Errata

Thesis

p. 14, line 4: 'The approximate CSF volume in man is 1500 mL’ => ‘The approximate volume of the cavity which CSF is contained within is 1500 mL’.

p. 71: The first two references should be omitted.

p. 45-65: ‘Results and discussion’ should be replaced with the text in Appendix A.

p. 14: Figure 1 should be replaced with the following figure:

p. 16, label of Figure 2: Changed to ‘Anatomical sketch of the arachnoid villi’.

p. 37: Figure 8 should be replaced with the following figure:

p. 36: Figure 7 should be omitted.

p. 35 line 7 and 12: ‘Figure 7’ => ‘Paper II Figure 3’.

p. 42: Figure 12 should be omitted.

p. 41: line 7: ‘Figure 12’ should be changed to ‘Paper V Figure 2’.

p. 43: Figure 13 should be omitted.

p. 43: line 9: ‘Figure 13’ should be changed to ‘Paper III Figure 3’.

Papers

Paper I, page 140 section ‘Parameter selection’: ‘min-1’ should be changed to ‘min’ and ‘s-1’ should be changed to ‘s’.

Paper III, Equations 7 and 8 on page 340 should be replaced with:

$|C_{out\;thres} - C_{out\;tot}| \leq 2 \;\mu l/(s \;kPa) \; (95 \% \; CI)$

$|\Delta C_{out\;thres} - \Delta C_{out\;tot}| \leq 2 \;\mu l/(s \;kPa) \; (95 \% \; CI)$
Appendix A

10 Results and discussion

10.1 Outflow conductance versus outflow resistance

The outflow pathways of the CSF system are characterised by a resistance ($R_{out}$), or a conductance ($C_{out}$), to flow. Here $R_{out}$ describes the resistance met by CSF when passing through the arachnoid villi or any other outflow pathway from the SAS, and $C_{out}$ describes the ‘ease’ with which CSF can pass through the same channels. $R_{out}$ is the most common CSF outflow parameter presented in international literature. $C_{out}$ and $R_{out}$ are interchangeable by inversion, but when studying the CSF system using the method of constant pressure infusion, representation by $R_{out}$ has some serious drawbacks when it comes to looking at the reliability of measurements. ICP is regulated to predefined levels, and thus the physiological disturbances will mainly affect the estimation of the net infusion flow, while the error in the ICP measurement is negligible. According to equation (1) $R_{out}$ is inversely proportional to the CSF outflow, and thus the estimated error, $\Delta R_{out}$, will be dependent on the actual size of $R_{out}$. Using $C_{out}$ on the other hand, the error will be independent of the size of $C_{out}$. These relationships are exemplified in Paper II (Figures 5 and 6). The advantage of using $C_{out}$ is thus that the interpretation of the error estimation will be greatly simplified, if the size of the error has the same meaning regardless of the size of the estimated parameter.

In studies I and IV the condition of the CSF outflow pathways was used merely as a numerical value and as input for simulations respectively, and so the parameter itself was never estimated. Thus, $R_{out}$ was used to ease the interpretation of the papers to the reader. In Papers II, III and V the reliability and variation of the estimated parameter were specifically addressed, and thus $C_{out}$ was used.

10.2 Pathological outflow conductance

$C_{out}$ in healthy individuals is higher than in patients with NPH, this makes the parameter a possible diagnostic tool and predictor of outcome after shunt surgery. Previous studies have found that a $C_{out}$ smaller than approximately 7 µl/(s kPa), as determined by a lumbar constant rate infusion or a lumboventricular perfusion, is indicative of a disturbed CSF system, and in a study performed with constant pressure infusion on a group of healthy individuals, a mean $C_{out} = 18$ µl/(s kPa) was found. Thus, in the area close to
the interval 7 - 18 μl/(s kPa) it is especially important to have reliable estimations. If the reliability is not good enough to clearly state whether an individual investigation is pathological or normal, an erroneous conclusion might easily be drawn from the data. This in turn would significantly reduce the sensitivity and specificity of the test.

When determining shunt function the precision of the measurement is not as crucial as in the preoperative case. \( C_{\text{out}} \) of most shunts is much larger (range 25-60 \( \mu \text{L/(s kPa)} \)) \(^3\) than the physiological \( C_{\text{out}} \) of the CSF system, and the main objective when looking at postoperative CSF dynamics is usually only to determine whether the shunt is functioning or not. Thus, an investigation resulting in \( C_{\text{out}} = 45 \pm 10 \mu \text{L/(s kPa)} \) will lead to the same conclusion as will \( C_{\text{out}} = 45 \pm 2 \mu \text{L/(s kPa)} \). Of course, a higher precision is always preferable and may also tell something about a partially occluded shunt.

### 10.3 Application of CSF model to air ambulance transportation

A model correctly describing a system under investigation is undoubtedly of great value when trying to determine the parameters of the system. In Paper I a proposed model of the CSF system was extended to incorporate intracranial air. It was proposed that expanding air affected ICP in a similar manner as the infusion of artificial CSF does, and thus equation (12) could be solved for the special case of air expansion during air ambulance transport.

The idea to investigate the effect of intracranial air on ICP during reduced ambient pressure was initiated by the neurosurgeons at the Umeå University Hospital. When air transport of a patient with suspected intracranial air was in question, an ordination was always made saying that the transport should be undertaken during preserved sea-level pressure for the safety of the patient. The question raised was whether or not this was actually necessary, and there was no answer to be found in the literature.

Simulations where different initial intracranial air volumes, cabin altitude rate of changes and resting pressures of the patient were considered showed that the model behaved in agreement with physical expectations. At normal maximum cabin altitude (8000 ft = 2438 m) the initial volume had increased by approximately 30% (Paper 1 Figure 2).

In Paper 1 Figure 4 simulations showing ICP as a function of cabin altitude are shown. For an intracranial air volume of 30 ml the estimated worst-case
increments of ICP from sea level to maximum altitude would be from 10 mm Hg to 21.0 mm Hg, or from 20 mm Hg to 31.8 mm Hg. Furthermore, the results of a non-compliant system showed that the end pressure primarily was determined by resistance and that the compliance primarily influenced the curve form of the pressure increase (Paper I Figure 4). Unlike a typical constant infusion curve, were the pressure at some point would reach equilibrium (Paper V Figure 1), there was an unceasing ICP increment (Paper I Figure 4). This was explained by the continuous increase in $I_{IA}$.

From the results of Paper I it was concluded that the proposed and extended model of the CSF system could be used to simulate the behaviour of ICP during air transport of patients with intracranial air. Main contributors to the elevation of ICP were the initial intracranial air volume and the aircraft altitude rate of change, or more precisely the rate of change of cabin altitude, which also depended on the cabin pressurization regulation of the plane. For a patient with large initial intracranial air volumes and high resting pressures, ICP may reach considerably high levels. The study in Paper I therefore supported a preserved sea-level pressure during air ambulance transportation.

10.4 Validation of infusion apparatus and $\Delta C_{out}$

10.4.1 Infusion test on experimental model

A new apparatus designed to perform standardized and automated infusion tests was constructed. In Paper II it was shown on an experimental model that the repetitiveness of the $C_{out}$ estimation was good, with a 95 % CI of less than $\pm 2 \mu$L/(s kPa) for the five steel pipes when physiological pressure fluctuations were present (n=6) (Paper 2 Figure 5).

In the same study (Paper II) a parameter representing the reliability of each individual investigation, $\Delta C_{out}$, was suggested and evaluated. Although $\Delta C_{out}$ can not be assumed to fully fulfil the statistical requirement of being calculated from independent sets of data, it was shown on an experimental model to reflect the reliability of each investigation in a valuable way. It furthermore satisfied the aim of giving easily interpreted information since it, for independent data, mathematically would correspond to the 95 % CI of the assessed $C_{out}$.

In the daily clinical routine, a small $\Delta C_{out}$ supports a correctly estimated $C_{out}$, while a large $\Delta C_{out}$ informs the investigator that a repeated infusion test is needed, or alternatively that the significance of the assessed $C_{out}$ should be reduced when diagnosing and selecting patients for surgery.
10.4.2 Infusion test on patients

Repeated constant pressure infusion tests were performed on 14 patients with suspected or treated INPH (Paper II). The correlation coefficient was $R=0.99$ ($p<0.05$) (Paper 2 Figure 8). The mean difference between the first and second infusion test was $-2.46 \mu$L/(s kPa) ($p<0.05$).

Despite the high correlation between the repeated measurements, there was a significant difference between the first and second infusion test. This suggested that the infusion test induced a physiological change to the system. Analysing the reliability parameter from patient measurements (Paper II) revealed that in spite of the systematic difference the $\Delta C_{out}$s overlapped in all but one case (Paper II Figure 7), supporting that $\Delta C_{out}$ will be a valuable indicator of reliability also in the clinical setting.

10.5 Reduction of investigation time

A concern often expressed within care giving organizations is the time consumption of different tests and procedures, and the cost that comes along with it. When performing a CSF infusion test a kind of ‘time consumption versus accuracy’ paradox is encountered, where there is a trade off between the parameters. In Paper III, an adaptive algorithm for the constant pressure infusion assessment of $C_{out}$ was developed. The main purpose was to adjust the investigation to each individual patient, and to reduce investigation time without reducing the reliability of the estimated parameter below clinically relevant levels.

Since the constant pressure infusion method is based on regulation of the pressure, the net infusion flow was the parameter most likely to vary the most. A parameter, $\hat{\Delta F}$, was defined as the 95 % CI of the net flow, and it was estimated by using an iterative signal analysis algorithm. The time difference of $\hat{\Delta F}$, $\hat{\text{diff}}\Delta F$, was calculated to find the point in time when the measured flow did not further substantially improve.

The differences $C_{out\text{thres}} - C_{out\text{tot}}$ and $\Delta C_{out\text{thres}} - \Delta C_{out\text{tot}}$ for all patients at 11 different levels of the threshold $\text{diff}\Delta F_{\text{thres}}$ was determined as well as the 95 % CI of the differences in $C_{out}$ and $\Delta C_{out}$ at five different threshold levels as compared with at total time. As expected the variation decreased with decreasing threshold level (Paper III Figures 4 and 5 and Table 1).

In Paper III Table 1 it can be seen that out of the threshold levels that fulfilled the clinical criteria, 0.04 $\mu$L/s was the level that reduced the investigation time
the most. At this threshold the difference $C_{\text{out, thres}} - C_{\text{out, tot}}$ was -0.3 µL/(s kPa), and $\Delta C_{\text{out, thres}} - \Delta C_{\text{out, tot}}$ was 0.4 µL/(s kPa). Both differences were significant ($p<0.05$), but found clinically negligible. The time reduction for different thresholds was estimated (Paper III Figure 6). Using the threshold level 0.04 µL/s, the reduction was $14.3 \pm 5.9$ min (mean ± SD, $n = 27$), $p<0.01$.

In Paper III it was shown that without substantially reducing the accuracy of the estimated parameter, the investigation time of a constant pressure infusion test could be reduced by approximately 25 % by applying an adaptive method of analysis.

10.6 ICP dependency of $R_{\text{out}}$

Although the linear relationship between ICP and outflow is such a central part of the CSF dynamic model, introduced by Marmarou$^{41}$ and used throughout this thesis, few studies have actually been specifically aimed at looking at and scientifically proving this relationship. Since the purpose of the model is to mimic the true physiological system and the model is based on a number of assumptions, validations that challenge these assumptions are important. The results of the simulations in Paper I as well as $C_{\text{out}}$ measurements in general and in Papers II, III and V specifically are all affected by the assumption of linearity. Therefore, in Paper IV the relationship between ICP and CSF outflow was investigated.

When using all elevated pressure levels (Paper IV, Figure 3), the quadratic term contributed significantly ($p<0.05$, $n=30\times6$). The pressure levels are presented in Table 1. Limiting the analysis to the first three pressure levels, there was no significant contribution of the quadratic term ($p=0.5$).

<table>
<thead>
<tr>
<th>Level</th>
<th>Mean ICP on each pressure level [mm Hg]</th>
<th>Mean ICP increase from baseline pressure [mm Hg]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level 1</td>
<td>16.6</td>
<td>4.9</td>
</tr>
<tr>
<td>Level 2</td>
<td>20.2</td>
<td>8.5</td>
</tr>
<tr>
<td>Level 3</td>
<td>23.6</td>
<td>11.9</td>
</tr>
<tr>
<td>Level 4</td>
<td>27.0</td>
<td>15.3</td>
</tr>
<tr>
<td>Level 5</td>
<td>30.2</td>
<td>18.5</td>
</tr>
<tr>
<td>Level 6</td>
<td>33.5</td>
<td>21.7</td>
</tr>
</tbody>
</table>
On the experimental model the relationship between standardized flow and pressure was linear in the entire pressure range (Paper IV Figure 5). This result was used as a verification that, apart from possible leakage at the incision point of the needles, the non-linear behaviour of the pressure flow relationship found in the patient investigations must have a physiological origin.

Thus, this study implied that the relationship between ICP and CSF outflow was linear in the region of normal and slightly increased ICP, that is, $R_{\text{out}}$ was independent of ICP in this region (Paper IV Figures 3 and 4). This was in accordance with previous studies who concluded a general linear relationship by visual inspection or a high correlation.\textsuperscript{25,26,8,53}

The relationship had a non-linear tendency, with a facilitated outflow when the pressure increment from resting pressure was larger (Paper IV Figures 3 and 4). For ICP larger than approximately 22 mm Hg, a decrease in $R_{\text{out}}$ was also seen by Davson et. al. when performing an infusion study on rabbit.\textsuperscript{17}

### 10.7 Comparison of infusion methods

Several different methods can be used to estimate $C_{\text{out}}$ of the CSF system. The methods may be divided into three main categories; constant pressure infusion,\textsuperscript{25} constant flow infusion\textsuperscript{13,32,33} and bolus infusion\textsuperscript{40,41}. When discussing and interpreting results, the outcome from the different methods are often mixed, even though the $C_{\text{out}}$ threshold for selecting patients for shunt surgery may differ. Thus, it is important to compare these methods in both experimental and clinical settings, and this was the aim of Paper V.

The four methods evaluated in Paper V (constant pressure infusion ($C_{\text{out\ cp}}$), constant flow infusion with dynamical analysis ($C_{\text{out\ dyn}}$), constant flow infusion with static analysis ($C_{\text{out\ stat}}$) and bolus infusion ($C_{\text{out\ bol}}$)), were compared on an experimental model without and with physiological pressure fluctuations (Paper V Figures 3a and 3b). The general agreement between the methods was good. However, with fluctuations $C_{\text{out\ bol}}$ was significantly larger than all other $C_{\text{out}}$ for pipes 1 and 2, and for pipe 3 $C_{\text{out\ bol}}$ was significantly larger than $C_{\text{out\ cp}}$ and $C_{\text{out\ dyn}}$ (Paper V Table 1).

In accordance with the results from the experimental model as well as previous clinical studies,\textsuperscript{33,49,56} the patient investigations (Paper V) indicated that $C_{\text{out\ bol}}$ was larger than $C_{\text{out}}$ as obtained by the other three methods (Table 2). However, no significant differences were found ($p=0.2$).
The finding that all methods had a high degree of agreement on the experimental model when no pressure fluctuations were added, and that \( C_{\text{out bol}} \) was significantly higher for the pipes with the lowest \( C_{\text{out}} \) when fluctuations were added, indicates that the differences between the methods was due to problems in the analyses caused by the disturbances. This was an important finding of Paper V, since the reason for the discrepancy between the methods has been an enigma which also was stated in the recently published guidelines on INPH.\(^{39}\)

An explanatory model to this discrepancy based on a difference in pressure increase, static and momentary measurements, visual fitting procedures and low resolution of measurement equipment was proposed (Paper V). The main thought was that a small induced pressure change compared to the pressure fluctuations, made it difficult to correctly estimate the pressure parameters of the bolus method. It is important to emphasise that in Paper V all infusion methods were implemented according to the way in which the methods are currently clinically used, in order to understand and explain the differences from that perspective.

Similarly to the results of Paper II, \( C_{\text{out}} \) was generally higher in the shunted than in the non-shunted patients, and especially for the constant pressure infusion method (Paper V Figure 4). This was expected since if a shunt is properly working \( C_{\text{out}} \) of the shunt should be considerably larger than \( C_{\text{out}} \) of the CSF outflow pathways.\(^{3,36}\) In Paper V \( C_{\text{out cp}} \) approached the expected \textit{in vitro} \( C_{\text{out}} \) of the shunts more than the other methods. This along with the advantage that the constant pressure infusion method generates a pressure/flow curve that in greater detail describes the characteristics of the system,\(^{24}\) supports the use of this method for \textit{in vivo} testing of shunt function.

Although the number of patients for which all four methods were successfully performed were only seven, and the inclusion of more patients are needed, the results of Paper V indicated that in the area of clinical importance (i.e. low \( C_{\text{out}} \), \( C_{\text{out}} \) as determined by the bolus infusion method does differ from \( C_{\text{out}} \) as determined by the steady state methods.

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**Table 2: Comparison between \( C_{\text{out}} \) in the preoperative patient group (Paper V).**

<table>
<thead>
<tr>
<th>( C_{\text{out cp}} ) ( [\mu\text{L/(s kPa)}] ) (n=7)</th>
<th>( C_{\text{out dyn}} ) ( [\mu\text{L/(s kPa)}] ) (n=7)</th>
<th>( C_{\text{out stat}} ) ( [\mu\text{L/(s kPa)}] ) (n=7)</th>
<th>( C_{\text{out bol}} ) ( [\mu\text{L/(s kPa)}] ) (n=7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.6 ± 1.6</td>
<td>8.5 ± 2.0</td>
<td>9.2 ± 1.4</td>
<td>12.3 ± 2.3</td>
</tr>
</tbody>
</table>
11 Impact of this thesis on cerebrospinal fluid infusion methods

The physiology of the CSF system and pathophysiology behind NPH are not fully understood, and means for discovering more details to correctly draw the larger picture are always sought for. One such mean is the infusion test. Manipulation of the CSF system by adding or withdrawing fluid gives us the possibility to estimate some of the dynamic parameters which determine the system. The information can be used as a predictive tool in the investigation of patients with suspected NPH, to determine whether as to perform shunt surgery or not.

In many Neurosurgical centra infusion tests are performed by putting together an infusion pump, one or two pressure transducers and a printer or a personal computer in a simple fashion. This is a problem since the equipment is likely to differ between every hospital, and the method of infusion and analysis are also likely to differ. Thus, the patient safety is in jeopardy due to lack of hazard analysis, and it becomes difficult to compare results from different studies. As a consequence, it is hard to determine the predictivity of the test.

Prior to the work of this thesis, a new infusion apparatus with standardised and automated infusion protocols, based on an extensive hazard analysis, was developed and clinically introduced. The work was performed as collaboration between the department of Biomedical Engineering and Informatics and the department of Clinical Neuroscience at Umeå University Hospital. In Paper II, the precision of the infusion apparatus was evaluated. This was an important step when introducing the new measurement device in medical care and before performing further studies. If the precision was not good enough there would have been an error in the estimated parameter simply due to the construction of the device, which would have affected the outcome of future clinical investigations as well as future research. In Paper II the precision of the infusion apparatus was found to be good, implying that it constituted a good basis for the following studies of this thesis.

In Paper II the parameter $\Delta C_{\text{out}}$ was also introduced and defined as the 95 % CI of the estimated $C_{\text{out}}$. Up until now, none of the infusion methods in clinical use give the user a numerical feedback concerning the reliability of the estimated parameter $C_{\text{out}}$ (or $R_{\text{out}}$). $\Delta C_{\text{out}}$ was shown to represent the reliability of each individual investigation. The reason why we felt that $\Delta C_{\text{out}}$ was a truly
important parameter to estimate, was that $C_{\text{out}}$ is used daily at many neurosurgical centres for prediction of shunt responsiveness. However, extreme pressure fluctuations related to for example coughing or body movement, as well as naturally vasogenic variations, will indirectly affect the $C_{\text{out}}$ estimate of an investigation. As a consequence, if $C_{\text{out}}$ is determined without any numerical feedback to the user, concerning the reliability of the results, it might be used for diagnostic purposes and for selecting patients for shunt surgery, although $C_{\text{out}}$ was determined in an unsatisfying manner. For research purposes information of the uncertainty of the measurement is also vital, and knowledge of this parameter could possibly have explained the variation in previous studies regarding the predictive power of $C_{\text{out}}$.

Thus, from Paper II it was clear that $\Delta C_{\text{out}}$ was a parameter that could, and should, be incorporated in all future infusion tests conducted with constant pressure levels to help the physician when deciding whether to shunt a patient or not.

Apart from constant pressure infusion, mainly presented and discussed in this thesis, constant flow infusion and bolus infusion were also discussed and applied (Paper V), since these are the two most commonly used infusion tests worldwide. For these two methods no estimation of the reliability of each individual investigation is available, and this is a major drawback. In Paper V it was found that there was no significant difference between the constant pressure and constant flow infusion methods, thus implying that either method could be used for estimating $C_{\text{out}}$, but for the continued usage of constant flow infusion the method should be complemented with a parameter stating the reliability of each investigation.

The parameter $\Delta C_{\text{out}}$ presented in Paper II was used to validate the adaptive algorithm developed in Paper III. The purpose of the algorithm was to reduce the investigation time for the constant pressure infusion test, without substantially affecting the result. Using this analysis algorithm, for the first time an adaptive and automated infusion test considering the individual pressure and flow variations of each patient can be performed. In the future it is possible that a modified version of this algorithm could be applied also to the method of constant flow infusion. Here most of the measurement uncertainty is found within the estimation of the pressure, and thus the analysis algorithm should focus on this area instead of on the infusion flow. Commonly the constant flow infusion method involves only one CSF infusion rate, as compared with six different pressure levels, but the algorithm has the potential to be useful in such
a way as to secure termination of the infusion when sufficient accuracy of the pressure measurement at the plateau level has been achieved.

In a future extended version of the adaptive analysis algorithm from Paper III the parameter $C_{\text{out}}$ together with $\Delta C_{\text{out}}$, presented in Paper II, could also be incorporated. Since $C_{\text{out}}$ and $\Delta C_{\text{out}}$ are determined in real time using constant pressure infusion, an estimation of the parameters will be at hand from the second and third pressure levels on, respectively. Thus, if $C_{\text{out}}$ is clearly pathological or clearly non-pathological, a higher $\Delta C_{\text{out}}$ could be accepted, while a $C_{\text{out}}$ within the indecisive region could justify longer measurement times with additional pressure levels to further reduce $\Delta C_{\text{out}}$. The same could be said for the method of constant flow infusion, where a real time estimation of $C_{\text{out}}$ could be guidance to how well mean ICP on the plateau pressure level needs to be determined.

It might be viewed as a contradiction that the relatively moderate expected increase in ICP shown in Paper I was considered dangerous, while the pressure elevations during the infusion tests in Papers II-V were much larger and fully accepted. This was because the patient groups were entirely different. In Paper I neurosurgical intensive care patients were considered, and in this situation the patient is in a more vulnerable state where the compensatory mechanisms may not be functioning to their full extent. In the patient groups considered in Papers II-V, the symptoms had developed over a long time, and there was no risk of creating pressure gradients. In the latter situation the brain is capable of handling a much larger pressure increase than in the first.

In Papers I and IV different properties of the most commonly used CSF dynamical model was investigated. In Paper I it was concluded, in a general sense, that the model behaved as expected under the prevailing conditions, i.e. the initial increase in ICP was faster due to lower compliance when resting pressure was higher, the increase in ICP was larger when the volume increase in the system was larger, either due to a larger initial volume or to a faster cabin altitude rate of change and ICP reached a steady, unceasing increment at higher ICP. The understanding of the CSF model and its behaviour is important when working with modifications of CSF infusion methods based on the model. Thus, from the point of view of CSF infusion methods Paper I constituted a basis for the continued work with the model of the CSF system used in this thesis. Also, an understanding of the model is vital for the research regarding the INPH syndrome, since the CSF shunt is explicitly changing the dynamics of the system leading to improvement of the patient.
Another property of the CSF model, the pressure dependency of $R_{out}$, also expressed as the relationship between CSF outflow and ICP, was investigated in Paper IV. In the model used to estimate $C_{out}$, the relationship between the parameters is assumed to be linear. The non-linearity found at high pressure elevations implied that $C_{out}$ as estimated by the linear model will be falsely high when pressure levels above 1.6 kPa are included in the analysis, regardless of the infusion method used to get there.

To reduce this error using the constant pressure infusion method, the increase between pressure levels could be reduced. It should be stressed though that the uncertainty in the linear regression line determining $C_{out}$ will decrease the lower the pressure range is. The constant flow infusion method will also be affected if the pressure increase from resting pressure is larger than 1.6 kPa. Here the appropriate infusion rate is more difficult to determine though, since commonly only one infusion rate is used and $C_{out}$ is an unknown parameter beforehand.

An increase in $C_{out}$ was also seen in Paper II, between repeated patient investigations. Thus, it is possible that the infusion procedure in itself affected the CSF system in such a way as to increase $C_{out}$. By reducing the maximum pressure increase it is also likely that the effect imposed by the infusion method on the CSF system would be reduced. This would be preferable, but the effect on the reliability parameter must not be forgotten.

In Paper V the bolus infusion method was evaluated against the constant pressure and constant flow infusion methods. All three infusion methods are based on the same mathematical model, and thus should yield the same parameter estimations. Since the bolus infusion method failed to render satisfying results in the most clinically relevant region, and an explanation as to this could be found, the results from this thesis implicate that a reconstruction of the bolus method is needed if it is to be continuously used. The infusion volume should be increased as to yield a larger impact on the system as compared with the physiological pressure fluctuations, and the analysis should be computerised as to avoid errors due to subjectivity. Also, a parameter reflecting the reliability of each individual investigation should be designed.

Thus, the results from this thesis recommend the use of a standardised infusion method with validated repeatability for performing infusion tests. Preferably the method of constant pressure infusion should be used, since $\Delta C_{out}$ is a mathematically well defined and easily interpreted parameter producing a numerical value available to the physician when using the test clinically or within research. The method should be further developed in such a way as to
reduce the maximum pressure increase, as to avoid the ICP area where the relationship between CSF outflow and ICP is non-linear. The method should also include the adaptive analysis developed in Paper III, as to minimize necessary investigation time. When the method of constant pressure infusion cannot be used, it is recommended that constant flow infusion is used as an alternative. The method should be complemented with an easily interpreted numerical value of individual reliability, as well as an adaptive analysis for individual time estimation.

12 Future studies

The work presented in this thesis has lead to ideas for future studies within the area. Patients with INPH are treated by shunt surgery, and postoperatively infusion tests can be used to check that the shunt is working properly. Today, most CSF shunts are adjustable, in the sense that their opening pressure can be adjusted postoperatively by a magnetic device. There are no criteria as to how these shunts should be adjusted for each individual patient, but the postoperative infusion test offers a possibility of developing such criteria, and this is an area that should be further investigated. Moreover, main focus within research and clinical applications so far has been on the static parameter $C_{\text{out}}$. In addition, interest for the dynamic compliance parameter has recently increased, and a study should be designed for developing and validating a satisfying method to estimate this parameter in a correct manner.

In this thesis traditional infusion patterns were utilized, and clinically available infusion methods were further investigated and improved. The next step in refining the infusion methods even more could be by adjusting the infusion patterns to individual patients, and using more advanced system identification methods to estimate the CSF dynamical parameters. Another research track that should be further investigated is phase contrast magnetic resonance imaging. This technique has the potential to estimate flow and volume of the CSF system in a non-invasive fashion, which could be a valuable complement to the infusion test.

The INPH population is elderly, and since the infusion test is invasive, there are few studies conducted on healthy age-matched populations which can be used as normal references. There is also a lack of infusion studies performed on patient groups with similar diseases, such as vascular dementia or Alzheimer’s disease. The new infusion method developed and validated in this thesis, based on a thorough hazard analysis and standardised protocols, will constitute the basis for
new studies investigating healthy elderly, as well as different well defined related patient groups. It is possible that the CSF dynamical profile of INPH patients will be different from those of the other patient groups between which differential diagnosis are difficult, and in that case infusion tests would be important as a standard investigation in dementia patients.