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

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OBJECTIVE The effect of CSF on blood coagulation is not known. Enhanced coagulation by CSF may be an issue in thrombotic complications of ventriculoatrial and ventriculosinus shunts. This study aimed to assess the effect of CSF on coagulation and its potential effect on thrombotic events affecting ventriculovenous shunts.

METHODS Two complementary experiments were performed. In a static experiment, the effect on coagulation of different CSF mixtures was evaluated using a viscoelastic coagulation monitor. A dynamic experiment confirmed the amount of clot formation on the shunt surface in a roller pump model.

RESULTS CSF concentrations of 9% and higher significantly decreased the activated clotting time (ACT; 164.9 seconds at 0% CSF, 155.6 seconds at 9% CSF, and 145.1 seconds at 32% CSF). Increased clot rates (CRs) were observed starting at a concentration of 5% (29.3 U/min at 0% CSF, 31.6 U/min at 5% CSF, and 35.3 U/min at 32% CSF). The roller pump model showed a significantly greater percentage of shunt surface covered with deposits when the shunts were infused with CSF rather than Ringer’s lactate solution (90% vs 63%). The amount of clot formation at the side facing the blood flow (impact side) tended to be lower than that at the side facing away from the blood flow (wake side; 71% vs 86%).

CONCLUSIONS Addition of CSF to blood accelerates coagulation. The CSF-blood–foreign material interaction promotes clot formation, which might 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.

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KEYWORDS cerebrospinal fluid; coagulation; hydrocephalus; ventriculoatrial shunt; ventriculosinus shunt

The effect of cerebrospinal fluid on blood coagulation is not well established. Some authors have suggested that CSF might enhance hemostasis since it contains proteins such as fibrinogen and tissue factor that might activate the clotting cascade.6,7,16 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.29

Ventriculoatrial shunts have effectiveness and complication rates that are similar to those for ventriculoperitoneal shunts.10,17,18,28 However, because of the thromboembolic complications associated with ventriculoatrial shunts, most neurosurgeons choose these shunts only for patients

ABBREVIATIONS ACT = activated clotting time; CR = clot rate; EVD = external ventricular drainage; PF = platelet function; Ratioimp = (total area of clots on the impact side)/(total visualized area of the impact side of the shunt); Ratiosaw = (total area of clots on the impact + wake side)/(total visualized area of the impact + wake side of the shunt); Ratiosw = (total surface of clots on the wake side)/(total visualized surface of the wake side of the shunt).


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in whom ventriculoperitoneal shunts are contra-indicated or not successful. 29

Ventriculosinus shunts have several advantages over the classic ventriculoperitoneal and ventriculoatrial shunts. First, overdrainage is prevented by maintaining a natural, self-regulating antisiphon effect of the internal jugular vein.11 Second, the shunt system is shorter in length, less complex, and confined to the skull, which minimizes the risk of mechanical failure and infection.2 While some authors have described excellent long-term results with these shunts, others have reported that obstruction due to clot formation in and around the distal shunt tip is an issue.13,20

The impact of the CSF-blood-shunt interaction in this kind of thrombotic complication remains a matter of debate. CSF, due to its composition, might enhance clot formation. To attenuate clot formation, some authors have recommended implantation of the ventriculosinus shunts with the tip opening directed against the blood flow (retrograde) to direct the CSF flow around the distal shunt tip. The constantly renewing CSF sleeve that results is believed to be protective against clot formation.13

In the present study, we assess the impact of CSF on blood coagulation and the impact of the CSF-blood–foreign material interaction on thrombotic shunt complications.

Methods

Two complementary experiments were 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 was approved by the independent ethics committee of the Ghent University Hospital. Participation in the study was offered to every patient who was not on a regimen of anticoagulant or antiplatelet drugs and was undergoing a lumbar puncture, external lumbar drainage, or external ventricular drainage (EVD). CSF and citrated venous blood (0.109 mol trisodium citrate/L, Terumo) were collected from each patient. As the puncture itself might contaminate the first sample from each patient, these first samples were never used for the study. Immediately after the collection of at least a second sample from any selected patient, CSF was added to blood from the same patient in increasing concentrations (Table 1). The different blood-CSF mixtures were recalcified (40 μl of 0.25 mol/L CaCl₂ solution) and analyzed using a Sonoclot Coagulation Analyzer (Sienco). The Sonoclot Signature, a qualitative graph generated by the coagulation analyzer, reflects the viscoelastic changes during the transition from liquid whole blood to a solid blood clot (Fig. 1). It consists of the activated clotting time (ACT), the clot rate (CR), and the platelet function (PF).

Dynamic In Vitro Experiment

The experimental setup is shown in Fig. 2. A roller pump, set in a nonocclusive modus, circulated heparinized whole blood (collected from 2 healthy donors) through phosphorylcholine-coated silicone tubing (LivaNova) that was partly submerged in warm (37°C) water. A syringe pump infused a Ringer’s lactate solution or CSF (collected from a patient undergoing EVD) through a Thecothane (Lubrizol) catheter (“shunt”) that was inserted through the wall of the tubing. The control shunts (no infusion) were purged with Ringer’s lactate and subsequently closed at the extravascular end to prevent blood from entering the lumen of the shunt. The infused volume was compensated for by an overflow tank. The distal opening of the shunts was aimed against the direction of the blood flow, that is, retrograde (Fig. 3). This roller pump model ran 13 times (5 with CSF infusion, 5 with Ringer’s lactate solution infusion, and 3 without infusion). A Sonoclot Coagulation Analyzer was used to compare the coagulability of the pure blood at the beginning of the experiment with that of the infusion fluid–blood mixture at the end of the experiment.

At the end of the experiment, the shunts were removed

| Table 1: Preparation of the 5 different blood-CSF mixtures |
|---------------------------------|-----------|-----------|-----------|-----------|-----------|
| **Variable**                    | **Mixt. No.** | **Mixt. No.** | **Mixt. No.** | **Mixt. No.** | **Mixt. No.** |
| Blood (μl)                      | 900       | 900       | 900       | 900       | 900       |
| Buffered 0.109 mol/L trisodium citrate (μl) | 100       | 100       | 100       | 100       | 100       |
| Calcium solution (μl)           | 40        | 40        | 40        | 40        | 40        |
| CSF (μl)                        | 0         | 10        | 50        | 100       | 500       |
| Vol CSF (%)                     | 0         | 0.952     | 4.587     | 8.772     | 32.468    |
along with the surrounding tubing wall and prepared for scanning electron microscopic evaluation. The samples were mounted in a horizontal position and analyzed with ×18 magnification. Two sides of the shunt were visualized: the impact side, defined as the flank facing the blood flow, and the wake side, defined as the opposite flank, facing away from the incoming blood flow.

Scanning electron microscopic images are 2D projections of 3D cylindrical objects. As can be seen in Fig. 4, debris more distant from the image center is projected smaller 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 (MathWorks), was executed. This script applied the appropriate mathematical formulas to the projected surface areas to simulate unrolling the cylinder instead of projecting it onto a 2D plane.

At each side, the surface covered with clots was delineated (version 150, ImageJ for Windows, available for download at https://imagej.nih.gov/ij/index.html) and expressed as a percentage of the visualized surface at the same side (Ratio\(_\text{impact} = A_{\text{clot impact}}/A_{\text{impact}}\), Ratio\(_\text{wake} = A_{\text{clot wake}}/A_{\text{wake}}\), where A represents area). Next, the total surface of the clots (impact side + wake side) was expressed relative to the visualized total surface [Ratio\(_\text{total} = (A_{\text{clot impact}} + A_{\text{clot wake}})/(A_{\text{impact}} + A_{\text{wake}})\)].

**Statistical Analysis**

Statistical analyses were performed using IBM SPSS Statistics (version 22.0, IBM Corp.). In the static experiment, a parametric paired 2-sample t-test was used after objectifying normality to compare each Sonoclot parameter (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 measured before the start of the experiment were compared with those of the blood–infusion fluid mixture after the experiment by using a nonparametric Mann-Whitney U-test. The amount of visualized shunt surface covered with clots was compared between the different infusion fluids (CSF, Ringer’s lactate, or no infusion fluid) by a nonparametric Mann-Whitney U-test. A 1-sample t-test was used after objectifying normality to evaluate if there was a difference between clot formation on the impact and the wake sides of the shunt (Ratio\(_\text{impact} - \text{Ratio}_{\text{wake}}\)). Statistical significance is set at p < 0.05.
Results

Static Study

Samples were obtained from 15 individuals. The characteristics of the study population are shown in Table 2, and the results of the Sonoclot coagulation analysis of the different blood-CSF mixtures are shown in Table 3. CSF concentrations of 9% and higher significantly decreased the ACT, and CSF concentrations of 5% and higher significantly increased the CR. No significant effect on the PF was found.

Dynamic In Vitro Experiment (roller pump model)

Hemodilution

The concentration of the infusion fluid increased during the experiment and depended on the infusion rate through the shunt and the evacuation of the infusion fluid–blood mixture into the overflow tank. The calculated concentration of the infusion fluid at the end of the experiment was 5.88%, as each loop ran for 60 minutes, the total blood volume was 32 ml, and the infusion rate was set at 2 ml/hr.

TABLE 2. Study population characteristics

<table>
<thead>
<tr>
<th>Sample No.</th>
<th>Age (yrs)</th>
<th>Source of CSF</th>
<th>Symptoms or Suspected Diagnosis</th>
<th>Blood Platelet Count (10^3/µl)</th>
<th>Total Protein (mg/L)</th>
<th>Coagulation Test Results*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>59</td>
<td>LP</td>
<td>FTD</td>
<td>201</td>
<td>38.6</td>
<td>Normal</td>
</tr>
<tr>
<td>2</td>
<td>59</td>
<td>LP</td>
<td>Cerebral palsy</td>
<td>201</td>
<td>50.0</td>
<td>Normal</td>
</tr>
<tr>
<td>3</td>
<td>43</td>
<td>LP</td>
<td>White matter lesions</td>
<td>227</td>
<td>25.2</td>
<td>Normal</td>
</tr>
<tr>
<td>4</td>
<td>29</td>
<td>ELD</td>
<td>CSF rhinorrhea</td>
<td>NA</td>
<td>71.5</td>
<td>NA</td>
</tr>
<tr>
<td>5</td>
<td>68</td>
<td>LP</td>
<td>NOSD</td>
<td>307</td>
<td>151.9</td>
<td>NA</td>
</tr>
<tr>
<td>6</td>
<td>47</td>
<td>LP</td>
<td>Cognitive dysfunction</td>
<td>637</td>
<td>40.5</td>
<td>NA</td>
</tr>
<tr>
<td>7</td>
<td>48</td>
<td>LP</td>
<td>Vasculitis</td>
<td>253</td>
<td>115.2</td>
<td>Normal</td>
</tr>
<tr>
<td>8</td>
<td>50</td>
<td>LP</td>
<td>CVA</td>
<td>183</td>
<td>58.1</td>
<td>Normal</td>
</tr>
<tr>
<td>9</td>
<td>61</td>
<td>EVD</td>
<td>SAH</td>
<td>394</td>
<td>NA</td>
<td>Normal</td>
</tr>
<tr>
<td>10</td>
<td>70</td>
<td>EVD</td>
<td>SAH</td>
<td>413</td>
<td>NA</td>
<td>Normal</td>
</tr>
<tr>
<td>11</td>
<td>68</td>
<td>LP</td>
<td>Neurosyphilis</td>
<td>178</td>
<td>41.4</td>
<td>Normal</td>
</tr>
<tr>
<td>12</td>
<td>70</td>
<td>LP</td>
<td>AD</td>
<td>105</td>
<td>NA</td>
<td>Normal</td>
</tr>
<tr>
<td>13</td>
<td>39</td>
<td>LP</td>
<td>Narcolepsy</td>
<td>235</td>
<td>18.6</td>
<td>Normal</td>
</tr>
<tr>
<td>14</td>
<td>58</td>
<td>LP</td>
<td>AD</td>
<td>180</td>
<td>NA</td>
<td>Normal</td>
</tr>
<tr>
<td>15</td>
<td>19</td>
<td>LP</td>
<td>MS</td>
<td>260</td>
<td>17.5</td>
<td>Normal</td>
</tr>
</tbody>
</table>

AD = Alzheimer’s disease; CVA = cerebrovascular accident; ELD = external lumbar drainage; FTD = frontotemporal dementia; LP = lumbar puncture; MS = multiple sclerosis; NA = not available; NOSD = neuromyelitis optica spectrum disorder; SAH = subarachnoid hemorrhage.

* International normalized ratio, activated partial thromboplastin time, and prothrombin time.

Sonoclot Coagulation Analyzer

The differences in the Sonoclot parameters before and after the experiment, grouped by infusion fluid, are shown in Table 4. The ACT was higher after the experiment in the Ringer’s lactate and control groups. In the CSF group, there was no significant difference in ACT measured before and after the experiment. Both the CR and the PF increased during the experiment, and this increase was more pronounced in the CSF group.

Differences in Clot Formation in Function of the Infusion Fluid

Compared with control shunts, Ringer’s lactate–infused shunts had fewer clots and CSF-infused shunts had more clots. Table 5 shows the medians of the 3 ratios. Figure 5 shows the differences between the ratios, depending on the infusion fluid.

Ratio_impat, Ratio_wake, and Ratio_total were significantly higher for CSF shunts than for Ringer’s lactate shunts. The Ratio_wake was significantly higher for CSF shunts than for control shunts.

TABLE 3. Results of the patient study and comparison of ACT, CR, and PF values for different CSF concentrations in the blood-CSF mixtures

<table>
<thead>
<tr>
<th>Parameter</th>
<th>0%</th>
<th>1%</th>
<th>5%</th>
<th>9%</th>
<th>32%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean ACT (sec)</td>
<td>164.9</td>
<td>160.4</td>
<td>158.9</td>
<td>155.6*</td>
<td>145.1*</td>
</tr>
<tr>
<td>Mean CR (U/min)</td>
<td>29.3</td>
<td>30.9</td>
<td>31.6*</td>
<td>31.3*</td>
<td>35.3*</td>
</tr>
<tr>
<td>Mean PF</td>
<td>3.7</td>
<td>3.8</td>
<td>3.3</td>
<td>3.5</td>
<td>4.1</td>
</tr>
</tbody>
</table>

* p < 0.05.

TABLE 4. Comparison of the difference of ACT, CR, and PF values measured before and after the experiments for CSF, RL, and control

<table>
<thead>
<tr>
<th>Variable</th>
<th>Infusion Fluid</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CSF</td>
</tr>
<tr>
<td>Median ACT difference</td>
<td>0.0</td>
</tr>
<tr>
<td>Median CR difference</td>
<td>6.3</td>
</tr>
<tr>
<td>Median PF difference</td>
<td>2.3</td>
</tr>
</tbody>
</table>

RL = Ringer’s lactate.

* p < 0.05.
TABLE 5. Impact of the infusion fluid on the amount of clot formation on the different shunt surfaces

<table>
<thead>
<tr>
<th>Variable</th>
<th>Infusion Fluid</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RL</td>
</tr>
<tr>
<td>Median Ratio_impact</td>
<td>0.59</td>
</tr>
<tr>
<td>Median Ratio_wake</td>
<td>0.71</td>
</tr>
<tr>
<td>Median Ratio_total</td>
<td>0.68</td>
</tr>
</tbody>
</table>

The amount of clot formation tends to decrease when shunts are perfused with Ringer's lactate but tends to increase when shunts are perfused with CSF.

* Clot formation on CSF-perfused shunts is significantly higher than that on Ringer's lactate-perfused shunts.
† Statistical significance was reached when the Ratio\_wake of control shunts was compared with that of CSF-perfused shunts.

Discussion

The effect of CSF on blood coagulation might be an issue in thrombotic complications of ventriculostial and ventriculosinus shunts.29

We performed 2 complementary experiments to assess the effect of CSF on blood coagulation and the role of the CSF-blood-shunt interaction in distal shunt obstruction. The first experiment evaluated the effect of CSF on the thromboelastogram by analyzing different blood-CSF mixtures. The second, a custom-made roller pump model, assessed the amount of clot formation on the shunt surface in more realistic conditions.

Influence of CSF on Hemostasis

The first experiment showed that adding CSF to blood makes blood hypercoagulable. This was demonstrated by the accelerated conversion from fibrinogen to fibrin and gradual shortening of the ACT after the addition of CSF. These effects became statistically significant at CSF concentrations of at least 5%–9%. Interestingly, the same critical concentration was found in the roller pump model. The increase in CR and higher platelet activation are most likely due to thrombin formation on the surface of the activated platelets15 and are only found in the group in which 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.14 In healthy individuals, there is an imbalance between the concentrations of tissue factor and tissue factor pathway inhibitor in CSF, making CSF a procoagulant substance. Apart from these clotting factors, immunoglobulins and other immunological factors, such as C3, can cause neuroinflammation, leading to a procoagulant state.6 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.26 Further research is necessary to elucidate this mechanism.

Based on our results, we can support the finding of clinical series that, under normal circumstances, shunting CSF to the dural venous sinuses or superior vena cava will not lead to thrombosis of the venous sinuses or superior vena cava.24,31 Concentrations of CSF in the superior sagittal sinus and superior vena cava are below 5%, as CSF inflow is approximately 0.35 ml/min for a blood flow of more than 200 ml/min.5,13,22 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 place 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 (Fig. 6). This CSF sleeve is believed to protect against clot formation by preventing adherence of proteins and platelets to the foreign material’s surface.12,13

The protective effect of a constantly renewing fluid sleeve was confirmed by the reduced clot formation on Ringer’s lactate–infused shunts compared with controls. However, increased clot formation was observed on CSF-infused shunts. Therefore, contradictory to the protective effect of a fluid sleeve in general, a CSF sleeve is harmful. The CSF sleeve might 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.15,20
Wake Zones

A wake zone, characterized by a slow, nonlaminar flow, develops directly distal to an object placed in the bloodstream (Fig. 7).12 The current study supports the hypothesis in the literature that, due to the characteristic flow conditions, more clot formation occurs on the wake side of a shunt.2,22 This procoagulant effect might be reinforced when CSF is drained to a wake zone. The local slow, nonlaminar flow might result in accumulation of CSF, which promotes hemostasis.

Distal Shunt Tip

When blood reflows into the shunt system, it will become stagnant, and the risk of intraluminal clot formation is increased.12 The development of a blood-CSF mixture in the distal shunt system might even increase this risk further.

In the absence of a 1-way valve, reflowing of blood may occur due to a sudden increase in pressure in the superior sagittal sinus or a decrease in intracranial pressure (Val-salva maneuver or lumbar puncture, respectively).9,25

Shunt Material and Design

Several shunt-related factors, such as material and design, might have an influence on clot formation. The shunt material should be biocompatible. Silicone and polyurethanes, which have a suitable profile, are typically used.4 In this study, Tecothane, a noncoated aromatic polyether urethane, was used. Although Tecothane is known to have superior hemocompatibility, clot formation was visualized on the surface of all shunts. Different coatings could be used to further reduce the thrombogenicity of biomaterials.2 Typical examples are phosphorylcholine and heparin.2,19 Phosphorylcholine might counteract the procoagulant effect of CSF by preventing protein adhesion to the foreign material's surface.8,19 Heparin-eluting and non-eluting coatings exist.2 Heparin-eluting coatings have a limited duration of action and are developed to reduce clot formation in the acute setting.2 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.1,21 Heparin noneluting coatings theoretically have a permanent antithrombotic effect and are known to reduce thrombus formation on vascular grafts and vascular stents.2 In conclusion, both a phosphorylcholine and a heparin non-eluting coating might be useful in reducing the general thrombogenicity of venous shunts and might also counteract the procoagulant effect of CSF.

The shunt design, in addition to the material, might affect the amount of clot formation. The results of this study indicate that the wake zones should be 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 in a retrograde direction. Ideally, the distal shunt tip should be oriented perpendicular to the blood flow (neutral position). Thus, CSF will not drain along the shunt surface or into wake zones. CSF can be prevented from entering the distal shunt tip by using a 1-way valve.

Strengths and Limitations of the Study

To our knowledge, this is the first study to address the question as to how the interactions between CSF, blood, and foreign material affect clot formation. One of the strong points of this study is the combination of a static and a dynamic experiment.

The static experiment was designed to minimize confounding factors. The blood and CSF were obtained from the same donor to exclude possible immunological reactions due to incompatibility. The coagulation tests were not disturbed because there was 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.

However, not all aspects of the in vivo situation are modeled. The influence of the endothelium covering the wall of the blood vessel is perhaps the most important factor that is not addressed. An intact endothelium counteracts coagulation, but when the endothelium is damaged or irritated, it
FIG. 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 toward the wake side, which causes a slow, nonlaminar flow.

releases thrombogenic factors.\textsuperscript{27,29} Endothelial damage is unavoidable when the shunt is implanted. Irritation can 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 was 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.\textsuperscript{15}

Overdilution was 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.\textsuperscript{23}

Conclusions

Adding CSF to blood enhances coagulability starting at 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 between CSF and the outer shunt surface and accumulation of CSF in wake zones should be avoided. To prevent luminal clot formation (internal shunt obstruction), blood should be prevented from entering the shunt tip using an appropriate 1-way valve.

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Disclosures
The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions
Conception and design: Vandersteene, Baert, Van Roost, Dewaele, De Somer. Acquisition of data: Planckaert, Van Den Berghe, Henrotte, De Somer. Analysis and interpretation of data: Vandersteene, Planckaert, Van Den Berghe, Henrotte. Drafting the article: Vandersteene. Critically revising the article: all authors. Reviewed submitted version of manuscript: Vandersteene. Approved the final version of the manuscript on behalf of all authors: Vandersteene. Statistical analysis: Vandersteene, Planckaert, Van Den Berghe, Henrotte. Administrative/technical/material support: Vandersteene, Baert, Van Roost, Dewaele, De Somer. Study supervision: Vandersteene, Baert, De Somer.

Supplemental Information
Previous Presentations
Portions of this work were presented in a master’s thesis by authors G. M. J. Planckaert and T. Van Den Berghe in 2016 under supervision of authors D. Van Roost, E. Baert, and J. Vandersteene, without public disclosure.

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