Comparison between 3 infusion methods to measure cerebrospinal fluid outflow conductance  

Clinical article

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**Object.** There are several infusion methods available to estimate the outflow conductance (Cout) or outflow resistance (Rout = 1/Cout) of the CSF system. It has been stated that for unknown reasons, the bolus infusion method estimates a higher Cout than steady-state infusion methods. The aim of this study was to compare different infusion methods for estimation of Cout.

**Methods.** The following 3 different infusion methods were used: the bolus infusion method (Cout bolus); the constant flow infusion method, both static (Cout stat) and dynamic (Cout dyn) analyses; and the constant pressure infusion method (Cout cpi). Repeated investigations were performed on an experimental model with well-known characteristics, with and without physiological pressure variations (B-waves, breathing, and so on). All 3 methods were also performed in a randomized order during the same investigation in 20 patients with probable or possible idiopathic normal-pressure hydrocephalus; 6 of these patients had a shunt and 14 did not.

**Results.** Without the presence of physiological pressure variations, the concordance in the experimental model was good between all methods. When they were added, the repeatability was better for the steady-state methods and a significantly higher Cout was found with the bolus method in the region of clinically relevant Cout (p < 0.05). The visual fit for the bolus infusion was dependent on subjective assessment by the operator. This experimental finding was confirmed by the clinical results, where significant differences were found in the investigations in patients without shunts between Cout of the visual bolus method and Cout stat, Cout dyn, and Cout cpi (4.58, 4.18, and 6.12 μl/[second × kPa], respectively).

**Conclusions.** This study emphasized the necessity for standardization of Cout measurements. An experienced operator could partly compensate for difficulties in correctly estimating the pressure parameters for the bolus infusion method, but for the general user this study suggests a steady-state method for estimating Cout.

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**KEY WORDS** • intracranial pressure • normal-pressure hydrocephalus • outflow conductance • outflow resistance • infusion test

It is generally accepted that CSF infusion tests, aimed at estimating the outflow conductance, Cout (or its reciprocal, outflow resistance [Rout]) of the CSF system, are important tools in the diagnosis and management of INPH.24 They are also very useful after shunt treatment to determine whether the shunt is working properly.9,11 The predictive power of Cout concerning outcome after shunt surgery has been debated for a long time, with studies both supporting it,5,7,27,30 and finding it less valuable.10,15,19 A difficulty when trying to determine the predictability of Cout is that different centers use different infusion methods. The methods may be divided into 3 main categories: constant pressure infusion,1,13 constant flow infusion,8,17,18 and bolus infusion,23,24 where each method has its advantages and drawbacks. The results from the different methods are often mixed but interpreted in the same manner, even though the cutoff levels for the methods are not necessarily the same and proper control studies for each method are missing.

The theoretical background on which the infusion methods are based is the mathematical model developed by Marmarou et al.23 It results in the following differential equation that can be solved for different kinds of external inflows (Iext):

\[
dP_{ic}/dt + kP_{ic}\cdot C_{out} - kP_{ic}( I_{ext} + C_{out}P_{r} ) = 0, \quad \text{[eq. 1]}\]

where P_{ic} is the intracranial pressure, P_{r} is the resting pressure of the patient, dP_{ic}/dt is the time derivative of P_{ic}, and k is a constant describing the elastance.
Measurement of CSF outflow conductance

(k = 1/[0.4343PVI], where PVI is the pressure volume index). According to the model, any kind of infusion pattern would lead to the same \( C_{\text{out}} \), as long as the appropriate solution to the differential equation is used. However, comparisons between the bolus infusion method and the constant flow infusion method conducted in patients have shown a systematically and significantly higher \( C_{\text{out}} \) with the bolus infusion method.18,25,28

The aim of this study was to compare the bolus infusion method with the constant flow infusion method and the constant pressure infusion method. This was possible due to the access of an infusion apparatus with simultaneous control of pressure and flow.1 The comparison should be conducted in an experimental model of the CSF system as well as in patients, with the application of all methods during the same investigational session. We set out to address the following main question: Does \( C_{\text{out}} \) determined by steady-state infusion methods differ from that determined by the bolus infusion method?

Methods

Patient Population

All patients included had communicating hydrocephalus that was visible on MR imaging studies and probable or possible diagnosis of INPH according to the INPH guidelines.21 The indications for the infusion tests were as part of a preoperative investigation to determine whether to perform shunt surgery or as a routine postoperative follow-up investigation to confirm a functioning shunt. The study included 32 patients (preoperative [25 patients]; postoperative [7 patients]). Twelve patients were excluded prior to analysis due to investigational problems; in 1 case the data recording did not function correctly, and the other 11 investigations were terminated after the application of only 1 of 3 infusion methods. The reasons were headache and nausea in 1 case, blockage of the orifice of the infusion needle during withdrawal of CSF in 6 cases, and 4 patients did not want to continue after completing the first method. Thus, the study population consisted of 20 patients (14 patients preoperatively and 6 patients postoperatively). The mean age of the 20 patients was 72.6 ± 9.0 years (± SD); 6 of the patients were women and 14 were men. All aspects of this study were approved by the local ethics committee. After receiving written as well as oral information, informed consent was obtained from all patients included in the study.

The Infusion Apparatus

The infusion apparatus used to perform the investigations has previously been described.1 The apparatus was personal computer–based and included an electronic control unit, 2 pressure transducers, a peristaltic pump, an emergency stop, and a set of disposable tubing. Data collection and communication between software and hardware were performed using 2 standard data acquisition cards. The electronic control unit included pressure amplifiers, analog safety checks that stop the pump at dangerously high or low ICP, and a signal to ensure communication with the personal computer. A built-in horizontal laser line was used for zero level alignment of the equipment in relation to the patient.

Experimental Model

The experimental model has also previously been described.1 It consisted of a cavity formed in polymethylmethacrylate, and the shape corresponded to the compliance of the CSF system and was deduced from the pressure-volume relationship first presented by Marmarou et al.23 The elastance coefficient \( k \) was chosen to be 0.089 ml−1 (PVI = 25.9 ml).26 Resting pressure was set to 1.56 kPa through outflow to a container with continuous overflow. Changeable T304 stainless steel tubing (denoted “pipe” henceforth) connected the cavity and the overflow container. The conductance of the pipe simulated the \( C_{\text{out}} \) of the CSF system. A peristaltic pump was used to produce physiological pressure variations in the model, related to the volume variation due to cerebrovascular variation in a human.1 The infusion apparatus was connected to the model using a double lumen arrangement. The liquid used in the model was deaerated water, to avoid errors due to bubbles of air in the system.

Patient Investigations

The investigation was started at 8:30 a.m. after 12 hours of bed rest. The patient was placed on a specially designed bed with a hole in the back, and while the patient was in the sitting position, 2 needles (outer diameter 1.2 mm) were inserted in the L3–4 interspace. The patient was then placed supine, and the zero-pressure reference level of the infusion apparatus was placed at the center of the auditory meatus. The data collection sampling rate was 100 Hz, and the data were resampled to 1 Hz. Initially, ICP was measured during 20 minutes of rest (Fig. 1), and the resting pressure (\( P_r \)) was calculated as the mean pressure over the last 5 minutes. A sample of CSF was taken. The resting pressure measured prior to taking the sample was reestablished (by regulating the pump flow until the pressure was within 50 Pa from the resting pressure), and a period of 5 minutes was allowed to pass before the infusion started. Every investigation was composed of 3 different infusion methods: infusion to constant pressure levels, bolus infusion, and constant flow infusion. The different infusion techniques are described briefly in Infusion Methods and Analyses and in detail in studies by Andersson,1 Czosnyka,6 Katzman and Hussey,17 and Marmarou23 and their colleagues. The order in which the infusion methods were applied for each patient was randomly selected.

Before the start of a new method, ICP spontaneously decreased toward resting pressure during a period of 5 minutes. If ICP did not reach resting pressure during this time, it was regulated back to the resting pressure and then left to stabilize for another 5-minute period before the next method was applied.

Investigations on Experimental Model

The same equipment used in patients was applied to the experimental model of the CSF system. The measure-
ment protocol was almost the same; however, the resting pressure measurement was 10 minutes shorter, and the relaxation times after each infusion increased from 5 minutes to 15 minutes, since a long investigation time was not a limiting factor in the model. Seven pipes of different lengths and inner diameters were used to simulate C_out of the system. On 6 pipes, C_out was measured once without the addition of pressure variations, and 6 times when pressure variations were added. On 1 pipe, investigations without and with pressure variations were repeated 6 times each.

Infusion Methods and Analyses

**Constant Pressure Infusion.** The constant pressure infusion method has previously been described. The ICP was regulated to 6 consecutive, predetermined pressure levels in steps of 0.4 kPa (3 mm Hg). The first pressure level was set to be the nearest level at least 0.4 kPa greater than the resting pressure. On each pressure level, the mean ICP was measured, and the flow needed to maintain that constant pressure level was determined. The measurement time on each level was 7 minutes in the experimental model and for patients with suspected INPH, and 5 minutes for patients who had a shunt. The outflow conductance given by this analysis method was denoted C_out_cpi. It was assessed as the slope of the linear regression between flow and corresponding mean pressures for all elevated levels.

**Bolus Infusion.** The bolus infusion test has previously been described. At maximum pump speed (~ 15 ml/minute) approximately 4 ml of artificial CSF was infused. Three consecutive bolus infusions were performed, and between each bolus the relaxation time was 5 minutes for the patients and 15 minutes in the experimental model. Two analysis methods were used to estimate the bolus outflow conductance (C_outbol). A visual fitting as well as a computerized fitting (fminsearch in Matlab, Mathworks, Inc.), which utilizes the simplex search algorithm, was applied to the exponentially declining pressure curve (Fig. 2) giving C_outbol vis and C_outbol fit, respectively (see Appendix for mathematical details).

For the visual fit on investigations performed in the experimental model, all bolus infusion curves were included in the analysis except those in which the pressure increase (P_p − P_start) was less than 0.53 kPa (4 mm Hg). For the patient material, with too large B-waves present it was not possible to perform a computerized fit of the bolus relaxation curve in an adequate way; that is, the physiological model given by Equation 4 in Appendix was not sufficient to mathematically describe the measured data, often resulting in a horizontal line. Therefore, another exclusion criterion was adopted: B-waves with amplitude larger than one-third of the total pressure rise. All bolus curves were scaled in the same manner (0–30 mm Hg), and the end of the infusion phase was marked. Five biomedical engineers familiar with time pressure curves were given the exclusion criteria and information of the characteristics of B-waves. They performed a visual inspection and selected the bolus infusion curves that should be included in the analysis. For exclusion the distinct majority (4 or 5) of observers had to reject the bolus infusion curve.

**Constant Flow Infusion.** The constant flow infusion test was based on the method originally presented by Katzman and Hussey and further developed by Czosnyka et al. Artificial CSF was infused at a constant rate of approximately 1.5 ml/minute. The infusion was continued for 20 minutes. Analyses were made using both a static (C_out_stat) and a dynamic (C_out_dyn) method (see Appendix for mathematical details).
Measurement of CSF outflow conductance

Statistical Analysis

To test differences between the methods on the experimental model, 1-way ANOVA statistical tests were used. Separate tests were performed for each pipe. In cases of equal variance, the Bonferroni post hoc test was applied; otherwise, the Dunnett T3 post hoc test was used. For patients, the paired sample t-test was used and Bonferroni correction for multiple tests was applied. The significance level was always $\alpha = 0.05$.

Results

Experimental Model

In Fig. 3, $C_{\text{out\,cpi}}$, $C_{\text{out\,dyn}}$, $C_{\text{out\,stat}}$, $C_{\text{out\,bol\,vis}}$, and $C_{\text{out\,bol\,fit}}$ are shown, separated for each pipe, without (Fig. 3 upper) and with (Fig. 3 lower) the addition of physiological pressure variations. The general agreement between estimates from different analysis methods was good, but with variations (Fig. 3 lower). The $C_{\text{out\,bol\,vis}}$ was overestimated in the area of low $C_{\text{out}}$. Table 1 displays the significant differences found in the experimental model when physiological pressure variations were present. The standard deviation after controlling for the variation between pipes, describing the repeatability, was lower for the steady-state methods ($C_{\text{out\,cpi}}$ 1.19 μl/[second × kPa], $C_{\text{out\,dyn}}$ 1.83 μl/[second × kPa], $C_{\text{out\,stat}}$ 1.55 μl/[second × kPa], $C_{\text{out\,bol\,vis}}$ 3.15 μl/[second × kPa], and $C_{\text{out\,bol\,fit}}$ 3.48 μl/[second × kPa]) [all values are SDs; 42 measurements]. The mean PVI (with physiological pressure variations) was 22.3 ± 4.7 for the dynamic fitting of constant flow infusion, and 22.5 ± 15.9 according to the computerized fitting analysis of the bolus infusion method.

Patients

Table 2 provides an overview of the successfully performed analysis for $C_{\text{out}}$ estimation and summarizes the reasons for incomplete investigations or analyses. In Fig. 4, the individual $C_{\text{out}}$ for each of the 20 patients is displayed. Correlations and differences between analysis methods for the preoperative patient investigations are shown in Table 3. Good agreement was found between the steady-state methods while the visual bolus method produced a higher estimate of $C_{\text{out}}$.

The higher $C_{\text{out}}$ estimates of the bolus methods compared with the other 3 methods is further visualized in Fig. 5, showing the mean $C_{\text{out}}$ for all patients without a shunt in whom analyses were achieved from all 5 methods (8 patients). For this patient group, the PVI was 22.3 ± 12.3 for the dynamic fitting of constant flow infusion and 22.5 ± 15.9 according to the computerized fitting analysis of the bolus infusion method.

Discussion

In the recently published guidelines on INPH, it was stated that for unknown reasons $C_{\text{out}}$ as determined by the bolus infusion method is higher than those determined by steady-state infusion methods. In this study, we investigated this enigma by performing triple infusion tests during the same session, in an experimental model with well-known characteristics and in a group of patients. The results in the experimental model indicate that the physiological pressure variations caused a bias when using the bolus analysis method. Correlation analysis and comparison of $C_{\text{out}}$ in the preoperative patient investigations confirmed this difference between steady-state methods and the bolus method (Fig. 5). These findings are supported by previous studies that compared bolus infusion with constant infusion.

Reasons for Differences Found in $C_{\text{out}}$ Estimates

The accuracy of these types of measurements is dependent on the relationship between the pressure change...
and the precision of the measured pressure. One difference between the bolus infusion method and the steady-state infusion methods was the magnitude of the created pressure increase. For constant pressure infusion, there was always an increase of at least 2.4 kPa, and for constant flow infusion the increase was in the range of 2–3 kPa for a typical patient. Also, both these methods used steady-state recordings, which made the methods less sensitive to variations, for example, B-waves. With these similarities in methodological approach, it was not surprising that the 2 steady-state methods produced correlated and similar \( C_{\text{out}} \) estimates.\(^6\) For the bolus infusion method, there was a wide range of increase in pressure, from 0.5 to 4.0 kPa. However, for this method, the crucial pressure changes were the momentarily measured pressure decreases on the relaxation curve, which were always much smaller, and especially when \( C_{\text{out}} \) was low. The relaxation phase and the physiological variations are partly in the same frequency range, which limits the signal processing options for extracting \( C_{\text{out}} \)-related data from the curve and therefore making the method more susceptible to the physiological variations. On the other hand, it could as well be argued that the impulse response of the bolus method could be seen as an advantage, since it is likely to induce a minimal perturbation to the CSF system and therefore potentially measure a more physiological \( C_{\text{out}} \). However, previous studies have shown that there may be physiological causes behind the systematic differences, such as a transient vasogenic response to the pressure increase of the bolus.\(^1^4\) Furthermore, the bolus

Fig. 3. Upper: \( C_{\text{out}} \) for each pipe as measured by the 5 different methods when no physiological pressure variations were present. For the first 3 pipes, ICP did not reach a plateau pressure during constant flow infusion. Lower: \( C_{\text{out}} \) for each pipe as measured by the 5 different methods when physiological pressure variations were present. The error bars show SEM (6 measurements per pipe). For the first 3 pipes, ICP did not reach a plateau pressure during constant flow infusion.
infusion method estimates parameters from 2 separate phases, PVI from the pressure increase and $C_{\text{out}}$ from the relaxation phase. These 2 phases may be asymmetrical, and since PVI is used for estimation of $C_{\text{out}}$, any error in the estimation of PVI will affect the $C_{\text{out}}$ estimation. All these phenomena could serve as an explanation for the difference between methods.

A fundamental assumption is that the CSF system can be represented by a lumped model. The bolus approach with dynamic response including propagation of added volume between different compartments, not accounted for by the lumped model, could be a source of error in the bolus analysis.

An explanation of the significantly higher $C_{\text{out}}$ found with the visual bolus method (Figs. 3 lower and 5) could lie in a systematic error in the visual fitting. It is likely that the operator intuitively expected a pressure decrease following a typical exponential curve. This was satisfied in the region of high $C_{\text{out}}$ where there were marked pressure decreases. Therefore, the differences were limited to the low $C_{\text{out}}$ region, where the pressure decreases were small compared with the pressure variations, and a tendency to create a more pronounced exponential shape than what was actually present must be suspected.

In the same way that constant infusion can be estimated by computerized fitting, so can the bolus infusion. An objective computerized analysis was implemented that worked well for the experimental model. However, it became clear that not all bolus relaxation curves were suitable for this kind of automated analysis. Therefore, a selective criterion based on B-wave magnitude was adopted. Although this new approach of analyzing the bolus relaxation curves for determination of $C_{\text{out}}$ had better agreement with the estimations from the steady-state infusion methods, methodological problems related to

### TABLE 2: Overview showing successfully performed $C_{\text{out}}$ estimations

<table>
<thead>
<tr>
<th>Case No.</th>
<th>$C_{\text{out cpi}}$</th>
<th>$C_{\text{out dyn}}$</th>
<th>$C_{\text{out stat}}$</th>
<th>$C_{\text{out bol vis}}$</th>
<th>$C_{\text{out bol fit}}$</th>
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</table>

* Patients in Cases 1–14 were preoperatively investigated and those in Cases 15–20 underwent follow-up for shunt function. For 18 patients, all 3 infusion methods were completed. The missing estimates were due to the following: constant pressure infusion—blockage of the orifice of the infusion needle; constant infusion—unreliable fit, no plateau reached, or stomach ache; bolus infusion—exclusion criteria (25 of 60 bolus infusions were removed from the computerized fitting and 15 of 60 from the visual fitting).
physiological variations, for example, B-waves, and a tendency for overestimation on patient data are still to be resolved.

Threshold Levels for Shunting

In the INPH guidelines it is stated that the threshold for $C_{\text{out}}$ using the bolus method compared with steady-state methods is clearly higher. The current study supports that statement, but the results do not fully explain the even larger difference in $C_{\text{out}}$ described in the literature. One further factor which might have influenced earlier studies is the resolution of the measurement system. From Equations 2 and 3 in the Appendix it can be seen how the pressure decrease from $P_p$ to $P_t$ (Fig. 2) was essential for determining $C_{\text{out}}$. Because of this sensitivity to the accuracy of the measured pressure for the bolus method, a too low resolution or a small systematic error might significantly affect the estimated $C_{\text{out}}$. In cases with large compliance and low conductance the pressure relaxation will be slow, resulting in a small expected pressure decrease. For example, monitoring equipment with a typical resolution of 1 mm Hg (0.13 kPa) is not sufficient for bolus measurements. In clinical application, there is typically an average of 3–4 rapid bolus responses to obtain consistency. This results in larger pressure increases ($P_p - P_{\text{start}}$) and larger pressure decreases ($P_t - P_{\text{start}}$), because the relaxation generally does not reach $P_{\text{start}}$ of the previous bolus infusion (Fig. 1). Averaging over multiple bolus infusions would thus reduce the error, but this is illustrative and emphasizes the importance of a high resolution of the recording system. It also indicates that a higher bolus volume, like the 10 ml suggested by Takeuchi et al. could improve the accuracy of the determined $C_{\text{out}}$.

Shunt Test With High $C_{\text{out}}$

When investigating shunt function by a CSF infusion test, typically a large flow in the shunt is expected if the shunt is working properly ($C_{\text{out}}$ for Strata and Codman shunts are approximately 58 and 23 μl/[second × kPa], respectively). In this study, shunt malfunction was suspected in 1 patient (Case 12 in Fig. 4), while the investigations in the other 5 patients were routine follow-up visits performed approximately 3 months postsurgically (Strata shunts). Thus, well-functioning shunts were expected.

The $C_{\text{out}}$ was generally higher in the patients with shunts than in those without, and specifically $C_{\text{out}}$ approached the expected $C_{\text{out}}$ of the shunts. The constant pressure infusion method is designed to measure outflow on pressure levels above resting pressure, and for most patients this will also mean that outflow is measured through an open shunt. Thus, it was always the joined $C_{\text{out}}$ of the shunt and the patient that was determined by this method.

<table>
<thead>
<tr>
<th>Paired Methods</th>
<th>No. of Pairs</th>
<th>Mean Difference (μl/[second × kPa])</th>
<th>Correlation</th>
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<td>2.51</td>
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* Statistically significant value.
Measurement of CSF outflow conductance

The constant infusion method initially measures CSF outflow in the ICP region where even a properly working shunt could be closed, and in those cases $C_{\text{out}}$ would be underestimated. Thus, Equation 5 in the Appendix is not completely applicable for estimating $C_{\text{out}}$ in patients with shunts. In most cases, this will not pose a problem for determining shunt function, but it makes it more difficult to compare with $C_{\text{out}}$ from the in vitro shunt test and to determine partial occlusion of the shunt. This exemplifies an advantage of the constant pressure infusion method, which generates a pressure/flow curve that in greater detail describes the characteristics of the system.11

Methodological Differences

The resting pressure for the experimental model is known; however, in patients, there will be a natural physiological variation, and an uncertainty in the estimation can be expected. Furthermore, performing an infusion test in a patient is likely to introduce some changes to the CSF system. Influence on the resting pressure, $C_{\text{out}}$, and PVI have been shown,1,16 and to remedy this problem the order in which the protocols were applied was randomized. The constant pressure infusion does not use the resting pressure as a parameter to calculate the outflow conductance, in contrast to the other 2 infusion methods.

The reference pressure $P_0$ is not included in the selected CSF model described in Equation 1.3 For dynamic analyses where PVI is estimated, the parameter $P_0$ will affect the estimates of $C_{\text{out}}$ and this could be a reason for differences between dynamic and steady-state estimation approaches. For dynamic constant flow infusion analysis, $P_0$ can be estimated and included in the model.9 However, the small difference between $C_{\text{out\ dyn}}$ and $C_{\text{out\ stat}}$ suggest that the effect would be limited in this material (Fig. 5).

A pressure plateau must be reached to be able to perform the static analysis of the constant infusion. If the infusion time is too short or the ICP becomes too high due to a low $C_{\text{out}}$, this might not happen. In those cases the dynamic analysis method is needed.

A high compliance of the system when performing a bolus infusion or a constant flow infusion might result in very small pressure changes, thereby making it difficult to obtain a good estimate of $C_{\text{out}}$. In this study, using only 20 minutes for the infusion, this was the reason for exclusion of 2 constant flow infusions. Due to high compliance, roughly 1 of every 5 bolus infusions was excluded because it did not reach the 4 mm Hg threshold. With a pressure-regulated method, such as the constant pressure infusion, the analysis is not dependent on a reasonable compliance.

Obstruction of the needles was a problem in some cases when using the constant pressure infusion method since it requires both infusion and withdrawal of CSF. In some cases the orifices of one or both needles lay close to tissue, which resulted in blockage of the orifice of the infusion needle when CSF was withdrawn. The needles could be slightly adjusted and twisted (without producing another hole in the dura), but the problem was not always resolved, and in those cases the pressure-regulated method could not be performed.

A measure of the reliability of the estimated $C_{\text{out}}$ should be implemented for all infusion methods; currently it is only the constant pressure infusion method that provides such a measure.

Operator and analysis skills were most important for the bolus method. The bolus infusion method works according to theory and in the hands of an operator with extensive experience of bolus infusion curves who in real time by visual inspection can determine if a bolus infusion curve is suitable for analysis; the method can be used to estimate $C_{\text{out}}$. However, small pressure responses and physiological variations with frequency ranges overlapping with the relaxation phase complicate the analysis, and this can easily cause substantial errors in the estimate for the less experienced users.

For the computerized bolus analysis method, there was a better agreement with the steady-state methods, but a tendency for overestimation was still present, the repeatability was still better for the steady-state methods, and the use of a bolus selection procedure was needed. Although we have identified one possible source of error, it does not exclude a physiological basis for increased $C_{\text{out}}$ by the bolus method. Further work is necessary to fully understand the reasons for the discrepancy.

Conclusions

In this study we compared the 3 most common infusion methods in an experimental model and in patient investigations. For the experimental model without added physiological pressure variations, there was a good concordance between all 3 infusion methods, confirming the theoretical basis. With added variations to the experimental model there was still good agreement between the steady state methods while a significantly higher $C_{\text{out}}$ was found using the visual bolus infusion method. The preoperative patient investigations supported this finding.

The difference between methods emphasized the importance of referring to method when presenting a $C_{\text{out}}$ value and the necessity to standardize these measurements. The need for an operator with extensive experience for the bolus infusion method and the better repeatability of
the steady-state methods suggests a steady-state method as the recommended approach for estimating $C_{out}$. For determining compliance as well as studying physiological responses, the bolus method still has clinical relevance. Its main advantage was the shorter investigation time, and further development of the steady-state methods should focus on improving the efficiency to reduce investigation time.

**Appendix**

**Mathematical Details for Bolus Infusion**

For the visual fit, the outflow conductance was given by

$$C_{out\ bol\ vis} = \frac{\ln \left( \frac{P_t - P_p}{P - P_p} \right)}{k \cdot t},$$

[eq. 2]

where $t$ was defined as any time instant along the fitted curve after the bolus infusion had stopped, $P_t$ was the pressure at time $t$, and $P_p$ was the pressure where the visually fitted curve crossed the point of ended infusion. For every bolus infusion, the elastance coefficient $k$ was calculated as

$$k = \frac{\ln \left( \frac{P_t}{P_{start}} \right)}{V}.$$

[eq. 3]

Here, $V$ was the infused volume of artificial CSF and $P_{start}$ was the mean pressure over the last 5 seconds prior to each bolus infusion. $C_{out\ bol\ vis}$ was calculated at $t = 30, 60, 90,$ and 120 seconds for each bolus using Equation 2. The final $C_{out\ bol\ vis}$ that resulted from each investigation was the mean value of all 12 estimates from the 3 bolus infusions.

The `fminsearch` algorithm was used to fit Equation 4 to the relaxation part of the pressure curve, $P_{bol\ relax}$, measured after bolus infusion

$$P_{bol\ relax} = \frac{P_t}{1 + \frac{1}{P_p} \left( e^{\left( \frac{C_{out\ bol\ vis}}{P_p} \right)} - 1 \right)}.$$

[eq. 4]

$P_t$ was taken as the mean of the first 10 seconds after infusion stopped.

**Mathematical Details for Constant Flow Infusion**

For the static method the plateau pressure ($P_{plateau}$), estimated as the mean pressure over the last 5 minutes of infusion, was used in the following equation:

$$C_{out\ stat} = \frac{P_{ent}}{P_{plateau} - P_{i}}.$$

[eq. 5]

For the dynamic method, the `fminsearch` algorithm was used to fit Equation 6 to the pressure curve, $P_{const\ inf}$, measured during infusion

$$P_{const\ inf} = \frac{P_t + \frac{L_{ent}}{C_{out\ dyn}}}{1 + \left( \frac{1}{C_{out\ dyn}} \right) e^{\left( \frac{C_{out\ dyn}}{P_{start}} \right)}},$$

[eq. 6]

$C_{out\ dyn}$ and $k$ could thus be estimated.

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Measurement of CSF outflow conductance


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