the usage of a one-way valve;
- 2) Adding CSF to blood had a procoagulant effect.

Reflux of blood into a VV shunt was evaluated in an experimental model. It proved to be caused by the dynamic pressures at the proximal (ventricular) and distal (venous) ends of the shunt. The pressure waves in the brain ventricles and the SSS originate from the phase difference between the cerebral arterial inflow and venous outflow during the heart-cycle (11). The atrial pressure wave has 3 peaks reflecting atrial contraction, ventricular contraction and atrial filling driven by systemic venous return (12). After implanting a VV shunt, CSF will drain to the venous system until the mean ventricular pressure equalizes the mean venous pressure. However, the proximal and distal pressure waves differ in amplitude, morphology and phase, causing alternating pressure differences over - and pulsatile reflux of blood into the shunt system. The resulting relatively static blood-CSF mixture in the shunt promotes clot formation and shunt obstruction or thromboembolic complications.

To verify if the procoagulant effect of CSF also exists in humans and whether it may have an impact on the amount of clot formation in and around a VV shunt, we performed two complementary experiments. A static experiment evaluated the effect on coagulation of different blood-CSF mixtures, using a viscoelastic coagulation monitor. A dynamic experiment confirmed the amount of clot formation on the shunt surface in a modified Chandler loop. We found that adding CSF to blood enhances coagulability starting from a concentration of 5-9%. When CSF is shunted to the venous system, concentrations are generally below this critical threshold. However, as discussed below, CSF may concentrate in specific situations, resulting in accelerated clot formation and shunt obstruction or thrombo-embolic complications.

After the unexpected and disappointing results of the clinical trial with the VS shunt, we hypothesized that also the position of the shunt tip against the sinus wall is a predisposing factor for shunt obstruction (6). Theoretically the risk of clot formation is minimal in the center of a vessel as a result of several factors. First, due to shear stress the blood velocity is minimal at the wall and maximal in the center of the sinus. Second, platelets and clotting factors tend to migrate to the side while red blood cells are predominant in the center (13). Third, irritation of the endothelium by a catheter stimulates endothelial overgrowth and the release of hemostatic proteins (14).

To ensure an optimal position of the shunt tip in the SSS, Baert and colleagues developed a new dural venous sinus access device (DVSAD) (Figure 1 and

Manuscript 1 Figure 6) that, when correctly implanted, secures the shunt tip in the center of the sinus (15).



Figure 1. Ventriculosinus shunt with DVSAD

Left: the ventriculosinus shunt containing the DVSAD Right: close-up of the DVSAD in the superior SSS [1]. It consists of an intravascular tip [2], a stabilizing epidural base plate [3] and an extravascular catheter [4].

Below we discuss several factors concerning the further development of this device, taking into account possible reflux due to pressure waves at the proximal and distal end of the shunt and the procoagulant effect of CSF. Although the device is developed to access the SSS, the central position of the shunt tip and the recommendations below also count for VA shunts (for example providing access to the distal superior caval vein).

Orientation of the distal shunt opening

The disappointing results of the prospective clinical trial with the retrograde VS shunt, urged us to reevaluate the advantages of the retrograde orientation that, according to El-Shafei, are essential in preventing thrombotic shunt obstruction (3, 4, 16-18):

- Impact effect: the blood flow causes the ICP to remain higher than the static Psss. This assures a constant drainage of CSF and prevents regurgitation of blood to the shunt system (17).
- CSF sleeve: the draining CSF is deflected by the blood stream and flows over the catheter surface, forming a constantly renewing CSF sleeve.
 According to El-Shafei, the CSF sleeve discourages clot formation (17).
- 3) Flow conditions: the shunt tip is located in an impact zone. The stream lines hitting the impact zone cause shear stress and clear developing clots. After hitting the impact zone the streamlines deflect and move on, without stagnation of blood (17).

Impact effect

Experimental and numerical models substantiated that the impact protects against reflux of blood due to positional changes and Valsalva maneuvers (17, 19). However, the protective effect was only partial and reflux of blood still occurred during provocation maneuvers (19). The above experimental and numerical models were static, neglecting the intracranial and venous pressure waves. In the experimental model described in the present thesis, the impact effect could only be objectified in the static situation. When pulsations were applied, the impact effect disappeared. These results indicate that the laminar flow is lost in the dynamic situation. The combination of cranial and venous pressure waves caused pulsatile reflux of blood into the shunt system, regardless of the orientation (retrograde or anterograde) of the shunt.

CSF sleeve

The beneficial effect of the constantly renewing CSF sleeve has never been substantiated. We found that, although a fluid sleeve does discourage clot formation, the coagulation promoting properties of CSF still result in a net thrombogenic effect.

Flow conditions

A quantitative comparison of clot formation on the impact and wake side of the shunts after running the modified chandler loop showed that, in accordance to El-Shafei's theory (17), less clot formation occurred on the impact side.

Conclusion

The retrograde position has no real hydrodynamic advantage, as the impact effect only partially protects against reflux of blood due to positional changes and Valsalva maneuvers and does not protect against reflux of blood due to ventricular and venous pressure waves (19). Knowing that the CSF sleeve enhances clot formation, the retrograde position may promote, rather than prevent, clot formation and should thus be discouraged. However, we cannot recommend the anterograde position either. In this position the shunt tip is located in a wake zone were blood will stagnate and CSF will accumulate (17). Both effects will promote clot formation and may result in obstruction of the distal shunt tip or cause thrombo-embolic complications (17). Based on the above findings we suggest a neutral - perpendicular to the blood flow - orientation of the DVSAD distal opening. In this position, CSF will immediately be carried away by the blood flow. The contact between CSF and the shunt surface will thus be minimal and CSF will not accumulate in wake zones. Also, in the neutral position, the shunt tip will not be subjected to unfavorable flow conditions.

One-way valve

As positional changes, Valsalva maneuvers and the interaction between ventricular and venous pressure waves cause reflux of blood into a valveless shunt system, a one-way valve is always needed (19).

However, a one-way valve has consequences on the relation between the venous and cranial pressures, as it will allow CSF to drain to the venous system whenever the ICP becomes higher than the venous pressure, but will prevent blood to return in the opposite situation. By consequence CSF will drain to the venous system until the ICP is lower than the venous pressure during the complete hart cycle. Also, when orienting the shunt tip neutrally, one should realize that the shunt volume locally reduces the vessel's cross-sectional area. This results in an increase in flow velocity and, in conformity with Bernoulli's principle, a local decrease in pressure. The above effects will render the ICP to be lower than the static venous pressure during the whole heart cycle. This situation, which is the opposite of the physiological relation, may eliminate the capacity of the ICP to adapt to the venous pressure and may cause symptoms of intracranial hypotension. In normal circumstances the cranial pressure is 1.6 times higher than the Psss (20). This causes the distal part of the cerebral veins to collapse. As explained in Chapter 5, the collapsed part of the cerebral veins will dilate in response to an increase in venous pressure.

The added intracranial blood volume will cause the ICP to increase and remain higher than the Psss. It is thus essential that the ICP remains significantly higher than the venous pressure in the steady state condition, to preserve this natural regulation mechanism and to prevent reflux to the shunt system when the venous pressure suddenly increases (Valsalva maneuver) (17). This can be achieved by using a valve with a certain differential pressure instead of a very low pressure valve as currently advocated for VS shunting (4, 5).

Distal catheter

In the animal model, pulsatile reflux of blood was observed, despite the usage of a competent one-way valve. This reflux is caused by a combination of the compliance of the silicone shunt system distal to the valve, the ventricular and venous pressure waves and the inertia of blood corpuscles that hit the CSF column at the distal shunt tip. By consequence it can be prevented by a oneway valve, but only if the valve is implanted close to the entrance of the distal catheter in the venous structure and when the compliance of the shunt system distal to the valve is kept minimal. The former can be achieved by using a stiffer material and by reducing the shunt's diameter (according to Laplace's law).

Strengths

The goal of this experimental work was to clarify causes of thrombotic complications of VV shunts. The two essential results are the thrombogenic effect of the CSF and the pulsatile reflux of blood due to the interaction between the ventricular (proximal end of the shunt) and venous (distal end of the shunt) pressure waves.

Each of these findings was confirmed by two complementary experiments with different methodologies.

The thrombogenic effect of the CSF sleeve was objectified in a static (viscoelastic coagulation monitor) and a dynamic (modified Chandler loop) model.

The static experiment was designed to minimize confounding factors. The blood and CSF came from the same donor to exclude possible immunological reactions due to incompatibility. The coagulation tests were not disturbed because there is no need for heparinization.

The dynamic experiment was designed to approximate the in vivo situation. Special attention was paid to the flow conditions, the position of the shunt in the vessel and the infusion of CSF through the shunts.

The pulsatile reflux of blood to the shunt system was observed in the experimental goat model and confirmed by an experimental in vitro model. Also, the first results of the numerical model that is currently being developed, are compatible with a pulsatile reflux.

We are convinced that the double confirmation of our essential findings makes these more robust.

Recommendations for future research

This thesis identifies the procoagulant properties of CSF and the pulsatile backflow of blood to the shunt system as predisposing factors for thrombotic complications of VV shunts. It also discusses a promising novel venous access device (DVSAD) and suggests modifications to the current design of this device that theoretically would circumvent the above mentioned predisposing factors for thrombotic complications.

At present no in vivo or in vitro experimental data exist that prove or indicate that this device or the suggested modifications to its design are effective in preventing thrombotic complications.

Future research can now focus on the in vitro and in vivo evaluation of prototypes of the DVSAD and the suggested modifications to its design. To do so, the models presented in this thesis can be used. There are however some limitations.

The size of the SSS of the goat allowed the usage of a sinus catheter that is identical to the catheter used by El-Shafei in humans. However, the SSS of the goat is considerably smaller than that of humans and the length of the intravascular catheter of the DVSAD should be adjusted so that it ends with its tip in the center of the sinus. By consequence evaluation of the DVSAD in a goat model will require extensive miniaturization of the device.

The combination of the small SSS and the hypercoagulable state of goats may excessively promote shunt obstruction. This mainly interferes with the assessment of the long-term effectiveness of the DVSAD. However, in a first stage, the implantation technique and the tolerance to the device have to be evaluated. We consider the non-hydrocephalic goat suitable for this purpose.

A hydrocephalic animal model will be indispensable to assess the efficacy of the DVSAD to treat hydrocephalus and to evaluate the long term shunt survival. Goats have anatomical characteristics that may be convenient for the induction of non-obstructive hydrocephalus. However, although the technique used in this thesis, a suboccipital injection of kaolin, was effective in producing a non-obstructive hydrocephalus, it provoked a pronounced aseptic meningitis that had an unacceptable clinical impact and clearly overshadowed the resulting hydrocephalus. The development of better tolerated techniques that do not depend on meningitis to induce hydrocephalus may be the subject of further research.

In conclusion, the goat model may be useful in the research and development process of the DVSAD, but the final testing of the (long term) efficacy of the device will utterly be reserved for a human prospective clinical trial.

The impact of adding a one-way valve to the shunt system and the best differential pressure to preserve the physiological coupling between the ICP and the venous pressure are currently evaluated as part of a master thesis.

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Summary

CSF, that is produced by the choroid plexus, flows through the cerebral ventricles to the subarachnoid space where it is absorbed to the SSS. Hydrocephalus develops when the CSF flow is hampered or when the absorption capacity is diminished. At present, the pathology is treated by draining CSF to the peritoneal cavity or the right atrium of the hart by a VP- or VA shunt. VA shunts suffer from thrombotic complications, which is the main reason why most neurosurgeons reserve the technique for patients for whom VP shunts are contra-indicated or not successful. Unfortunately, the present treatment of hydrocephalus has a failure rate of about 50% in the first two years after implantation. An important cause of shunt failure is siphoning by which the CSF column within the catheter exerts suction through gravity when the patient is in a sitting or standing position. This effect leads to shunt-related intracranial hypotension and aspiration of the choroid plexus into the proximal catheter. Intracranial hypotension causes headaches, nausea, vomiting and even subdural haematomas, while aspiration of the choroid plexus is a major cause of shunt obstruction. Complex and expensive devices to counteract siphoning exist but are not always sufficient.

The VS shunt drains CSF to its natural resorption site, the SSS. The technique prevents siphoning by preserving the natural, self-regulating anti-siphon effect of the IJV.

Although a promising technique, early attempts were not successful due to thrombotic obstruction of the distal catheter. El-Shafei claimed, based on extensive experimental and clinical work, that he solved this issue by implanting the sinus catheter with the tip directed against the blood flow ('retrograde'). According to El-Shafei, this position has the following advantages:

- The ICP remains always higher than the static pressure in the sinus due to the impact effect. This assures a constant drainage of CSF and prevents regurgitation of blood to the shunt system.
- The draining CSF is deflected by the blood stream and flows over the catheter surface, forming a constantly renewing CSF sleeve. According to El-Shafei, the CSF sleeve discourages clot formation.
- 3) The shunt tip is located in an impact zone (facing the blood flow). The stream lines hitting the impact zone cause shear stress and clear developing clots. After hitting the impact zone, the streamlines deflect and move on, without stagnation of blood. However, in the wake zone (the 180° opposite site, facing away from the incoming flow) some of the running fluid separates from the stream lines and stagnates. Stagnation of blood promotes clot formation.

El-Shafei reports excellent clinical results with a shunt survival rate of 95% after a mean follow up of over 6 years. However, the protocol of his follow up is not clear.

These promising results are in stark contrast to the results of the small prospective trial conducted in our center were 80% (11/14) of the RVS shunts failed due to clot formation at the distal shunt tip. The reason for these very

different results is not clear. The surgeon who performed all surgeries, carefully respected the technical recommendations of previous literature, and even went to Cairo to learn the technique from professor El-Shafei himself. Our results are however in line with the experience of other colleagues that used the technique in a very limited number of patients as a rescue operation (personal interviews). Furthermore, it is striking to us that VS shunts did not become the standard of care, despite the substantial potential advantages and the promising early clinical results. On the contrary, it has become very quiet about this technique, that neurosurgeons seem to be reluctant to use.

Up to now, it remains uncertain why VV shunts (VA shunts and VS shunts) suffer from thrombotic complications. We wanted to clarify this issue, as a first step in a bigger research project aiming at the development of a new, long-lasting VS shunt.

We already hypothesized that the position of the shunt tip against the sinus wall is a predisposing factor for shunt obstruction. Theoretically the risk of clot formation is minimal in the center of a vessel as a result of several factors. First, due to shear stress the blood velocity is minimal at the wall and maximal in the center of the sinus. Second, platelets and clotting factors tend to migrate to the side while red blood cells are predominant in the center. Third, irritation of the endothelium by a catheter stimulates endothelial overgrowth and the release of hemostatic proteins.

In the present thesis we identified two characteristics, specific to VV shunts, that predispose to thrombotic complications. During an experimental nonhydrocephalic goat model, we observed pulsatile reflux of blood into the shunt system despite the presence of a one-way valve and regardless of shunt orientation (anterograde or retrograde). We also found that adding CSF to blood enhances blood coagulation.

A dynamic experimental model proved that the interaction of pressure waves at the ventricular (proximal) and venous (distal) end of the shunt causes alternating pressure differences over the shunt that result in pulsatile reflux into the distal catheter. The resulting relatively static blood-CSF mixture in the shunt, promotes clot formation and shunt obstruction. Pulsatile reflux of blood also occurred in the presence of a one-way valve. The combination of the intracranial and venous pressure waves causes variations of total pressure in the shunt. As the silicone shunt system distal to the valve is compliant, it might distend and permit reflux of blood when the transmural pressure becomes maximal.

The procoagulant effect of CSF was confirmed by evaluating the coagulability of different blood-CSF mixtures, using a viscoelastic coagulation monitor. A dynamic roller pump model (modified Chandler loop) confirmed that the procoagulant effect of CSF effectively results in more clot formation on the surface of VV shunts. It also confirmed that more clot formation occurs at the wake side of shunts compared to the impact side.

To ensure an optimal position of the shunt tip in the SSS, we developed a new DVSAD (Chapter 4, Figure 7) that, when correctly implanted, secures the shunt tip in the center of the sinus.

Taking into account possible reflux due to pressure waves at the proximal and distal end of the shunt and the procoagulant effect of CSF, some suggestions concerning the further development of the device can be made. Although the DVSAD is developed to access the SSS, the central position of the shunt tip and

Summary - Samenvatting

the recommendations below are also valid for VA shunts (for example providing access to the distal superior caval vein).

Pulsatile reflux can be prevented by a one-way valve, but only if the compliance of the shunt system distal to this valve is kept minimal. This can be achieved by implanting the valve close to the entrance of the shunt in the venous structure, by reducing the inner diameter of the distal catheter and by using a stiffer material to manufacture this catheter.

A one-way valve with a minimal differential pressure will render the ICP to be lower than the static venous pressure during the whole heart cycle. This situation, which is the opposite of the physiological relation, may eliminate the capacity of the ICP to adapt to the venous pressure and may cause symptoms of intracranial hypotension. By consequence we recommend using a valve with a certain differential pressure instead of a very low pressure valve as currently advocated for VS shunting. What exactly the ideal opening pressure should be is the subject of ongoing research in the context of a master thesis.

The procoagulant effect of CSF will have a minimal impact when the distal opening of the shunt is oriented neutrally, meaning perpendicular to the direction of the blood flow. In this position, CSF will immediately be carried away by the blood flow. The contact between CSF and the shunt surface will thus be minimal and CSF will not concentrate in wake zones. Also, in the neutral position, the shunt tip will not be subjected to the unfavorable flow conditions of a wake zone.

The in vitro and in vivo models described in this thesis provide a roadmap to evaluate new prototypes of the VS shunt, that take the above suggestions into

account. The prototypes can be evaluated, with regard to dimensions, implantation technique, safety and tolerance, in the non-hydrocephalic experimental goat model. However, in order to be able to evaluate the (long term) efficacy of new prototypes to treat hydrocephalus, a hydrocephalic model will be necessary. Goats have anatomical characteristics that may be especially convenient for the development of a model of non-obstructive hydrocephalus. However, although the technique used in this thesis, a suboccipital injection of kaolin, was effective in producing a non-obstructive hydrocephalus, it provoked a pronounced aseptic meningitis that had an unacceptable clinical impact and clearly overshadowed the resulting hydrocephalus. The development of better tolerated techniques that do not depend on meningitis to induce hydrocephalus may be the subject of further research.

Samenvatting

Cerebrospinaal vocht (CSV) wordt geproduceerd door de plexus choroideus in de laterale hersenventrikels. Het stroomt doorheen het ventrikelsysteem naar de subarachnoïdale ruimte rond de cerebrale hemisferen en wordt vandaar geresorbeerd naar de sinus sagittalis superior (SSS). Hydrocephalie ontstaat wanneer het evenwicht tussen aanmaak en afvoer van CSV wordt verstoord ten nadele van de afvoer. Deze aandoening wordt momenteel behandeld met VP- en VA shunts, die het CSV afvoeren naar respectievelijk de peritoneale holte of het rechter atrium van het hart. VA shunts zijn progressief in onbruik geraakt naar aanleiding van trombotische complicaties. Momenteel worden zij door de meeste chirurgen enkel nog gebruikt wanneer VP shunts gecontraindiceerd of niet succesvol zijn. Alhoewel VP shunts frequent geïmplanteerd worden sinds de jaren 1950 blijft het percentage shunt falen hoog. Ruim de helft van de shuntpatiënten ondergaat een chirurgische revisie gedurende de eerste twee jaren na implantatie. Een belangrijke oorzaak van shunt falen is het sifon effect waarbij, door de inwerking van de zwaartekracht op de vloeistofkolom in de distale katheter, een aanzuigeffect effect ontstaat wanneer de patiënt zit of staat. Dit aanzuigeffect leidt tot intracraniële hypotensie en aspiratie van de plexus choroideus in de proximale katheter. Intracraniële hypotensie resulteert in hoofdpijn, nausea en braken en faciliteert het ontstaan van subdurale hematomen. Het aanzuigen van de plexus in de proximale katheter is de meest frequente oorzaak van shuntobstructie. Sinds 1950 werden verschillende complexe en dure medische hulpmiddelen ontwikkeld die het sifon effect tegengaan. Met deze hulpmiddelen is de groep patiënten die lijden aan overdrainage gereduceerd maar zeker niet volledig verdwenen.

De ventriculosinus shunt draineert CSV naar de fysiologische resorptieplaats, de SSS. Hierbij wordt het natuurlijke, zelfregulerende antisifon effect van de vena jugularis interna behouden. De eerste klinische experimenten met de techniek waren niet succesvol omwille van shuntobstructie door klontervorming aan de distale tip. Om deze reden werd de techniek aanvankelijk verlaten. Vele jaren later verklaarde El-Shafei dat klontervorming aan de distale shunttip kan vermeden worden door de shunt tegen de richting van de bloedstroom ('retrograad') te implanteren. Volgens El-Shafei heeft deze positie de volgende voordelen:

- Wanneer de bloedstroom botst tegen de drainerende CSV kolom wordt de kinetische energie van de bloedproducten omgezet naar potentiële energie. Hierdoor blijft de intracraniële druk steeds hoger dan de statische druk in de SSS. Dit wordt 'het impact effect' genoemd door El-Shafei. Het impact effect verzekert een constante drainage van CSV en voorkomt reflux van bloed naar het shuntsysteem.
- 2) CSV stroomt, direct na het verlaten van de shunt en onder invloed van de bloedstroom, over het shuntoppervlak. Het vormt op deze manier een zichzelf vernieuwende CSV mof over de katheter. Volgens El-Shafei beschermt deze CSV mof tegen klontervorming.
- 3) De shunttip bevindt zich in een 'impact zone', dit is de plaats waar de stroomlijnen botsen tegen het shuntoppervlak en afbuigen. Door de wrijving met het shuntoppervlak worden zich ontwikkelende klonters weggespoeld. In de 'wake zone', die zich direct stroomafwaarts van de shunt bevindt, zal een deel van het bloed de laminaire stroming verlaten en stagneren. Stagnering van bloed bevordert de stolling.

El-Shafei beproefde de techniek bij meer dan 100 patiënten en rapporteerde een shunt overleving van meer dan 95% na ruim 6 jaar follow up. Het is echter onduidelijk hoe zijn patiënten postoperatief precies opgevolgd werden.

Deze veelbelovende resultaten staan in schril contrast met de resultaten van een kleine prospectieve klinische studie bij ons op de dienst die na 4 maanden werd gestaakt omwille van een onaanvaardbaar hoog aantal shuntobstructies (11/14 of 80% van de patiënten). De oorzaak van de shuntocclusie was telkens klontervorming ter hoogte van de distale shunt tip. Het is onduidelijk waarom onze resultaten zo ver afwijken van deze van El-Shafei. Gezien de chirurg, die alle implantaties uitvoerde, voor aanvang van de studie zelf naar Caïro reisde om de techniek van professor El-Shafei te leren lijkt het weinig waarschijnlijk dat een verschillende chirurgische techniek de oorzaak is. Onze resultaten komen wel overeen met deze van collega's die de VS shunt implanteerden bij beperkt patiënten zij een aantal waarvoor geen andere behandelingsmogelijkheid zagen (persoonlijke communicatie). Het is verder verwonderlijk dat de VS shunt, ondanks de belangrijke theoretische voordelen en de bemoedigende gepubliceerde klinische resultaten geen ingang vindt in de behandeling van hydrocephalie. Integendeel, het is de laatste jaren erg stil geworden rond de VS shunt en neurochirurgen lijken terughoudend om deze techniek te gebruiken.

In overeenstemming met vroegere literatuur verdenken wij de perifere positie van de shunttip, tegen de bloedvatwand, als voorbeschikkende factor voor klontervorming. Theoretisch is de kans op klontervorming minimaal in het centrum van een bloedvat omwille van verschillende factoren. Door wrijving met de wand zal de stroomsnelheid minimaal zijn in de periferie en maximaal in het centrum van een bloedvat. Bloedproducten verdelen zich zo dat stollingsfactoren en bloedplaatjes zich aan de wand en rode bloedcellen zich in het centrum van het bloedvat bevinden. Verder veroorzaakt het contact tussen de sinuskatheter en de bloedvatwand irritatie van het endotheel. Het endotheel zal hierdoor woekeren en hemostatische proteïnen vrijzetten.

In deze thesis identificeerden we enkele karakteristieken, specifiek voor VV shunts, die voorbeschikkend zijn voor trombotische complicaties.

Tijdens het dierexperiment (niet-hydrocephaal geitmodel) stelden we een pulserende terugstroom naar de distale katheter vast. Deze terugstroom deed zich voor ondanks de retrograde positie van de shunt en de aanwezigheid van een competente eenrichtingsklep. In dit experiment bemerkten we ook dat de interactie met CSV de bloedstolling bevordert.

In een dynamisch experimenteel model bewezen we dat de interactie tussen dynamische drukgolven in de hersenventrikels (proximale shuntuiteinde) en in de SSS of het rechter atrium (distale shuntuiteinde) aanleiding geven tot alternerende drukverschillen over de shunt. Deze alternerende drukverschillen resulteren in een pulserende terugstroom van bloed naar de distale katheter. Hierdoor ontstaat een relatief statisch CSV-bloed mengsel. Zowel stase van bloed als de interactie met CSV zijn voorbeschikkend voor klontervorming. De pulserende reflux doet zich ook voor als een eenrichtingsklep wordt gebruikt. Dit is enkel mogelijk als het shuntsysteem distaal van de klep voldoende compliant is om uit te zetten wanneer de transmurale druk in de shunt toeneemt. In dat geval zal een kleine hoeveelheid bloed het systeem binnendringen.

Het stolling bevorderend effect van CSV werd bij de mens bevestigd door de evaluatie van verschillende bloed-CSV mengelingen met een visco-elastische coagulatie monitor. In een dynamisch rollerpomp model werd daarenboven aangetoond dat dit effectief aanleiding geeft tot meer klontervorming op het oppervlak van VV shunts. In dit model werd ook vastgesteld dat er meer klonters gevormd worden op het shuntoppervlak dat zich in de 'wake' zone bevindt in vergelijking met het shuntoppervlak dat zich in de 'impact' zone situeert.

Gebaseerd op de hypothese dat de positie van de shunttip tegen de bloedvatwand klontervorming bevordert, ontwikkelden Baert en collega's een DVSAD waarbij de shunttip in het centrum van de SSS gestabiliseerd wordt.

De bevindingen van deze thesis, de pulserende terugstroom van bloed en het coagulatie bevorderend effect van CSV, hebben implicaties voor de verdere ontwikkeling van het DVSAD.

De pulserende terugstroom van bloed kan enkel voorkomen worden door een éénrichtingsklep indien de compliantie van het shuntsysteem distaal van deze klep minimaal gehouden wordt. Factoren die hiertoe bijdragen zijn het implanteren van de klep nabij de intrede van shunt in de SSS, het verkleinen van de diameter van de distale katheter en het vervaardigen van deze katheter uit een weinig compliant materiaal.

Een éénrichtingsklep met een minimale openingsdruk zal de intracraniële druk doen dalen tot onder de veneuze druk. Deze niet fysiologische relatie veroorzaakt mogelijks intracraniële hypotensie en interfereert met de natuurlijke regulatiemechanismen die de intracraniële druk doen stijgen wanneer de veneuze druk toeneemt. Om deze reden raden wij aan een klep te gebruiken met een hogere openingsdruk. Wat de ideale openingsdruk zou zijn is het onderwerp van een lopende masterthesis. Het stolling bevorderend effect van CSV zal een minimale impact hebben wanneer de distale shunttip neutraal, d.w.z. onder een hoek van 90° met de bloedstroom, geïmplanteerd wordt. In deze positie is er slechts een zeer beperkte contactzone tussen het CSV en het shuntoppervlak, bevindt de shunttip zich niet in een wake zone en zullen de bloedproducten niet het shuntsysteem binnendringen, onder invloed van hun traagheid.

Prototypes van het DVSAD kunnen geëvalueerd worden met de in vitro en in vivo modellen die in deze thesis besproken worden. Het niet-hydrocephaal diermodel laat toe de dimensies, de implantatietechniek en de veiligheid van de prototypes te evalueren. Voor de boordeling van de (lange termijn) effectiviteit van het DVSAD zal een hydrocephaal model nodig zijn. Omwille van anatomische eigenschappen zijn geiten goed geschikt voor de ontwikkeling van een diermodel voor niet obstructieve hydrocephalie. De techniek die in deze thesis gebruikt werd induceerde effectief een niet obstructieve hydrocephalie maar de klinische impact van de chemische meningitis was van dien aard dat wij deze als onaanvaardbaar hebben ervaren. De ontwikkeling van minder invaliderende technieken, die niet afhankelijk zijn van een chemische meningitis om hydrocephalie te induceren, kan deel uitmaken van toekomstig onderzoek.

Jelle Vandersteene was born in Ghent, Belgium on December 29th After graduating from 1984. secondary school in 2003, he travelled through India and Nepal during 7 months. In 2004 he started medical training at Ghent University and graduated with great distinction in 2011. During medical training, he spent 1 year at the Universitat de València in the context of Erasmus an exchange program. Between 2011 and 2018 Jelle combined his residency of neurosurgery with scientific work, mostly focusing on the evaluation and development of a new ventriculosinus shunt. Jelle lives in Ghent with Annejo and their two children, Lena and Wannes.