The effect of hyperventilation upon cerebral blood flow and metabolism in patients with fulminant hepatic failure

Gitte Irene Strauss

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Department of Hepatology, Rigshospitalet, University of Copenhagen, Denmark.

Correspondence: Gitte Irene Strauss, Department of Hepatology A 2212, Rigshospitalet, University of Copenhagen, Blegdamsvej 9, 2120 Copenhagen, Denmark.

E-mail: gstrauss@daldnet.dk

Official opponents: Henrik Vildstrup and Martin Lauritsen.

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1.0 INTRODUCTION AND AIM

"Over the oxygen supply of the body, carbon dioxide spreads its protecting wings - especially as it cares for the brain which, for unknown reasons, may not lack air in warm blooded animals whereas skin and muscle may tolerate ischemia of a tourniquet for more than half an hour." These poetic words of the virtues of carbon dioxide (CO₂) were extolled by Miescher-Rüsch [1] in 1855. Four years before Donders [2] had described the reactions of blood vessels to changes in respiratory activity. However, almost a century had to pass before the exquisite sensitivity of intracranial blood vessels to changes in arterial carbon dioxide tension (PaCO₂) was finally demonstrated [3], and the first quantitative measurements of cerebral blood flow (CBF) in relationship to changes in PaCO₂ were performed [4].

Fulminant hepatic failure (FHF) is a devastating condition elicted by an acute liver injury with the development of hepatic encephalopathy. The most feared complication in patients with FHF is the development of cerebral edema and intracranial hypertension is still not completely understood. The glutamine hypothesis, which was suggested in 1986 by Brusilow and Traystman [6], advocates that a shift of water into the astrocytes is a result of intracellular glutamine accumulation; osmotic changes that result in brain edema [7-9]. Also changes in CBF are assumed to be of importance for the development of cerebral edema in FHF, as CBF correlates to brain water content and subsequently intracranial pressure in experimental models [10-12].

Spontaneous hyperventilation is often observed in liver failure. Stanley et al [13], suggested that the ventilatory stimulation that arises in liver failure might be caused by stimulation of peripheral chemoreceptors. Also lactate acidosis, renal impairment, hepatic encephalopathy and a high sympathetic tone are common complications in FHF, which all stimulate hyperventilation.

Hyperventilation lowers PaCO₂ (hypocapnia) and produces vasoconstriction and lowering of CBF (1). Patients with FHF with overt stages of hepatic encephalopathy are in some liver failure centres intubated and mechanical normoventilated, as hyperventilation is assumed to induce brain hypoxia [14]. It remains, however, unknown if hyperventilation in the early stage of FHF, well before brain edema has evolved, is beneficial or harmful to these patients.

Before a detailed presentation of the main findings in this study it may be helpful to review how PaCO₂ modulates CBF in healthy subjects.

1.1 CARBON DIOXIDE AND MECHANISM OF ACTION

In the normal brain, the constancy of CBF and cerebral blood volume relies upon the intrinsic ability of the cerebral resistance vessels to alter their diameter in response to variations in blood pressure (CBF autoregulation) and changes in metabolic demands. One of the major products of cerebral metabolism, CO₂, can alter cerebrovascular resistance and ultimately affect CBF [15]. CO₂ is freely diffusible between arterial blood and brain tissue. Thus it can diffuse into the vascular smooth muscle cell from either brain tissue or the vessel lumen, while hydrogen ions in the vessel lumen are prevented from reaching the smooth muscle cell by the blood-brain barrier [16]. Even though the chemical reaction between CO₂ and tissue water is simple:

\[
\text{CO}_2 + \text{H}_2\text{O} \leftrightarrow \text{H}_2\text{CO}_3 \leftrightarrow \text{HCO}_3^- + \text{H}^+
\]

the physiologic mechanisms that underlie the responses of the cerebral vessels to changes in CO₂ have not been simple to ascertain. The main mechanism of this effect upon cerebral vessels appears to be perivascular pH [17, 18], but there may be additional, yet unknown, mechanisms. There is also evidence to support that factors such as prostanooids [19-21] and nitric oxide [22] are involved in the response, whereas the influence of peripheral/central [23] nerves is conflicting, at least during hypercapnia. The influence of these factors on the cerebral carbon dioxide reactivity has mostly been explored during hypercapnia, while only few studies have addressed their influences in hypocapnic responses.

1.1.1 Extracellular fluid [H⁺]

In 1961, Gotoh et al suggested that the action of CO₂ was mediated by direct effect of [H⁺] on cerebrovascular smooth muscles [24]. Indeed, the majority of experimental studies support the concept that CO₂ regulates the cerebral circulation primarily by changes in pH in the extracellular fluid surrounding the vessels [17, 18, 25-28]. Kon- tos et al, found that marked changes in PaCO₂ did not affect cerebral vessel diameter unless a change in extracellular fluid pH occurred [17, 18]. However, it is not certain whether the effects on cerebral vessels are due solely to changes in extracellular fluid pH, or whether and to what extent changes in intracellular pH also contribute [29]. There is experimental evidence to show that the extracellular pH influences the vasodilatory response to a greater extent than the intracellular pH, as Toda et al [30], found that hypercapnic vasodilation in dog cerebral artery strips was reversed by infusion of sodium-bicarbonate, i.e., pH was raised while Pco₂ remained stable. In other experimental studies, blockade of adenosine triphosphate (ATP)-sensitive potassium channels completely inhibits the hypercapnia induced vasodilation [31, 32] as well as the hypocapnia-induced vasoconstriction [33]. These findings suggest that opening and closure of these channels are of importance for the vascular responses to alterations in PaCO₂. Recently, Nakahata et al [34], showed that blockade of ATp-sensitive potassium channels with glibenclamide completely abolished hypercapnia-induced vasodilation only when pH was decreased. Thus, CO₂-induced alteration in pH appears to affect ATP-sensitive potassium channels either by opening (hypercapnia-induced acidosis) or closure (hypocapnia-induced alkalosis) of the potassium channels.

1.1.2 Prostaglandins

Prostaglandins appear to be mediators of the cerebral CO₂ response to hypercapnia [19]. Several studies have shown that hypercapnia elicits vasodilation that is accompanied by increased prostanooid synthesis, and that this vasodilation is inhibited by indomethacin, a cyclo-oxygenase inhibitor [19, 35, 36]. By contrast, other studies in...
other species did not find an effect of indomethacin on CBF [37, 38]. Also, indomethacin had no effect on dilator or constrictor pros-
tanoids concentration in cerebrospinal fluid of newborn pigs in re-
sponse to hypocapnia [39]. Nor did indomethacin affect pial arteri-
olar constriction in response to hypocapnia, or vasodilation when PaCO2 was raised from hypocapnia to normocapnia [39].

1.1.3 Nitric oxide
Nitric oxide plays an important role in the tonic regulation of cere-
brovascular tone and contributes to the changes in CBF produced by
hypocapnia [40-42]. It has been suggested that the extracellular ac-
dosis associated with hypocapnia might activate nitric oxide syn-
thesase and increase nitric oxide production [22]. However, other
studies suggest that nitric oxide is not solely responsible for the hy-
percapnia-induced vasodilatation [41, 42]. It is assumed that the va-
sodilator response to nitric oxide in the cerebral circulation is sec-
ondary to stimulation of guanylyl cyclase [40] and involves acti-
vation of potassium channels [43].

1.1.4 Neural pathways
Definitive evidence to support the participation of either central
and/or peripheral neural reflex pathways in mediating effects of CO2
on the cerebral vessels are lacking [44]. However, in newborn pig-
lets, Moore et al [45] showed that the hypocapnic vasodistraction was attenuated after alpha blockade in the forebrain and brainstem
and after cord transection, whereas the hypcapnic reactivity was unaltered by these procedures.

1.2 AIMS
The aims of the present clinical studies were to evaluate CBF and ox-
idative and amino acid metabolism in patients with FHF with special
focus on the effect of short-term mechanical hyperventilation upon
these measures. Also the influence of hyperventilation upon arterial content and cerebral fluxes of certain biomarkers and neu-
ropeptides is investigated and discussed.

2.0 PATIENTS AND METHODS
2.1 PATIENTS
From February 1996 until June 2000, patients with FHF referred to
the department of Hepatology, Rigshospitalet, were enrolled con-
secutively. All patients were investigated within 24 hrs after the first
appearance of stage III-IV hepatic encephalopathy, and after intuba-
tion and mechanical ventilation had been instituted. All patients
had arterial lines, central venous catheters and a catheter placed
retrogradely in the internal jugular bulb. They all received N-acetyl-
cysteine and 20% glucose intravenously, and were all sedated with
propyleneamine oxide (99mTc-HMPAO) were used. In the clinical
setting of FHF where mechanical hyperventilation is necessary, these
methods are, however, too time-consuming. Accordingly, Transcran-
dial Doppler technique (TCD) and the arterio-venous oxygen differ-
cence (AVDO2) technique were evaluated as bedside methods to mon-
tor CBF responses to hyperventilation in patients with FHF (III).

2.2 METHODS TO EVALUATE CBF
AND CEREBRAL CO2 REACTIVITY
The aims of the present clinical studies were to determine the effect
of hyperventilation upon global and regional CBF as well as the cere-
bral metabolism of different substances. For this purpose tracer-kin-
etic methods were used. These methods are based upon the cerebral
uptake and wash-out of a freely diffusible inert tracer administered
either intravenously or by inhalation. Two different tracer kinetic
methods were applied, i.e., the Kety-Schmidt technique and Single
Photon Emission Computed Tomography (SPECT) (II-VII). As
tracer substances, 133Xenon and Technetium-99m Hexamethyl
propyleneamine oxide (99mTc-H-MP-AO) were used. In the clinical
setting of FHF where mechanical hyperventilation is necessary, these
methods are, however, too time-consuming. Accordingly, Transcran-
dial Doppler technique (TCD) and the arterio-venous oxygen differ-
cence (AVDO2) technique were evaluated as bedside methods to mon-
tor CBF responses to hyperventilation in patients with FHF (III).

2.2.1 The Kety-Schmidt technique
The Kety-Schmidt technique is based on Fick's principle and is con-
considered to be the "Gold Standard" for measurement of global CBF in
man [46]. In our clinical studies (II-VII), we applied the modified
Kety-Schmidt technique, i.e., the desaturation mode. In this setting
the brain is saturated by infusion of 133Xenon at a constant rate for
30 minutes, and followed by a desaturation period of 10 minutes,
where blood samples are obtained pairwise from the radial artery
and internal jugular vein [47]. The Kety-Schmidt technique is
widely acknowledged as an accurate technique for determination of
global CBF. However, one critical assumption of the Kety-Schmidt
technique is that the average 133Xenon tension of the brain is the same
as the 133Xenon tension of the cerebral venous blood. In the experimen-
tal setting with a wash-out period of 10 minutes this as-
sumption is not usually met, due to heterogeneously perfused cere-
bral tissues, leading to under representation of low flow areas such as
cerebral white matter and hence, a systematic overestimation of
global CBF [47, 48]. By computer simulation Madsen et al [47],
demonstrated that the modified Kety-Schmidt technique overesti-
mates global CBF by 10 to 15% in healthy subjects, and proposed a
simple conversion algorithm of measured CBF to "ideal" CBF. How-
however, since the experiments by Madsen et al [47] were performed on
healthy subjects, the assumptions by which the correction procedure
is based may be invalid when applied to patients with FHF. Accord-
ingly, this correction algorithm was not applied in the present clin-
ical studies.

2.2.2 Single Photon Emission Computed Tomography
SPECT was applied to evaluate the regional CBF distribution pat-
tern (II) as well as the global and regional cerebral CO2 reactivity
to hypocapnia in patients with FHF (III). Quantitative measurements
of CBF during normoventilation and hyperventilation were ob-
tained with 133Xenon as the tracer substance. The use of freely dif-
fusible tracers for the tomographic CBF calculation method is more
complex, but founded on the same physical assumptions as origi-
nally proposed and described by Kety and Smith [46]. 1) simultan-
eous arrival of the tracer to all parts of the brain following adminis-
tration, 2) instantaneous equilibrium between brain and blood, and
3) cerebral blood flow remains constant during the period of mea-
surement. CBF values derived from SPECT studies are prone to inac-
curacies due to problems with attenuation correction, Compton
scattered radiation, the partial volume effect, and estimation of the
arterial input function from the lung curve input function [49, 50].
Apart from the methodological problems, the most critical
comparison between the Kety-Schmidt technique and SPECT, is that
SPECT studies derive their CBF-values from one representative

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Table 1. Comparison of $^{133}$Xe SPECT and the Kety-Schmidt technique in patients with FHF.

<table>
<thead>
<tr>
<th>Condition</th>
<th>SPECT</th>
<th>Kety-Schmidt</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rest</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CBF (mL/100g/min)</td>
<td>43:9</td>
<td>41:4</td>
</tr>
<tr>
<td>PaCO$_2$ (kPa)</td>
<td>4.9±0.7</td>
<td>5.0±0.3</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>76:13</td>
<td>80:12</td>
</tr>
<tr>
<td><strong>Hyperventilation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CBF (mL/100g/min)</td>
<td>36:7</td>
<td>34:5</td>
</tr>
<tr>
<td>PaCO$_2$ (kPa)</td>
<td>3.8±0.4</td>
<td>3.9±0.3</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>74:14</td>
<td>73:12</td>
</tr>
<tr>
<td>CO$_2$ reactivity</td>
<td>1.9±0.7</td>
<td>2.0±0.9</td>
</tr>
</tbody>
</table>

CBF: cerebral blood flow; PaCO$_2$: arterial carbon dioxide tension; MAP: mean arterial blood pressure; CO$_2$ reactivity: cerebral carbon dioxide reactivity.

whole brain slice, while CBF obtained by the Kety-Schmidt technique is from the entire brain volume. To assure that no major systematic error was applied in our studies (III-VII), we determined global CBF by both techniques in six patients with FHF, and found similar CBF values for the Kety-Schmidt technique and SPECT, i.e., 41±4 vs. 43±9 mL/(100g×min) (NS) during normoventilation, and 34±5 vs. 36±7 mL/(100g×min) (NS) during hyperventilation (unpublished data) (Table 1).

Since $^{133}$Xenon only allows for evaluation of regional CBF with low-image resolution, $^{99m}$Tc-HMPAO was used as tracer to obtain high-resolution SPECT images of regional CBF distribution pattern during hyperventilation (II). This tracer only yields relative CBF values. After intravenous administration of $^{99m}$Tc-HMPAO approximately 70-80% of the primary complex reaches the brain across the blood brain barrier [51]. Inside the brain it is rapidly converted to its non-diffusible hydrophilic complex and retained for many hours [52]. Similar to the Kety-Schmidt technique, SPECT has a low time resolution and requires transportation of the patient to the tomograph. The advantage is that it allows for regional CBF determinations.

### 2.2.3 Transcranial Doppler Sonography

The TCD method determines the mean flow velocity ($V_{mean}$) of flow in blood vessels. Measurements of $V_{mean}$ were obtained from the middle cerebral artery through the temporal window with a 2 mHz probe and an insonation depth of 45-55 mm. The middle cerebral artery is the most extensively evaluated intracerebral vessel studied by TCD. The average $V_{mean}$ in healthy adult subjects derived from previous studies is 62 (33-90) cm/s [53, 54], but may be affected by a variety of factors such as hematocrit, PaO$_2$ and PaCO$_2$ in the same manner and direction as these factors affect CBF. The TCD technique has previously been evaluated as a reliable tool to evaluate relative changes in CBF in autoregulation studies where mean arterial pressure is raised by infusion of norepinephrine both in healthy man and in patients with FHF [55, 56]. Relative changes in $V_{mean}$ however only reflect actual changes in CBF when the diameter of the insonated vessel and the perfusion territories remain unchanged during the study. In patients with FHF, it was found that the TCD technique correctly reflects changes in CBF during hyperventilation, but the numerical value of the CO$_2$ reactivity was slightly underestimated as compared to CO$_2$ reactivity obtained by the Kety-Schmidt technique and SPECT (Figure 1) (III). This slight discrepancy is probably caused by a decrease in the diameter of the middle cerebral artery produced during hyperventilation in patients with FHF, since the CBF/$V_{mean}$ ratio decreased slightly from rest to hyperventilation, i.e., from 0.014 (range, 0.011 to 0.020) to 0.012 (range, 0.009 to 0.021) cm$^3$/g (p=0.047) (III). Although, the TCD method only provides relative CBF values, it has several advantages over both the Kety-Schmidt technique and SPECT: it is non-invasive, relatively inexpensive, less time consuming and has a high time resolution. Moreover, the technique can be applied bedside and provides on-line information on cerebral circulation, and alterations in this.

### 2.2.4 Arterio-venous oxygen difference method

This method is based on Fick's principle. As long as the cerebral metabolic rate of oxygen is constant, then changes in AVDO$_2$ will reflect variations in CBF, i.e., AVDO$_2$ varies inversely with CBF. However, it must be emphasised that this relationship only holds true as long as the normal relationship between CBF and metabolism is maintained [57]. The AVDO$_2$ method has most of the same advantages as the TCD technique, but requires placement of an internal jugular bulb catheter and an arterial line. The disadvantage is that blood samples are obtained from one internal jugular vein only, thus the possibility exists of overlooking severe ischemia in brain tissue drained by the opposite internal jugular vein, and although the catheter is correctly placed in the internal jugular bulb there will be an extracranial contamination of 2% to 3% [48]. In patients with FHF, we found that the AVDO$_2$ method yielded the same global CO$_2$ reactivity in response to hyperventilation as those obtained by the Kety-Schmidt technique (Figure 1) (III). Thus, the AVDO$_2$ method is a reliable and easy way to evaluate the effect of mechanical hyperventilation upon CBF in the clinical setting of FHF, as long as the normal relationship between CBF and metabolism is maintained.

### 3.0 Main findings and discussion

#### 3.1 CBF in FHF

Wide variations in CBF have been reported in patients with FHF (Table 2). In the present work (III-VII), a reduced CBF was found in patients with FHF using both TCD technique (I) as well as tracer methods to measure absolute CBF (III-VII). This finding is in accordance with a number of previous studies [12, 14, 58-61]. Only, Ede et al [62] and Jalan et al [63-65] have reported significantly higher CBF values than that reported in other previous studies (Table 1). In the study by Ede et al [62] they report a normal value of 120 mL/(100g×min) using their technique. This is a much higher global CBF value than reported previously in healthy subjects [66], i.e., ~50 mL/(100g×min). The studies by Jalan et al [63-65] were, contrary to other previously published studies, performed during ongoing intracranial hypertension. In one of the clinical papers by Jalan et al [65], two groups of patients were included, one with intracranial hypertension and another without intracranial hypertension, demonstrating that only the group of patients with

Figure 1. Cerebral CO$_2$ reactivity obtained by the Kety-Schmidt technique (KS), transcranial Doppler sonography (TCD), arterio-venous oxygen difference (AVDO$_2$) and internal jugular bulb saturation (svO$_2$) in patients with FHF. The TCD technique slightly underestimated the CO$_2$ reactivity compared to the other methods (ANOVA, p=0.047) (III). Reprinted with permission from publisher. (Straus et al, Liver Transpl 2001).
intracranial hypertension had increased CBF, i.e., 85 (23–134) mL/(100g × min), whereas the patients without intracranial hyper-
tension had a reduced CBF, i.e., 45 (23–56) mL/(100g × min), cor-
responding to other studies of patients with FHF without intracran-
ial hypertension (Table 2). Thus, there seems to be evidence to sup-
port that CBF is low unless intracranial hypertension has evolved in
patients with FHF. Whether this increase in CBF develops gradually
or immediately before surges of intracranial hypertension in the
clinical setting is not possible to unravel from the present studies in
this thesis (I-VII) but studies of rats have shown that CBF gradually
increases during the course of FHF [67].

The pathophysiological reason for the decreased CBF found in
this thesis may rely on a number of different mechanisms:

3.1.1 Hepatic encephalopathy and sedation

Increased neural activity increases the energy expenditure for ion-
pumping and transmitter synthesis, resulting in increased energy
decrease. At high levels ammonia is neurotoxic, and leads to functional
disturbances of the central nervous system [74], but it is conflicting
whether ammonia per se affects CBF. Some studies have demon-
strated that acute ammonia infusion dilate cerebral vessels and in-
creases CBF [10], while others found that CBF decrease [75]. In
the present thesis, there was no relationship between CBF and arterial
ammonia levels in patients with FHF (Figure 2) (IV). Contrary, Ja-
lan et al [65] found a positive correlation between CBF and arterial
ammonia. This discrepancy may be due to time differences, as the
patients in this thesis were investigated well before the development
of cerebral edema and intracranial hypertension, while the patients
in the study by Jalan et al [65] were investigated later during the
cerebral illness of FHF.

Since the brain lacks urea cycle enzymes, ammonia removal from
the brain relies on the formation of different amino acids, mostly
glutamine and alanine, which are the main nitrogen carriers out of
the brain (IV). A recent study shows that accumulation of glutamine
per se only plays a limited role as a cause of cerebral edema in
FHF, as mild hypothermia prevented cerebral edema in an animal
model of FHF despite glutamine accumulation [76]. However, these
findings do not preclude other important contributions of glutamine
to the cerebral complications in FHF as hypothermia may have
everal other effects on the brain that may have contributed to
the protective effect. In accordance with the experimental study by
Mastor et al [77] we found that patients who subsequently died of
intracranial hypertension had significantly higher cerebral ammo-
nia uptake and cerebral glutamine efflux as compared to patients
who survived (IV), suggesting that ammonia and glutamine plays
an important role for the subsequent surges of intracranial hyper-

![Figure 2](image-url)
tension. Whether or not this effect is cytotoxic, or is a combination of a cytotoxic and vasogenic effect is not possible to settle from the present study (IV).

Although the exact mechanism of ammonia toxicity is unresolved, hyperammonemia and cerebral glutamate accumulation appears to have several other effects on brain and cerebral metabolism that may contribute to or exaggerate cerebral edema formation and induce cerebral vasodilatation, including effects on cerebral energy metabolism [78], lactate/pyruvate production [79], astrocytic glutamate transport [80], brain ATP depletion by activation of NMDA receptors [81], nitrosative/oxidative stress and induction of the mitochondrial permeability transition in cultured astrocytes [82]. The present clinical studies do not allow for any conclusions on the cellular effects of hyperammonemia and cerebral glutamate accumulation, nor do they allow for conclusion on their effects upon CBF later during the disease course of FHF. However, in the early stages of FHF hyperammonemia and glutamine accumulation did not affect CBF and cerebral oxidative metabolism (VII).

3.1.3 Acetaminophen and CBF
Recent studies have revealed evidence that acetaminophen inhibits prostaglandin E2 production in rat cerebral endothelial cells possibly by acting against cyclooxygenase-2 [83]. Accordingly, inhibition of prostaglandin E2 production could also to some extent have influenced CBF in patients with FHF, as prostaglandin E2 is a vasodilator and acetaminophen intoxication was the reason for FHF in most of the patients (I-VII). Notwithstanding, CBF in patients without acetaminophen intoxication was similar to patients with acetaminophen intoxication, i.e., 38 (28-55) vs. 40 (28-54) mL/(100 g min) (NS). Patients with acetaminophen intoxication attempted to have a better outcome in larger series of FHF, and it is possible that this inhibitory effect upon cyclooxygenase-2 may play a role in this setting by inhibiting the gradual increase in CBF that seemed to evolve during the disease course.

In conclusion CBF is reduced within the first 24 h after development of stage III-IV hepatic encephalopathy. Increase in CBF seems to be a phenomenon that takes place later during the disease course, and only evolve in patients who subsequently develop intracranial hypertension. The low CBF values found in the studied patients in this study can be explained by the presence of hepatic encephalopathy and sedation by midazolam.

3.2.1 Global cerebral CO2 reactivity
Cerebral CO2 reactivity is the change in CBF per unit change in PaCO2, defined as the % change in CBF divided by the ΔPaCO2 (in mmHg). First at the relationship between PaCO2 and CBF was thought to be linear, however, later studies have shown that it is sigmoid, with a CO2 reactivity that increases at high PaCO2 levels and decreases at low PaCO2 levels.

3.2.2 Central cerebral CO2 reactivity
In this thesis global CO2 reactivity was found normal in patients with FHF compared to controls. All clinical studies of cerebral CO2 reactivity to hypocapnia performed on patients with FHF are displayed in Table 3 (III) [12, 14, 58, 84, 85]. All these studies reported almost similar cerebral CO2 reactivity, except for one study where the hypocapnic CO2 reactivity appeared much higher [85]. One explanation for this apparent discrepancy could be that by Sari et al [85], contained pooled data of patients with hepatic encephalopathy and septic encephalopathy. Thus, that study was not completely comparable with the other studies, which only contained patients with FHF. As can be seen from Table 3, values of CO2 reactivity varied widely among patients with FHF. In two of the studies [12, 58], a paradox increase in CBF to hypocapnia, i.e., a negative CO2 reactivity, was found in one patient (Table 3). Neither mean arterial blood pressure nor intracranial pressure was measured in these studies. Alteration of these pressures during the study period may have accounted for the apparent increase in CBF to hypocapnia. That is, if intracranial pressure was high before institution of hyperventilation, and subsequently was reduced during hypocapnia, then the resultant cerebral perfusion pressure is increased, and thereby also CBF. Likewise, if mean arterial pressure drops significantly during hyperventilation, then the resultant cerebral perfusion pressure is reduced and thereby CBF. Methodological problems should also be considered as well as time difference, as it cannot be excluded that cerebral CO2 reactivity is completely lost later during the course of FHF [84].

The cerebral CO2 reactivity is influenced both by the oxygen status and by the mean arterial blood pressure, as both hypoxia and hypotension induce vasodilatation [86]. Thus, vasodilation induced by either hypoxia or hypotension may blunt the cerebral CO2 reactivity during hypercapnia. In 1996, Larsen et al [84] explored the cerebral CO2 reactivity in a prospective study including both patients with FHH and rats with thioacetamide-induced liver failure. It was found that patients with FHH had a reduced cerebral CO2 reactivity during hypercapnia as compared to healthy subjects, -2.2 vs. -4.6% mmHg\(^{-1}\), while it was normal during hypocapnia (Table 3) [84]. This finding was in accordance with a retrospective study of patients with FHH published by Durham et al a year before [58]. Accordingly, Larsen et al suggested that the cerebral CO2 reactivity curve is left-shifted in FHH, i.e., CO2 reactivity decreases during hypercapnia, while it is relatively preserved during hypocapnia (Figure 3) [84].

Animal studies have reported that cerebrovascular reactivity to hypercapnia is blunted following acute elevation of blood ammonia levels [87-89]. Thus, it could speculated that the increased blood

### Table 3. Previous published studies on cerebral CO2 reactivity to hypocapnia in healthy subjects and patients with FHF.

<table>
<thead>
<tr>
<th>Hyperventilation</th>
<th>Normalventilation</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Healthy Subj</td>
<td></td>
</tr>
<tr>
<td>Larsen (1990) [84]</td>
<td>39 (24-44)</td>
</tr>
<tr>
<td>Moller (2002) [102]</td>
<td>42 (37-43)</td>
</tr>
<tr>
<td>FHF</td>
<td></td>
</tr>
<tr>
<td>Sari (1990) [85]</td>
<td>52 ± 43 (5)</td>
</tr>
<tr>
<td>Aggarwal (1994) [12]</td>
<td>47 (23-78)</td>
</tr>
<tr>
<td>Larsen (1996) [84]</td>
<td>61 (28-116)</td>
</tr>
<tr>
<td>Strauss (2001) [III]</td>
<td>43 (31-53)</td>
</tr>
</tbody>
</table>

Note: a) this study contains patients with both septic and hepatic encephalopathy
b) calculated from the reported values

* A marginal increase in CBF may be present by transcranial doppler (TCD) mean flow velocity (cm/s)
ammonia levels could be responsible for the blunted CO₂ reactivity in patients with FHF, as arterial ammonia levels are significantly elevated (IV) [90].

In the brain, ammonia is detoxified by the formation of glutamate. A recent study by Okada et al [91], have demonstrated that glutamine exerts a modulatory effect on the cerebral vasoreactivity to CO₂. They showed that a threefold increase in plasma glutamine concentration induced by infusion of glutamine blunted the cerebralvascular CO₂ reactivity in rats. Furthermore, they showed that co-infusion with arginine completely counteracted the effect of glutamine upon cerebralvascular reactivity, i.e., restored CO₂ reactivity. From these studies it is suggested that glutamine inhibits the recycling of citruline to arginine. Consequently, the availability of arginine for nitric oxide synthesis is reduced [91]. In patients with FHF arterial (IV) and brain glutamine content is increased [92], thus glutamine could be responsible for the blunted CO₂ reactivity in FHF during hypercapnia.

Hypothermia appears to restore the hypercapnic cerebral CO₂ reactivity in patients with uncontrolled intracranial hypertension [93]. This may be explained by the vasoconstriction induced by hypothermia, which shifts the autoregulation curve to the left, thereby restoring at least some of the vasodilatation capacity of the cerebral vessels.

In patients with FHF, we detected high circulating levels of two potent vasodilators, calcitonin gene-related peptide and vasoactive intestinal peptide (V). These neuropeptides exert their effects on vascular smooth muscle receptors localised on the abluminal side of the blood-brain barrier and they do not seem to pass the blood-brain barrier to a greater extent. Thus, the circulating neuropeptides probably do not influence cerebralvascular tone to a major extent, unless the blood-brain barrier is disrupted [94, 95]. As they are stored in perivascular nerves, it cannot be excluded that high brain levels of one or both these two vasodilators play a role for the blunted cerebral CO₂ reactivity in FHF. Since, the effect of calcitonin gene-related peptide on cerebral vessels is mediated through opening of potassium channels, especially the calcium dependent but also to a minor degree the ATP dependent potassium channels [96], it could be speculated that the blunted CO₂ reactivity to hypercapnia in FHF is due to already opened ATP dependent potassium channels produced partly by high brain levels of calcitonin gene-related peptide.

3.2.2 Regional CO₂ reactivity

Even though global CO₂ reactivity is normal in patients with FHF there may be alterations of regional CBF and CO₂ reactivity, which may turn imminent regional cerebral ischemia into manifest ischemia. Furthermore, alterations of PaCO₂ may result in redistribution of blood flow from regions with a relatively high tissue pressure and low CO₂ reactivity to regions with a high CO₂ reactivity and relatively low tissue pressure, referred to as a Steal phenomenon. On the other hand hypocapnia may redistribute blood flow from regions with low tissue pressure and high CO₂ reactivity to regions with high tissue pressure and relatively low CO₂ reactivity, the so-called inverse steal phenomenon [97]. In a study addressing the regional CBF distribution pattern prior to and during hyperventilation in patients with FHF, we found neither steal nor inverse steal phenomena in patients with FHF (II). We also found preserved and similar CO₂ reactivity to hypocapnia in all brain regions (Figure 4 (II), which is in accordance with a retrospective study by Durham et al [58]. Thus, global as well as regional cerebral CO₂ reactivity to hypocapnia is preserved in patients with FHF.

3.2.3 Cerebral autoregulation and hyperventilation.

Cerebral autoregulation is impaired in patients with FHF [56], and is re-established shortly after recovery of liver function [98]. The reason for the impaired cerebral autoregulation in FHF is not completely settled, but has been suggested to result from gradual cerebral vasodilation [11]. This vasodilation hypothesis was supported by the observation where moderate hypocapnia (PaCO₂ ~3.0 kPa) restored cerebral autoregulation in five of seven patients with FHF (Figure 5) (I). On the other hand global CBF was found to be decreased compared to normal values in the subsequent studies (III-VII). This finding does not support the vasodilation theory, as responsible for impairment of autoregulation (III-VII). If vasodilation does not account for the impaired cerebral autoregulation in patients with FHF what could then be the explanation of the restoration of cerebral autoregulation following hyperventilation? Although the nature of the association between hypocapnia and cerebral autoregulation was not investigated in the present work, a number of possible explanations may be considered.

If patients prior to intubation had been hyperventilating spontaneously for some time, then the institution of mechanical normoventilation would render the patient relatively hypercapnic if mechanical ventilation was instituted at a level of PaCO₂ that was higher than the spontaneous PaCO₂. Hypercapnia shortens the autoregulatory plateau, i.e., increases the lower limit and decreases the upper limit of autoregulation, whereas hypocapnia widens the autoregulatory plateau (Figure 6). Hence, in a state of relative hypercapnia cerebral autoregulation will be abolished, while it would subsequently be restored by re-institution of hyperventilation. It cannot be excluded that relative hypercapnia was of importance for the impaired cerebral autoregulation, but in other conditions with impaired cerebral autoregulation where spontaneous hyperventilation is not a prominent feature, e.g. neurotrauma, autoregulation is also
restored by mechanical hyperventilation. Another explanation could be that the cerebral autoregulation curve is right-shifted, i.e., lower limit reached at a higher cerebral perfusion pressure, corresponding to a functionally impaired cerebral autoregulation. Thus, cerebral autoregulation is impaired in the “physiological” range of mean arterial blood pressures, and since hypocapnia widens the plateau of the cerebral autoregulation curve it may be restored during hyperventilation. Indeed, this could be an explanation as rats subjected to portacaval anastomosis demonstrated a right-shift of the autoregulation curve that was not affected by ammonia infusion [99]. In the study by Dethloff et al [99], the lower limit of autoregulation was ~25% right-shifted. In healthy subjects lower limit of autoregulation was ~60 mmHg, corresponding to a lower limit of ~75 mmHg if the lower limit of autoregulation is right-shifted to the same extent as in rats with portacaval anastomosis. Mean arterial blood pressure was >75 mmHg in 6 of 7 patients with FHF (I), thus a right-shift of the autoregulation curve does not appear to be the only explanation, although it cannot be excluded that the lower limit of autoregulation is present at even higher blood pressure levels in FHF.

To conclude, loss of cerebral autoregulation and recovery during hyperventilation have been described in other diseases affecting the brain, such as acute bacterial meningitis [100-102], and acute head injury [103]. It is likely that a common denominator, which is influenced by alkalosis is responsible. Whether this common denominator is cerebrovascular tone, metabolic changes, hyperventilation. However, it is not possible from our study (II) to conclude that frontal hypoperfusion is present in FHF and that this is aggravated by moderate hyperventilation, as we did not have any measures of regional cerebral oxidative metabolism.

The presented data in this thesis have demonstrated that the frontal areas and the basal ganglia have relatively lower rCBF than the posterior regions. This distribution pattern has also been demonstrated in other conditions such as acute bacterial meningitis [109] suggesting that it is either the unconsciousness that results in this altered distribution pattern or the sedatives administered. Against administration of sedatives as the reason for the altered rCBF distribution pattern in patients with FHF speaks that the same rCBF distri-
Cerebral glucose metabolism in mol (100 g min)\(^{-1}\) was 41 (31 – 43) 3.15 (–77-58) 11.7  3.3

Cerebral glucose metabolism in mol (100 g min)\(^{-1}\) was 37 (32-57) 27.2 (4.4-50) 11.8  2.7

Cerebral oxygen metabolism in mol (100 g min)\(^{-1}\) was 190 (140-210) 0.92 (0.11-2.23) mL (100 g min)\(^{-1}\) 86  18

Cerebral oxygen metabolism in mol (100 g min)\(^{-1}\) was 190 (150-200) 0.65 (0.02-1.45) mL (100 g min)\(^{-1}\) 93  17

Oxygen-glucose index was ~4.6 ~7.6

Oxygen-glucose index was ~5.1 ~1.6


Healthy subjects FHF FHF

Normoventilation

Cerebral oxygen metabolism in µmol (100 g min)\(^{-1}\) was 190 (140-210) 0.92 (0.11-2.23) mL (100 g min)\(^{-1}\) 86 ± 18

Cerebral glucose metabolism in µmol (100 g min)\(^{-1}\) was 37 (32-57) 27.2 (4.4-50) 11.8 ± 2.7

Cerebral lactate metabolism in µmol (100 g min)\(^{-1}\) was ~2 (~5-4) –1.6 (~13-7.6) 3.01 ± 3.78

Oxygen-glucose index was ~5.1 ~1.6 7.6 ± 1.9

Hyperventilation

Cerebral oxygen metabolism in µmol (100 g min)\(^{-1}\) was 190 (150-200) 0.65 (0.02-1.45) mL (100 g min)\(^{-1}\) 93 ± 17

Cerebral glucose metabolism in µmol (100 g min)\(^{-1}\) was 41 (31 – 43) 3.15 (~77-58) 11.7 ± 3.3

Cerebral lactate metabolism in µmol (100 g min)\(^{-1}\) was ~12 (~15 – 5) ~1.6 (~69-3.15) 1.85 ± 3.22

Oxygen-glucose index was ~4.6 ~9.5 8.9 ± 1.3

All values are in µmol/100g/min except those with * which are in mL/100 g/min.

Table 4. Previous published studies of cerebral oxidative metabolism in patients with FHF.

Table 5. Previous published data on cerebral oxygen, glucose and lactate metabolism during normoventilation and hyperventilation in patients with FHF and healthy subjects.

3.2.6 Cerebral oxidative metabolism and hyperventilation

In accordance with other studies on patients with FHF cerebral oxygen metabolism was reduced in patients with FHF investigated in this thesis (Table 4) [72, 14, 61, 63]. By contrast, the results on cerebral glucose metabolism in patients with FHF have ranged from reduced [14, 61] to normal [14], and even increased cerebral glucose metabolism [63]. The study with increased cerebral glucose metabolism [63] was contrary to the other studies performed on patients with ongoing intracranial hyperperfusion. It has been suggested that ammonia may interfere with cerebral energy metabolism, including stimulation of certain glycolytic enzymes, inhibition of certain enzymes in the TCA cycle, and induction of the mitochondrial permeability transition in astrocytes leading to energy failure [78, 111]. The results on cerebral glucose metabolism in patients with FHF investigated in this thesis [VII] do not corroborate this hypothesis, as all glucose taken up by the brain was aerobic metabolized, i.e., the oxygen to glucose index was normal. It cannot be excluded that these metabolic changes take place later during the disease course. Alterations in cerebral metabolism later during the disease course may be supported by the study by Jalan et al [63] which was performed during ongoing intracranial hypertension in patients with FHF, i.e., the oxygen to glucose index calculated from the reported cerebral metabolic rates is ~ 0.5 (Table 4). Notwithstanding there may be either a miscalculation in their reported metabolic rates or a misprint of the reported arterial and venous oxygen contents in their articles, i.e., PaO\(_2\) is 31 mL/dL, and CBF is 103 mL/(100g min) corresponding to a cmrO\(_2\) on ~ 3.2 mL/(100g min) [63]. If this recalculation of cmrO\(_2\) is correct the oxygen to glucose index is ~4.2 in the patients studied by Jalan et al [63] which is indeed lower than required for aerobic glycolysis.

Only one other study has evaluated the effect of shortterm hyperventilation on cerebral oxidative metabolism in FHF (Table 5) [14]. Wendon et al [14] found that hyperventilation produced a significant reduction both in CMRO\(_2\) and cerebral glucose metabolism in patients with FHF. As can be seen from Table 5 both the CMRO\(_2\) and cerebral glucose metabolism varied widely among patients with FHF in the study by Wendon et al. Since they also found negative values of cerebral glucose metabolism (Table 5) it is likely that not all of their patients were in a steady state condition at the time of their measurements that normally is required for accurate sampling of CBF and AV differences of various metabolites.

Measurements of markers of astroglial (S-100b) and neuronal (NSE) damage during hyperventilation in patients with FHF, may support that moderate hyperventilation is safe, as the arterial concentrations as well as net brain flux of these markers were unaltered (VI). A borderline ischemia that is turned into manifest ischemia may be supported by the study by Jalan et al [63] which was performed during moderate short-term hyperventilation. In our study (VII), cerebral oxidative metabolism was not compromised neither during normoventilation nor during hyperventilation as a striking net cerebral lactate uptake was demonstrated during hyperventilation, which was only slightly decreased by hyperventilation, i.e., the lactate oxygen index remained positive, and the cerebral oxygen to glucose index remained unchanged and normal (VII). Contrary to our findings, Wendon et al [14] found that hyperventilation produced a significant reduction both in CMRO\(_2\) and cerebral glucose metabolism in patients with FHF. As can be seen from Table 5 both the CMRO\(_2\) and cerebral glucose metabolism varied widely among patients with FHF in the study by Wendon et al. Since they also found negative values of cerebral glucose metabolism (Table 5) it is likely that not all of their patients were in a steady state condition at the time of their measurements that normally is required for accurate sampling of CBF and AV differences of various metabolites.
3.2.7 Cerebral nitrogen balance and hyperventilation

Critically ill patients are most often in a state of negative whole body nitrogen balance (IV) [113, 114] which is due in part to muscle protein wasting. In patients with FHF (IV) also the brain has a negative nitrogen balance that is primarily caused by a manifest cerebral glutamine efflux (IV). No other comparable human studies have been published on cerebral nitrogen balance in FHF or other conditions. Thus, it is not possible to conclude that this is a specific feature of FHF, but there is evidence to support that hyperammonemia causes cerebral protein breakdown, as experimental studies have shown that ammonia results in a reduced cerebral protein content [115], and loss of glial fibrillary acidic protein has been demonstrated in humans with hepatic encephalopathy [116], as well as in experimental liver failure [117].

![Amino acid nitrogen efflux in patients with FHF (n = 14)](image)

**Figure 7.** Cerebral amino acid nitrogen efflux in patients with FHF (n = 14) before and after short-term mechanical hyperventilation.

![Glutamine efflux in patients with FHF (n = 14)](image)

**Figure 8.** Cerebral glutamine efflux in patients with FHF (n = 14) before and after short-term mechanical hyperventilation.

Short-term mechanical hyperventilation significantly reduced the cerebral nitrogen release, i.e., it became less negative (from \(-14.81 \pm 14.02\) to \(-4.69 \pm 6.26\) µmol (100g min\(^{-1}\)) (Figure 7) (IV). The ameliorated cerebral nitrogen balance was primarily caused by a reduction of the cerebral glutamine efflux, i.e., from \(-6.11 \pm 5.19\) µmol (100g min\(^{-1}\)) during normoventilation to \(-2.91 \pm 3.22\) µmol (100g min\(^{-1}\)) during hyperventilation (Figure 8) (IV). However, a decreased cerebral proline, alanine and tyrosine efflux, and increased cerebral uptake of branched chain amino acids, also contributed slightly to normalisation of the cerebral nitrogen balance during hyperventilation (IV). In that study, (IV) pH increased from \(7.46 \pm 0.05\) to \(7.54 \pm 0.05\) during hyperventilation. Since the pKa for glutamine is \(-2.17\) for the carboxyl group and \(-9.28\) for the amino group, respectively, this slight increase in pH cannot have influenced the amount of glutamine available for transport across the blood-brain barrier to a major extent, as only a small amount of glutamine will become ionised at that pH. Increased flux into the brain and/or decreased flux out of the brain could also account for the apparent reduction in glutamine efflux during hyperventilation. Recent studies have shown that active transport from brain to blood through sodium-dependent transport carrier systems is pH dependent, i.e., “flux” decreases with decreasing pH [118, 119]. Some of these transporter systems are also located on astrocytes and neurons. The astrocytic form being pH sensitive [120], while the neuronal form is not [121]. If the effect of pH on these carrier transport systems were linear, an increased transport out of brain as well as an increased astrocytic glutamine uptake would be expected to arise during alkalosis, with a resulting decrease of extracellular glutamine. We cannot exclude that pH may have influenced our results to some extent. However, alkalosis have been shown to stimulate muscle protein synthesis in critically ill patients [114], and in the perfused working heart [122]. During normoventilation we found evidence of cerebral protein degradation, as there was a net brain efflux of tyrosine and threonine, two essential amino acids. During hyperventilation this flux became zero, indicating that alkalosis may also inhibit protein degradation. A firmer conclusion on whether alkalosis stimulates protein synthesis or inhibits protein breakdown or a combination of both is not possible to determine from the data presented in this thesis.

4.0 CONCLUSIONS AND PERSPECTIVE

Only alteration of cerebral ammonia and glutamine metabolism is a prominent feature during the very early phase of the cerebral illness in patients with FHF. The cerebral oxidative metabolism was reduced in parallel with CBF, tightly matching the metabolic needs for oxidative metabolism. Although CBF is low during this early phase of FHF, our findings do not contradict that CBF gradually increases and plays a role for aggravation of cerebral edema and intracranial hypertension later during the course of FHF. Even a slight increase in CBF in patients with manifest cerebral edema can result in intracranial hypertension, as the brain is located in the rigid skull allowing for limited expansion only. Thus, the finding in the present thesis suggests that if an increase in CBF appears it is a secondary phenomenon that takes place later during the disease course, probably initiated by cerebral metabolic alterations during the early phase such as increased cerebral ammonia and glutamine fluxes.

From the present clinical studies performed in patients with FHF there was no evidence to support that short-term moderate mechanical hyperventilation is detrimental to the brain. Although global CBF was reduced further by hyperventilation, it did not compromise global cerebral oxidative metabolism. Using SPECT, we found that the perfusion in frontal brain regions and basal ganglia was lower as compared to the other brain regions. These regions had the same CO\(_2\) reactivity to hypocapnia as the other brain regions. However, moderate hyperventilation did not reduce regional CBF under the ischemic level.

Hyperventilation restored cerebral autoregulation in most pa-
patients, which from a clinical point of view is important as it may protect the brain from fluctuations in cerebral perfusion pressure, and secondary brain damage. Also hyperventilation appeared to normalise the cerebral nitrogen balance, which indicates that hyperventilation protects the brain from cerebral protein breakdown. Although alterations in pH may have influenced the efflux of glutamine to some extent, we cannot extrapolate that alkalosis increases flux through this carrier system, since pH sensitivity of the carrier system has been performed during reduced pH only.

Thus, from the present clinical studies of FHF, institution of hyperventilation for short-term periods appears safe. Although the present studies have addressed many of the effects of hyperventilation upon cerebral perfusion and metabolism in patients with FHF, many new questions have emerged.

In order to elucidate the chain of reactions that leads to recovery of autoregulation during hyperventilation, future studies should try to address possible factors responsible for the impairment of autoregulation, and also explore the value of therapeutic interventions such as selective cerebral vasoconstrictors, that would restore cerebral autoregulation as well as their clinical relevance. In experimental models the effect of glutamine infusion should be explored to address its effect upon cerebral autoregulation. Likewise, infusion of neuropeptides should be explored in animal models, to address whether high circulating levels of vasodilating neuropeptides can affect cerebral autoregulation. In patients with FHF, the effect of prolonged hyperventilation on cerebral autoregulation and outcome should be explored in large randomized controlled trials.

To elucidate if an exhausted vasodilatory capacity may account for the blunted cerebral hypercapnic CO₂ reactivity in FHF, the effect of infusion of vasodilating peptides, e.g., calcitonin gene-related peptide, on cerebral CO₂ reactivity should be explored in future studies. In order to address whether cerebral CO₂ reactivity to hyperventilation is lost during the course of FHF, daily evaluation of CO₂ reactivity should be performed in patients with FHF.

To address whether short-term hyperventilation compromise regional cerebral oxidative metabolism in patients with FHF methods such as positron emission tomography and/or magnetic resonance imaging should be used. To obtain a better understanding of the metabolic effects of hyperventilation intracerebral microdialysis should be applied concomitant with arterio-venous differences of oxidative substrates and amino acids. Intracerebral microdialysis should also be applied to measure alterations in brain pH during short-term, and during prolonged hyperventilation to evaluate if and when adaptation arise.

SUMMARY IN ENGLISH
Patients with FHF have a high risk of cerebral edema and intracranial hypertension. The pathophysiological background for this phenomenon is not completely settled, but alteration in CBF as well as cerebral metabolism seems to be of importance. Mechanical hyperventilation has a prompt effect on intracranial pressure. This effect is assumed to be caused by the hypocapnia induced alkalosis which produces vasoconstriction and thereby a decrease in CBF and cerebral blood volume. It has been stated that hyperventilation may be harmful to patients with FHF, but only few studies have addressed the effect of hyperventilation upon cerebral metabolism. In the present clinical studies we evaluated the effect of short-term mechanical hyperventilation upon cerebral circulation and metabolism in patients with FHF. Although global CBF was reduced in patients with FHF it tightly matched the cerebral oxidative requirements. Already in the early phase of FHF there was a prominent cerebral efflux of glutamine that could not be accounted for by cerebral ammonia uptake. Moderate hyperventilation reduced global CBF without compromising cerebral oxidative metabolism. In addition, moderate hyperventilation restored cerebral autoregulation in most patients with FHF, and normalised the cerebral nitrogen balance during short-term interventions. Studies of global and regional cerebral carbon dioxide reactivity showed normal global as well as regional cerebral carbon dioxide reactivity in almost all patients with FHF. However, cerebral perfusion in frontal brain regions as well as basal ganglia is low in FHF as compared to healthy subjects, which may make these regions at risk of hypoperfusion during pronounced hyperventilation. It is concluded that moderate short-term hyperventilation does not compromise cerebral oxidative metabolism. Recommendation of its prolonged use in FHF awaits further studies. Furthermore, the data of this thesis demonstrates that alterations in cerebral glutamine and ammonia metabolism precedes increases of CBF, which seems to be a phenomenon that takes place later during the disease course, i.e., immediately before intracranial pressure is rising.

ABBREVIATIONS
ATP  adenosine triphosphate
AVDO₂  arterio-venous difference of oxygen
CO₂  carbon dioxide
CBF  cerebral blood flow
CMRO₂  cerebral metabolic rate of oxygen
FHF  fulminant hepatic failure
GM P  guanosine monophosphate
PaCO₂  arterial carbon dioxide tension
SPECT  single photon emission computed tomography
TCD  transcranial doppler sonography
Vmean  mean flow velocity
⁹⁹mTc-HM-PAO  Technetium-99m Hexamethyl propyleneamine oxide

THIS THESIS IS BASED UPON THE FOLLOWING ORIGINAL PAPERS:

REFERENCES
3. Wolff HG, Lennox WG. The cerebral circulation: XII. The effects on pial


