To identify the patho-physiology of neurological deficits after aneurysmal subarachnoid haemorrhage, explore their interrelationship and identify tools which best measure these deficits

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Declaration

The candidate confirms that the work submitted is her own and that appropriate credit has been given where reference has been made to the work of others.

Copyright statement

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Abstract

Background:

Aneurysmal subarachnoid haemorrhage (aSAH) is a neurological catastrophe with 30-40% survival, 30% survivors left with moderate to severe disability and 66% survivors suffering functional or cognitive deficits compromising return to premorbid performance status. Delayed neurological deficit (DIND) is the most common cause of morbidity and mortality affecting the hospitalized aSAH patient. Although many theories have been proposed, we do not fully understand the patho-physiology of DIND or the nature of resultant cognitive and functional disability. Thereby, even with advances in overall patient care, the outcome of the patients afflicted with DIND remains suboptimal.

Aim:

The aims of this work are:

1. To elucidate physiological variables during course of delayed neurological deficit to explore DIND pathophysiology
2. To explore functional and cognitive deficits after aSAH by administering a battery of patient reported outcome scales, thereby better understand the correlation between different components of health status in aSAH patients and to derive a set of tools that will help easy, uniform and early identification of subtle but clinically significant neuro-psycho-social deficits in this patient group to guide appropriate management and rehabilitation.

Methods:

A prospective observational pilot study with a sample size of 16 patients was undertaken to investigate DIND pathophysiology. Eligible participants underwent invasive monitoring of regional cerebral blood flow, tissue oxygen concentration, energy metabolism and tissue ionic changes to cover the time epochs prior to development of DIND, during its onset, and with administration of Triple-H therapy. Descriptive analysis of the parameters over time was undertaken to compare patients who did / did not develop symptoms of DIND.

A questionnaire based survey was carried out with a sample size of 200 SAH patients using AKC short sentences test, The Dysexecutive Questionnaire, The Everyday Memory Questionnaire, Stroke Symptom Check-list, Wimbledon Self-report Scale and Stroke QOL to assess functional and cognitive deficits after aSAH. Descriptive analysis was done to identify patterns of deficits and identify tools that best help to pick-up these deficits. Logistic regression and structural equation modelling was done to pick interactions thereof.

Results:

In the pathophysiology study, 7 patients developed DIND. Large inter-subject baseline variations were observed in tissue perfusion and oxygenation in all patients. Changes in perfusion and oxygenation were not linked to symptoms. A trend was observed in energy metabolism with simultaneous escalation in both lactate and pyruvate between day 4-7 (coinciding with symptoms), in 6 patients with DIND and only 1 patient without DIND. The extracellular potassium ion concentration paralleled metabolic changes in 4/6 patients where ionic monitoring was undertaken. The ionic/metabolic changes were not related to change in perfusion or oxygenation. Triple-H therapy, particularly raised mean arterial pressure, improved symptoms. It led to improvement in cerebral perfusion and oxygenation but, did not lead to any changes in metabolic profile.

The questionnaire survey witnessed a 57% response rate. 76% of these patients experienced functional and cognitive difficulties. Nearly half returned to economic productivity. Even a third of patients with good Modified Rankin Score (MRS) at discharge failed to return to work. Cognitive disability and mood disorder explained 26% of the variance in patients' perceived MRS at follow up. Cognitive disability had a direct as well as indirect effect on MRS by affecting the patient's mood.

Conclusion:

Invasive neuromonitoring is well tolerated and safely provides valuable and timely information regarding DIND even in awake patients. This work provides baseline neurophysiology data to guide future studies. It questions current hypothesis for DIND pathophysiology and argues that besides ischaemia, DIND is related to increased metabolic demand outstripping the available supply, at least partly secondary to rising extracellular potassium concentration which drives sodium-potassium pump for maintenance of cellular homeostasis. Triple H therapy acts by restoring the balance.

Besides physical disability, a significant proportion of SAH patients are left with cognitive, speech, memory and affect deficits compromising return to social productivity. Mood plays a significant role in determining perceived well being and is in turn affected by cognitive ability. Mood and cognition are thus targets for holistic follow-up and rehabilitation, especially in good grade (i.e. with minimal physical disability) individuals. Patient reported outcome measures are easily administered, cheap and useful source of detailed outcome information regarding these parameters in this patient group.

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Abbreviations

AIND	acute ischaemic neurological deficit
AKC	AKC short sentences questionnaire
BI	Barthel index
CBF	cerebral blood flow
CBV	cerebral blood volume
CMRO2	cerebral metabolic rate of oxygen
CNS	central nervous system
CSD	cortical spreading depolarisation
CSF	cerebrospinal fluid
CSI	cortical spreading ischaemia
CT/A/P	computerised tomography/angiography/perfusion
CVP	central venous pressure
DEX	dysexecutive questionnaire
DIND	delayed ischaemic neurological deficit
DSA	digital substraction angiography
EBI	early brain injury
EFA	exploratory factor analysis
EMQ	every day memory questionnaire
GCS	Glasgow coma score
GOS	Glasgow outcome score
ICP	intracranial pressure
LDF	laser doppler flowmetry
MAP	mean arterial pressure
MRS	Modified Rankin Score
MTT	mean transit time

OEF	oxygen extraction fraction
PET	positron emission tomography
PROM	patient reported outcome measure
pTiO2	tissue partial pressure of oxygen
QOL	quality of life
RCT	randomised controlled trial
RTW	return to work
SAH	subarachnoid haemorrhage
SEM	structural equation model
SSC	stroke symptom checklist
TCA cycle	tricarboxylic acid cycle
TCD	transcranial doppler
TD	thermodiffusion flowmetry
triple-H	Hypertension, Haemodilution, Hypervolaemia
WFNS	World Federation of Neurological Surgeons
WSRS	Wimbledon self report scale

Ions- Na^{+}=sodium, K^{+}=potassium, Ca^{++}=calcium and Mg^{++}=magnesium

Cerebral arteries- ACA=anterior cerebral, A-Com=anterior communicating, MCA=middle cerebral, P-Com=posterior communicating and PCA=posterior cerebral.

Chapter 1

General Introduction

This chapter introduces the reader to the entity of delayed neurological deficit after aneurysmal subarachnoid haemorrhage- its potential etiology, pathophysiology, diagnosis, management and rehabilitation.

1.1 Overview of SAH-

Bleeding in subarachnoid space or subarachnoid haemorrhage (SAH) is a neurological catastrophe typically characterized by sudden onset 'worst ever' headache with/without loss of consciousness. It commonly affects individuals in their fifth decade and has a female predilection (Biller, 1987). With annual UK incidence around 6-8/100000 population, SAH is the most common type of stroke affecting the young and active population (Broderick, 1993 and Linn, 1996). 80% of these cases are caused by a weakness in the vessel wall, called an aneurysm. Diagnosis of SAH is made with computed tomography (CT) with or without lumbar puncture and the aneurysm is subsequently confirmed with either CT angiogram or formal angiography. Subsequent management includes clipping or coiling to secure the aneurysm and maintaining homeostasis while monitoring the patient in a neurological high dependency unit or intensive care unit where subsequent effects of the bleed can be dealt with. Clinical effects of aneurysmal SAH are devastating. Case fatality rates vary between 32-67% (Teunissen, 1996 and Johnston, 1998). 66% of survivors never return to the same quality of life as before SAH, with about 30% having moderate or severe disabilities (Hop, 1997). Long term subtle functional and cognitive deficits are common after subarachnoid haemorrhage even in those surviving with good physical ability. These are not fully realized when the patient is still in hospital setting, however, they form a major impediment for return to social and economic life (Hop, 1998). Until recently, in patients who survive the initial ictus, re-bleed and DIND were two main causes of death and disability. In past decade, early surgical clipping (Ross, 2002) and endovascular coiling (Molyneux, 2002) have curtailed the rate of re-bleed; as such delayed ischaemic neurological deficit remains the chief cause of moderate-severe deficits after SAH (Sen, 2003).

1.2 Delayed ischemic neurological deficit-

Delayed ischaemic neurological deficit (DIND) is defined as potentially reversible new, focal neurological deficit or impairment of level of consciousness (>2 points on GCS) occurring after the third post hemorrhagic day that cannot be explained by any other cause like re-bleeding, hypo-natraemia, hydrocephalus, seizure or infection, by means of clinical assessment, CT/MRI and appropriate lab investigations and persisting for at least 1 hour. It is thus a diagnosis of exclusion, usually associated with reversible hypo-densities on CT that may culminate into full blown infarction that should not be accounted for by any acute event or intervention (Vergouwen, 2010). Traditionally the infarction is believed to be ischaemic in origin, hence the name. In total, DIND affects a third of patients with aSAH (Kassell, 1985).

Studies of anatomical, radiological and clinico-pathological features suggest that DIND is a diffuse process with multi-factorial causation as detailed in the following sections. Predictors and prognostic indicators of DIND have been extensively explored; however robust evidence is only linked to the amount of blood on CT (Fisher, 1980 and Kistler, 1983). This blood load is quantified by Fisher grading system; those with higher Fisher grades are more likely to develop this complication.

In recent years much research has focused on better understanding of this complication. With advances in neuro-intensive care, better maintenance of homeostasis and use of prophylactic calcium channel blockers, the incidence of DIND has been reduced from 32.5 to 22-28.5% depending on Nimodipine use; however the outcome for those afflicted still remains bleak. 25.6% of those affected by DIND die, 45.9% have a poor outcome (Dorsch, 2002 & 2011). To be able to develop effective strategies for treatment and rehabilitation of DIND patients, a proper understanding of its patho-physiology and spectrum of cognitive impairment as a result of this is crucial.

1.3 Mechanism of delayed ischaemic neurological deficit-

Until recently, the term vasospasm was used almost synonymously with DIND; indicating the perceived linkage between angiographic spasm (vasospasm) and the clinical features of DIND. In the past few years, several other contributors to pathogenesis of DIND namely- early brain injury, cortical spreading ischaemia, inflammation and microthrombosis; have been explored. These are detailed as below, however a clear unifying hypothesis remains a challenge for both clinicians and researchers-

Vasospasm

Narrowing of the major cerebral arteries in patients with subarachnoid haemorrhage was initially demonstrated in 1951 by Ecker and Riemenschneider. This was eventually linked to development of infarcts on CT and on histopathology (Connolly, 1962; McKissock, 1965 and Kak, 1967). The arterial spasm was diagnosed on the trans-cranial doppler as a high velocity (>120-180cm/s) and more specifically as narrowing on CT angiogram or digital subtraction angiography. There was some temporal association between angiographic spasm and clinical symptoms of DIND. The concept of reduction of blood flow leading to infarction was theoretically promising and remained central to the idea of DIND pathogenesis for nearly 3 decades. Based on this principle, hyperdynamic therapy- hypervolaemia, hypertension and haemodilution (Triple-H) has been instituted to DIND patients and has been observed to cause symptomatic reversal (Kassell, 1982; Awad, 1987). Also, angioplasty, that reverses arterial narrowing, also reverses symptoms in some DIND patients (Jestaedt, 2008).

However, since the introduction of this idea, this concept has been challenged, by both animal studies (Weir, 1970) and clinical data (Wilkins, 1968) that found existence of severe angiographic spasm without symptoms and vice-versa . Further studies (Ohta and Ito1981; Vora,1999 and Dehdashti, 2004) observed that while arterial vasospasm

occurs in 70%, DIND occurs in only 33% of SAH patients. Temporal and spatial association between vasospasm and DIND was found to be weak (Rabinstein, 2004, 2005; Weidauer, 2007) and laminar cortical necrosis, not conforming to vascular territorial distribution is 13 times more common than wedge (arterial) infarcts in patients with DIND(Rabinstein, 2004-2005; Naidech, 2006; Lee, 2006; Weidauer, 2007). Therapeutically, nimodipine (a calcium channel blocker), is the only drug that has proven efficacy in reducing the incidence of DIND but has little effect on angiographic spasm(systematic review-Feigin, 1998); prophylactic Triple H therapy, although causing a significant reduction of vasospasm, does not have a role in prevention of DIND (Treggiari, 2003) and clazosantan and nicardipine-prolonged-release-implants, which effectively prevent angiographic spasm, do not affect incidence of DIND or outcome after SAH(Vajkoczy, 2005; CONSCIOUS trial, COSBID study group, 2012).

As such, while it may be interpreted that angiographic spasm –

- may lead to reduction in distal blood flow,
- be associated with territorial infarcts in some cases,
- contribute to the syndrome of DIND and
- patients might benefit from restoration of cerebral hemodynamics in symptomatic regions affected by severe vasospasm and prolonged mean transit time

-it does not offer the whole explanation for DIND.

Early Brain Injury

The constellation of events occurring in the first 72 hours of the ictus is collectively known as *early brain injury(EBI)* (Kusaka, 2004). These include raised intracranial pressure from aneurysmal haemorrhage, resulting ischaemia from reduction in global cerebral blood flow i.e. ‘stop flow phenomenon’, pathological signaling of

neurotransmitters leading to neuronal and glial apoptosis, disruption of the blood brain barrier, changes in the ionic milieu and cerebral oedema (Sehba, 2012). The effect of these events on cerebral physiology and metabolism has been studied for a long time; however its role in pathogenesis of DIND has only recently been explored (Pluta, 2009). While there was poor association between presence and treatment of vasospasm and clinical outcome, EBI has emerged as a potential contributor to the cascade of events that leads to poor outcome. It is early days and further research into elucidating pathways of EBI is underway.

Cortical Spreading Ischaemia

The concept of cortical spreading depolarization(CSD) was introduced by Leao in 1944. It was initially associated with migraine and head injury. Presence of this phenomenon after subarachnoid haemorrhage has been demonstrated by Drier et al in 2007. Physiological basis of CSD is a passive neuronal cationic influx due to blood breakdown products in the interstitium. This overwhelms the cellular sodium and calcium pumps and causes mass neuronal depolarization and cytotoxic oedema. This phenomenon is physiologically associated with cortical spreading hyperaemia and thus hyperoxia to enable recruitment of more sodium/potassium pumps for restoration of ion and water balance. However, in compromised states inverse coupling of CSD and perfusion occurs; giving rise to cortical spreading ischaemia (CSI). CSI reinforces cellular edema and eventually leads to calcium influx and mitochondrial damage leading to ischaemic cell death.

Clinical studies have demonstrated an association between areas of CSD clusters and CSI with laminar cortical infarcts on CT scan despite prevention of angiographic spasm (Dreier, 2007). The micro-vascular spasm concept of CSI agrees with previous

observations of increased mean transit times seen in DIND patients in absence of macro-vascular spasm.

The symptomatic correlate of CSI remains to be established; nevertheless this novel patho-physiological process appears promising.

Inflammation

Inflammation has long been implicated in the multi-factorial causation of DIND. Initial studies linked raised temperature after SAH to DIND (Rousseaux, 1980). Association with raised white cell count followed (Maiuri, 1987). Experimental evidence suggested that leukocytes are recruited in regions of decreased flow and transmigration of these activated cells led to propagation of infarct. Cytokines are suspected to mediate this process. Elevated lymphocyte subpopulations have been observed in cerebrospinal fluid of SAH patients with DIND (Mathiesen, 1996). Elevated level of cytokines has been shown in the central nervous system(CNS) in patients with SAH/DIND (Mathiesen 1993, 1997). In animal and in-vitro studies cytokines- particularly, interleukin1, 6 and TNF-alpha have been implicated in cellular damage resulting in increased infarct size (Rothwell, 1996). In patients, these inflammatory mediators have demonstrated a close relationship to angiographic spasm. Levels of these cytokines in DIND were shown to be as high as after bacterial meningitis and elevated levels seem to predate high flow velocities on transcranial doppler (Fassbender, 2001). The mechanism of action of cytokines is believed to be through mediation of angiographic spasm via endothelin-1 or non endothelin-1 pathway and direct cytotoxic effect on brain cells in interaction with adhesion molecules.

Besides pathogenesis, cytokine levels also serve in prediction of DIND. However, compartmentalization of these mediators is debated. Peripheral inflammatory mediators seem associated with CNS inflammatory response and peripheral neutrophil count, ESR

and CRP (McMahon, 2009) have been found to be associated with clinical severity/grade of SAH, DIND and infarct size. In patients with DIND, the levels of CSF cytokines have been found to be greater than serum cytokines in an ongoing study from our centre (al-Tamimi, 2010).

Therapeutically, interleukin-1(IL-1) antagonist IL1-RA is currently under investigation for prevention of DIND. The search for other mediators of inflammation after SAH is ongoing. Recently matrix metalloproteinase 9 has been implicated as an inflammatory mediator that is raised seven fold in patients with DIND as compared to controls. (Sarrafzadeh, 2012)

Microthrombosis

Coagulation cascade is initiated from platelet activation after aneurysmal rupture. Subsequently, elevated levels of procoagulants are naturally observed in days preceding DIND. Studies indicate role of coagulation in DIND pathogenesis. Elevated levels of serologic coagulation markers –vonWillebrand factor, tissue factor, fibrinopeptide A, fibrin degradation products, D-dimer and thrombin-antithrombin complexes have shown to be associated with incidence of DIND and development of infarction (Ohkuma, 1991; Hirashima, 1997; Peltonen, 1997; Suzuki, 1999; Frijns, 2006).

Plasminogen activator inhibitor-1(PAI-1) is an inhibitor of tissue plasminogen activator. High levels of PAI-1 are found in patients with DIND (Ikeda, 1997). Nimodipine inhibits PAI-1 and inhibition of this cascade is proposed as one of the mechanisms for effect of nimodipine (Roos, 2001; Vergouwen, 2007). PAI polymorphisms are associated with likelihood of DIND.

Micro-emboli are commonly seen on transcranial doppler in DIND patients(Romano, 2002) and are thought to result from the hyper-coagulable state. Microthrombi are

present on autopsy in DIND cases, micro thrombus load being proportional to the blood load on CT (Stein, 2006).

Thus there is an evolving understanding that DIND is a result of various inter-dependent pathologic processes culminating in a typical symptom complex and histological pattern of tissue damage. Diagnostic and management strategies aimed at any one of these mechanisms have proven insufficient. To be able to develop comprehensive preventive, diagnostic or treatment strategies, it is important to understand the patho-physiology at tissue level in these patients through the initial period after SAH that culminates into DIND. Current state of understanding about this is detailed in the following section.

1.4 Cerebral pathophysiology in delayed ischaemic neurological deficit-

Cerebral haemodynamics-

With all the aforesaid mechanisms of pathogenesis, impairment of cerebral blood flow (CBF) has been strongly proposed as the factor responsible for delayed ischaemic neurological deficit and has been extensively investigated.

Due to technical limitations, most information on cerebral blood flow in SAH is based on snap shot views in humans or animal models. There are few studies that map sequential changes in cerebral hemodynamics after SAH. A brief explanation about the course of cerebral hemodynamics, the relationship of cerebral blood flow to symptoms, and other parameters of cerebral physiology is detailed in the following paragraphs.

Global cerebral blood flow is noted to decline in all patients in the first week following SAH (James, 1968; Meyer, 1983; Hayashi, 2008).This decline is proportional to initial clinical (Hunt & Hess) grade (Appendix 1). However, the initial quantification of blood flow is not predictive of subsequent angiographic spasm or symptoms of DIND (Yoshida, 1996; Bergvall, 1973). In patients with good outcome, the global blood flow continues to improve after the first week while it remains low or even decreases further in those who develop DIND(Kawamura, 1992). The mean values of CBF are lower in symptomatic patients as compared to others and as compared to the contralateral side, but, this decrease is not statistically significant.

Though DIND is a diffuse process (Hijdra, 1986), focal changes better relate to symptoms as compared to global changes of CBF (Rijsdijk, 2008; Mickey, 1984). Focal patterns of ischaemia, normal CBF values, hyperaemia and vasoparalysis are all observed with DIND(Minhas, 2003; Gelmers, 1973; Heilbrun, 1972). Focal ischaemia has by far been the commonest pattern(Frykholm, 2004) but even in these patients, the CBF values noted have been above ischaemic threshold (Yamakani, 1983). The ischaemic insult has been quantified as severe and moderate; 6mls/100g tissue/min

being the cut off. Those with severely reduced CBF have progressed to infarction whereas those with moderate reduction have made radiological recovery.(Tagliaferri, 2006) No permanent hypodensities in CT have been observed with a CBF value above 18mls/100g tissue/min (Yonas, 1989).

Studies exploring CBF during recovery phase after DIND or after development of reversible hypodensities on CT show a hyperaemic pattern in good grade patients but a persistently lower CBF upto three months has been observed associated with poor outcome (Matsuda, 1990).

Brain tissue exhibits the phenomenon of autoregulation of blood flow, whereby with intact autoregulation the arterioles should dilate in response to major arterial spasm and preserve cerebral blood flow. As such, increase in both central and peripheral cerebrovascular resistance and impairment of cerebral autoregulation should be present if impairment of blood flow leads to DIND. This speculation has not been substantiated in all studies. While Grubb (1977) and Kawamura (1992) found autoregulation to be generally intact, Hattingen (2008) and Muench (2007) reported a complete absence of autoregulation in patients with aSAH. Other studies have found a variable absence of autoregulation. It is possible that autoregulation is perturbed during certain phases in these patients (Yundt, 1998; Soehle, 2004), but as most data is a snapshot view with small sample sizes, it may not be reflective of the whole picture.

Global CBF changes in SAH are independent of vasospasm. The temporal and spatial association of focal CBF changes with angiographic vasospasm is debatable. Trans - cranial doppler velocity, an indicator of angiographic spasm, has a poor correlation with simultaneous perfusion value(Minhas, 2003). Sviri (2006) showed that patients with severe vasospasm show significant decrease of regional CBF, maximum mean transit time and increase of regional oxygen extraction fraction in vasospastic territory corresponding with symptoms, Dankbaar (2009) found that region of lowest perfusion

corresponded to vasospastic territory in only 2/3rds of cases. This finding was further confirmed with simultaneous measurements of angiographic spasm on catheter angiography and hypoperfusion on positron emission tomography (Dhar, 2012). Studies to assess CBF in response to treatment are limited. Available data indicates a rise in CBF with induction of hypervolaemia and hypertension (Muench, 2007).

The above studies investigating CBF have all been done in different settings, employing different techniques to measure CBF directly or indirectly and different quantifications thereof to describe the state of cerebral perfusion. Moreover, these provide at best a snapshot view of an inherently dynamic process. As such while it is established that substantial alterations of cerebral blood flow occur in patients post SAH, no pattern of CBF change can be consistently associated with DIND.

Tissue oxygenation-

According to the traditional axiom- vasospasm led to low blood flow, resulting in low oxygen availability and ischaemic cell death-manifesting as DIND. Thus whilst CBF has been vastly studied, tissue oxygenation has been perceived a secondary change and has not received due attention. The current picture is more complex. Irrespective of blood flow, oxygen availability to tissue and its usage depends on other factors- i.e. pulmonary function and tissue metabolic activity, etc. which may be independently perturbed after SAH; hence the need to explore tissue oxygen dynamics after SAH. Akin to CBF and metabolism, the snap-shot values of brain tissue oxygen are lower in patients with a more severe bleed and differ between survivors and non-survivors. However, individual values of tissue oxygen have not shown much use in prediction of DIND or poor outcome(Meixenberger,2003; Jaeger, 2007).

In sequential studies, in the initial period following SAH, oxygen extraction fraction(OEF) remains in the normal range(Hayashi, 2008). Subsequently, with onset of angiographic

spasm, the OEF goes up(Carpenter, 1991; Yundt,1998). Areas with raised glutamate (indicating tissue hypoxia) are observed in patients with DIND despite CBF and energy metabolic parameters (lactate and pyruvate) in the normal range. These are global changes and may not correspond to the symptomatic territory (Sarrafzadeh, 2010). Frequent episodes of critical tissue hypoxia correlate with poor outcome.

Tissue levels of oxygen correlate with CBF trends 90% of times(Jaeger, 2005) but, presence of critical tissue hypoxia has been observed in symptomatic patients with rCBF above ischaemic threshold in upto 25% cases(Sarrafzadeh, 2010).

In COSBID trial, exploring cortical spreading depolarisations(CSD) in SAH, brain tissue hypoxia has been positively linked to frequency of CSD followed by a brief period of hyperoxia, the duration of which negatively correlated with the frequency of CSD. This decline was more than that explained by cortical spreading ischaemia and co-attributed to the increased metabolic demand due to CSD.

Therapeutically, cerebral blood flow and oxygenation do not always correspond. Increasing cerebral blood flow with hypervolaemia is associated with decrease of tissue oxygenation while raising it with hypertension leads to improvement (Muench, 2007). Histological changes (changes in dendritic structures and loss of spines) during CSD are comparable to those during anoxic depolarization. Increasing oxygen availability without affecting blood flow shortens the duration of CSD and improves local redox state (Takano, 2007).

The role of hyperbaric oxygen therapy in ameliorating DIND has been demonstrated in experimental setting however its clinical application is not yet possible (Matchett, 2009).

Thus oxygen availability changes independent of CBF in patients with SAH and has pathogenic and therapeutic implications in DIND which remain to be fully explored.

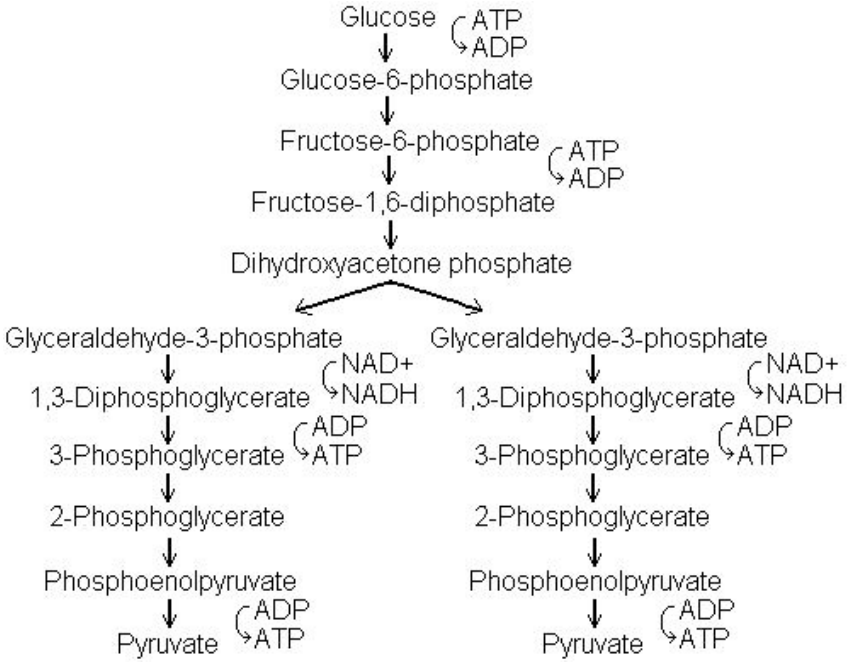
Energy metabolism-

Before we explore metabolism in DIND, here is a brief overview of basal cellular metabolism and the current understanding about the layout of these processes in brain cells to facilitate better appreciation of pathophysiology in DIND-

In any cell, glucose is required for catabolic and anabolic processes. The catabolic pathway produces energy and anabolic pathway uses glucose as a building block for proteins and nucleic acids. Catabolism of glucose to produce energy is divided into cytoplasmic (=anaerobic = glycolysis) and mitochondrial(=aerobic = Kreb's tricarboxylic acid cycle) components. The anabolic process involves pentose phosphate pathway.

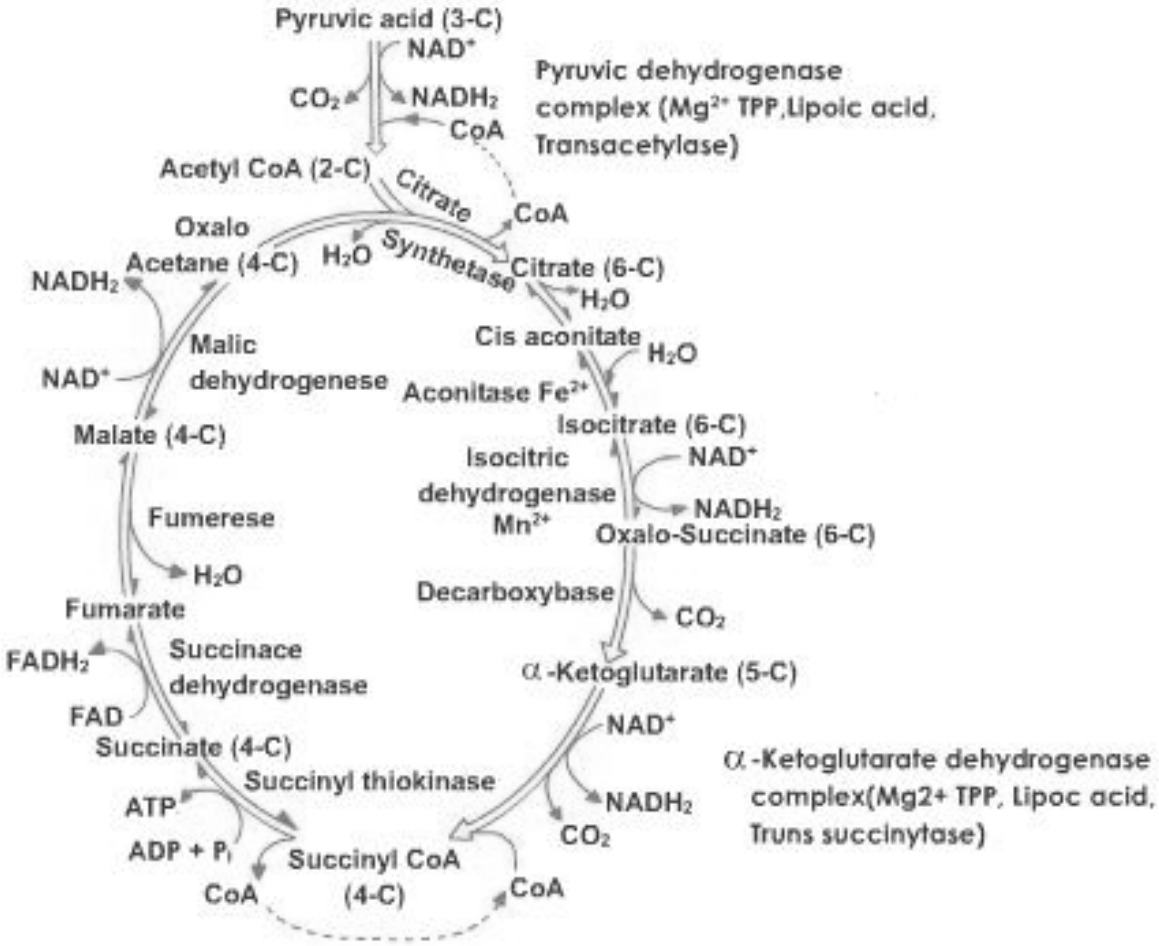
Glycolysis is the first step involving breakdown of a 6 carbon sugar(glucose) to a 3 carbon structure(pyruvate) with release of 2 mols of ATP and generation of 2 mols of reducing equivalents –$NADH^+$ as seen in the figure below-

Fig.1.41: Glycolysis: Breakdown of glucose to pyruvate generating 2 mols each of ATP and NADH

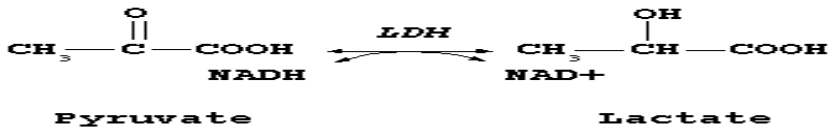


Pyruvate so obtained either enters mitochondria where it is fully metabolized to carbon dioxide and water via Kreb's tricarboxylic acid cycle-

Fig.1.42:TCA.cycle:Metabolism of pyruvate generating 4 $NADH^+$, 1$FADH^+$ and 1 ATP per pyruvate molecule metabolized. The reducing equivalents then enter the mitochondrial electron transport chain generating ATP. Every mol glucose generates 6 mols of ATP from glycolysis and 30 mols from Kreb's cycle.



Or, remains in the cytosol in equilibrium with lactate to regenerate NAD for glycolysis.



Fate of pyruvate depends on cell type, energy need and substrate supply.

Cerebral metabolism can be divided into glial and neuronal metabolism. Neuronal metabolism claims >60% of brain energy need with maintenance of cellular ionic milieu and synaptic transmission accounting for upto 80% of energy expenditure. Therefore upto now, most of the brain metabolic picture was equated to neuronal metabolism. However in recent years the glial metabolism has proven to be an active and complementary player in neuroenergetics (Pellerin and Magistretti, 1994).

Brain utilizes glucose as the primary energy source and both neurons and glia have the cellular architecture for glycolysis and tricarboxylic acid cycle. But, both cell types have different inbuilt preferential pathways for how they use their energy substrates. While neurons require more energy and mainly rely on oxidative metabolism, they prefer to use lactate as Krebs' cycle substrate in case of increased need and reserve glucose for pentose phosphate pathway, also crucial for neuronal maintenance and function. On the other hand astrocytes rely on glycolysis and excrete lactate as their metabolic byproduct. This is diagrammatically better explained in the figure below-

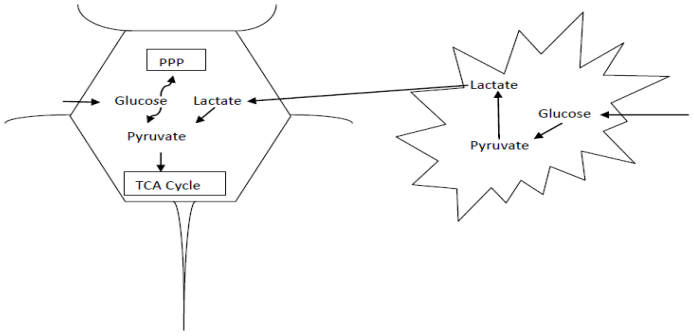


Fig.1.43:Glio-Neuronal Lactate Shuttle and basal metabolic pathways in glia and neurons.
Glycolysis happens in both glia and neurons. In neurons glucose is also needed for pentose phosphate pathway(PPP). Also neurons heavily rely on oxidative metabolism via tricarboxylic acid cycle(TCA) for their abundant energy needs. For this, they also use up lactate borrowed from glia via lactate shuttle to supplement pyruvate generated from neuronal glycolysis.

The overall respiratory quotient for brain remains 1, i.e. all net glucose entering brain is completely metabolized with oxygen to water and carbon di-oxide. Thus cerebral metabolism can be measured by indirect methods - assessing cerebral oxygen extraction fraction(OEF) which measures the difference between arterial and venous oxygen concentration and escalates in states of ischaemia to maintain a constant metabolic rate, or by measuring cerebral metabolic rate of oxygen consumption (CMRO2) which is the product of cerebral blood flow and oxygen extraction fraction; or by direct measurement of metabolites chiefly lactate and pyruvate in interstitium as carried out in microdialysis.

OEF and CMRO2 can both be measured either invasively whereby sampling from major vessels gives a global estimate of oxygen use or noninvasively using positron emmission tomography (PET) whereby a regional estimation is possible.

Cerebral metabolism in DIND:

Most of earlier understanding about the course of cerebral metabolism in DIND comes from PET studies investigating CMRO2. As mentioned previously, metabolic suppression is seen in all patients in the first few days after SAH(Hayashi, 2008). CMRO2 was noted to decrease out of proportion to CBF in the pre-spasm period, with an unchanged oxygen extraction ratio; thereby indicating a primary metabolic pathology (Carpenter, 1991). Grubb(1977) noticed that this decline was proportional to the severity of angiographic spasm and neurological deterioration.

Kawamura(1992) and Voldby(1985) have shown that in the 2nd week, there is coupling between CBF and metabolism, where in asymptomatic patients a gradual recovery of both CBF and CMRO2 has been observed but a decline noted in CBF and CMRO2 in symptomatic patients. This finding, however, has not been substantiated by Carpenter (1991) who noted increase in regional OEF with angiographic spasm (decreasing CBF), without affecting CMRO2 in similar setting. Comparing symptomatic and asymptomatic

patients, Kawai (2008) did not find significant difference in CMRO2. Just comparing patients with angiographic spasm Novak(2002) found that asymptomatic patients had hypermetabolism while symptomatic spasm was accompanied by hypometabolism. This was further supported by a decline in FDG glucose uptake, another indicator of metabolism, seen in severe cases of DIND by the same group (2006). Clinically significant metabolic derangements occured above the ischemic threshold.

While a study of OEF/CMRO2 provides an estimate of metabolic rate, it does not offer an understanding of metabolic processes. In the last decade, with the advent of microdialysis, the emphasis has moved on to explore the energy metabolites in closer detail to enable a better understanding of the processes involved in DIND.

5 compounds have taken the centre stage- glucose (the energy substrate), pyruvate (marker for aerobic metabolism), lactate (marker for anaerobic metabolism), glutamate (excitatory amino acid) and glycerol (marker for cell membrane damage). Sequential studies showed that lactate and lactate-pyruvate ratios were higher in DIND and preceded symptoms in 83% patients. Correlation with rCBF and symptoms revealed that glutamate and glycerol related most closely to decreased rCBF on PET. Lactate and glutamate rose early in symptomatic ischemia with a sustained ischemia leading to rise in lactate/pyruvate ratio. These changes were present at rCBF levels above threshold of 20ml/100g/min. Lactate/pyruvate ratios were most specific for indicating clinical ischaemia followed by levels of lactate and glutamate; the diagnostic specificity being 0.89(high). Glycerol indicated cell disintegration. It did not rise in reversible DIND patients but did in AIND (acute ischaemic neurological deficit) patients. Microdialysis changes were related to vascular territories. The clinical features improved with Triple H therapy but metabolic changes persisted (Schulz, 2000; Sarrafzadeh-2002,2004,2005). The microdialysis studies do not concur with PET data and are not self explanatory. The analysis of microdialysis metabolites has been geared to detect ischaemic changes, and

is not exploratory in nature. While rise of lactate is observed in DIND, a similar temporal trend, albeit with lower values, is observed in asymptomatic patients. Lactate/pyruvate ratio thresholds vary among different studies. Though the ratio is significantly higher in AIND as against asymptomatic and DIND patients, this difference is not found between DIND and asymptomatic patients. If lactate/pyruvate ratios are specific for DIND indicating anaerobic metabolism, these should be associated with low CBF or oxygenation, which again, has not been demonstrated.

Thus, all that can be concluded at this stage is that metabolic disturbances commonly occur after SAH and demonstrate variable interdependence with CBF, oxygenation and symptoms in these individuals.

Ionic disturbances-

Changes of the ionic milieu, mainly sodium (Na^+), magnesium (Mg^{++}), calcium (Ca^{++}) and potassium (K^+), seem to play an important part in neuronal activity and metabolism. In particular, Ca^{++} and K^+ seem to be involved in the patho-physiological processes underpinning DIND. While Ca^{++} is the final effecter of intracellular ischaemic damage and cell death, K^+ seems to play a role in pathogenesis.

Temporal profile of K^+ channel dysfunction suggests upregulation of voltage dependent and inwardly rectifying channels in the cerebral vascular smooth muscles in the first week following SAH, maximum dysfunction in ion transport proteins and conductance happening around day 7(Jahromi, 2008). Loss of K^+ homeostasis leads to depolarization and contraction of vascular smooth muscle culminating in angiographic spasm. Potassium channel antagonist Cromakalim is currently being investigated for treatment of vasospasm(Omeis, 2009; Kwan, 2000).

Besides, recent studies reveal that nitric oxide scavenging by hemoglobin or nitric oxide synthase inhibition by N-nitro-L-arginine induces cortical spreading ischemia when K+ is increased in the subarachnoid space, thus mediating CSI(Dreier- 1995,1998).

Increased K^+ also upregulates glucose metabolism by causing a shift in respiratory state (Nicklas, 1971) and regulation of Na^+ -K^+ gene expression by hyperoxia in MDCK cells serves to decrease metabolic demand (Wendt, 1998).

A detailed study of diagnostic, prognostic and therapeutic potential of potassium homeostasis in SAH has not been undertaken.

1.5 Neuromonitoring techniques

Animal / in vitro / autopsy studies have traditionally been the main source of information about cerebral pathophysiology during SAH. With recent advances in the neuromonitoring tools and techniques, the focus has now shifted to realtime monitoring of patients to obtain most clinically relevant first hand information. This chapter gives an update on current neuromonitoring tools and techniques.

The most basic neuromonitor is perhaps the intracranial pressure monitor. However its relevance in SAH patients has not been shown and is not a standard tool used in this patient group hence will not be further discussed here. Also, tools that provide general information about the patient i.e. mean arterial pressure, central venous pressure and jugular venous oxygen saturation are pretty standard and will not be described here. Instead in this chapter we will focus our attention on measurement of cerebral haemodynamics, oxygenation, metabolism and ionic concentration.

Techniques to measure CBF:

The first quantitative measurement of cerebral blood flow was attempted by Kety and Schmidt in 1945. They used Fick's principle to measure arteriovenous difference in concentration of inhaled inert gas -nitrous oxide. This was an invasive technique requiring jugular venous cannulation and provided the estimate of global cerebral blood flow. Subsequently the technique was modified, mainly by Ingvar and Lassen in 1961, who used clearance of radioactive substrates to measure focal values and highlight inhomogeneity of cerebral blood flow. Since then measurement techniques have improved. Some are snapshot techniques, that is, they make a one off measurement at a point of time chosen by the investigator, for example, using various radiographic tools. These can only provide one-off measurements as the patient has to be transported to

radiology suite for the test. These techniques provide an overview of temporal trends by obtaining snapshot views at different user defined time points. Others are continuous methods that record the complete clinical picture including clinical events. These techniques are bedside, however, most such techniques are invasive.

Of particular relevance of the two ways to measure CBF are the following, classified as per the data provided into snapshot techniques and continuous bedside techniques-

Snapshot Techniques-

SPECT- This is an imaging technique utilizing gamma rays. It involves injection of a radioisotope whose activity is captured through a gamma detector. Breakdown of this activity gives values of CBF in grey and white matter as well as in different areas of brain.

Stable Xenon enhanced CT- This technique is further evolution of diffusion/clearance principle and is accepted as a standard technique for quantification of global and regional CBF for patients with DIND. 26 to 33 percent stable inert gas xenon is inhaled as a xenon-oxygen mixture, this has affinity for lipid containing cerebral tissue and its clearance can be sequentially measured as it alters the density of the pervading cerebral tissue.

CT perfusion- The technique is a kinetic measurement of cerebral blood flow that utilizes intravenous injection of iodinated contrast material. Serial CT imaging is then undertaken to capture the flow of contrast through cerebral blood vessels. It’s the most recent tool for CBF measurement and due to its ease of use is the most widely used technique. Besides regional CBF it allows estimation of cerebral blood volume and mean transit time, albeit in previously specified limited area of brain tissue to contain radiation dose.

PET- Although expensive and not so widely available, positron emission tomography is a further refinement of perfusion CT principle. It utilizes metabolically active radioactive

substrate (glucose: FDG-18) that not only assesses CBF but also metabolic activity through measurement of CMRO2.

Diffusion and Perfusion MR- Magnetic resonance imaging (MRI) has been employed in measurement of CBF since early 90's. These methods are particularly useful for the radiological differentiation between ischaemic regions and penumbra and thus identify "tissue at risk". Being radiation free, availability of portable MRI scanners at the bedside is a possibility being explored in some units. However, the MR techniques are still to find widespread clinical use in assessment of DIND.

Continuous/Bedside methods-

Transcranial doppler (TCD) is the most widely accepted bedside method for measuring CBF. Two more portable methods – laser doppler flowmetry (LDF) and thermal diffusion flowmetry (TD); that offer assessment of CBF have been introduced in the last decade. They are still being used in the research context and usefulness in clinical setting needs to be established.

Transcranial doppler- This is a portable noninvasive indirect method that involves measurement of flow velocities in major cerebral vessels to provide an estimate of CBF where high blood flow velocities indicate vasospasm.

Due to ease of use and bedside availability, the technique had gained widespread popularity. With recent metaanalysis showing poor sensitivity, specificity and operator dependence of TCD data, both for angiographic spasm and DIND, this method has fallen into disrepute.

LDF- Laser doppler flowmetry (LDF) is an invasive technique involving placement of a probe that emits monochromatic laser light and measures the doppler shift caused by movement of red blood cells. The magnitude and frequency distribution of the wavelength changes are directly related to the number and velocity of red blood cells but unrelated to the direction of their movement.

LDF is a good tool for continuous real time monitoring of cortical CBF but it is not a quantitative measure of CBF and the probe is prone to artefacts from patient movement and probe displacement.

TD – Thermal diffusion flowmetry (TD) uses the principle that thermal conductivity of tissue varies proportionally with blood flow. The technique consists of inserting a probe with two thermistors in the region of interest. The distal thermistor heats up the brain 2 degree above ambient temperature. The proximal thermistor measures the power dissipated in doing so and thus gives a quantitative estimate of regional perfusion. Animal studies by Vajkoczy et al(2007) revealed that TD microprobes provide continuous real-time assessment of intraparenchymal regional blood flow that was comparable with measurement by xenon-enhanced CT. TD flowmetry was characterised by more favourable diagnostic reliability and was reported to be more sensitive than TCD ultrasonography in assessing patients with reversible vasospasm following intra-arterial injection of papaverine in patients with SAH.

Values of normal CBF and ischaemic thresholds: With extrapolation from animal data and studies in volunteers and stroke patients, the normal CBF was established at 80-100mls/100g tissue/min. for grey matter and 25mls/100g tissue/min for white matter. Threshold for irreversible damage was defined at 8ml/100g tissue/min and that of penumbral tissue at 20ml/100g tissue/min. The thresholds vary slightly with the technique used for measurement. Although in animal studies time elapsed since severing of blood flow is of paramount importance apart from perfusion values, in human studies such a relationship is not very distinct.

Techniques to measure brain tissue oxygen:

Tissue oxygenation can be measured using one of the following measures, classified again as snapshot and continuous.

Snapshot methods-

PET:OEF- This technique involves administration of radiolabelled oxygen ($^{15}O_2$) and carbon monoxide ($C^{15}O$) species to calculate oxygen extraction fraction(OEF) by Fick's principle. While the technique can be used for simultaneous estimation of cerebral blood flow, cerebral blood volume and cerebral metabolic rate of oxygen, it involves transporting the patient to the scanner and only offers snapshot view.

PET:(18) F-FMISO uptake-This is another estimate of tissue oxygenation using PET scan. It involves administration of tracer 18F-Fluoroimidasole that is reduced as it enters the intracellular compartment. Cellular oxygen oxidizes it back to original form which escapes extracellularly and thus intracellular retention of the compound serves as a marker of tissue hypoxia. It suffers the same limitation as calculation of OEF.

Continuous methods-

Licox- This is an invasive tool, that involves placement of probe (electrode) to measure the redox state of tissue and thus estimate its oxygen content. It is the most widely established equipment for continuous bedside real time monitoring. Values of oxygen in normal and diseased tissue using licox, as well as correlation with CBF measurements are well explored.

Paratrend- This is another invasive technique that incorporates optical fibre technology for simultaneous estimation of oxygen, pH and carbondioxide. It is not affected by redox state of the tissue and thus the values are less likely to be influenced by presence of other ions, unlike licox. However the tool is not so widely explored, established and available.

INVOS- This is a non-invasive technique. It utilizes near infrared spectroscopy (NIRS) for estimation of cerebral tissue oxygen. Though it offers non-invasive monitoring, it suffers from the usual problems encountered in NIRS technique i.e. noise and being able to monitor only surface oxygenation. This tool again has not been fully explored, established and available.

The normal values vary as per the method used.

Techniques to measure cerebral metabolism:

Two techniques are used to measure cerebral metabolism- PET and Microdialysis.

PET- As mentioned above positron emission tomography is a magnetic resonance imaging technique in which radioactive oxygen species $^{15}O_2$ is administered to measure cerebral metabolic rate of oxygen i.e. rate of cerebral metabolism. The advantage of the technique is that with certain modification it can be used to measure CBF, CBV and OEF simultaneously. The downside is that the patient has to be taken off the unit and it only gives a snapshot view. CMRO2 in normal tissue is around 44 micromol/100g/min.

Microdialysis- It is an invasive technique to monitor chemistry of extracellular space. It consists of a probe containing a semipermeable membrane with a pore size suitable to allow permeation of metabolites as well as neurotransmitters. The probe is inserted in the region of interest. A perfusion fluid similar in composition to normal tissue fluid is pumped at a slow rate at one end and the dialysate is collected at the other. The technique offers a continuous real time monitoring and has been utilized for exploring neurophysiology for over 30 years, however, with need for establishing robust clinical correlates of microdialysis findings, the technique still remains a research tool (Goodman,2009).

Techniques to measure ion concentration:

Currently microdialysis is the only technique that enables measurement of ions. As opposed to measurement of metabolic substrates, the measurement of ionic concentration is relative, as the microdialysis fluid contains these electrolytes in concentration similar to normal CSF. This leads to some buffering effect, the magnitude of which depends on the rate of infusion. There are standard values to compare at different rates available from previous studies. Unfortunately the microdialysis machine does not provide ionic measurement option. This can be done in frozen microdialysate samples. The samples need to be transferred from microdialysis vials to airtight containers and frozen quickly after collection to avoid any volume loss. Techniques available for subsequent measurement include- enzyme immunoassay, flame photometry and ion chromatography. Most recently Bhatia (2010) developed a flow cell for use with online microdialysis. This flow cell is not commercially available and currently only measures potassium ion concentration. Further work is underway to improve ionic monitoring in future.

1.6 Treatment of Delayed Neurological Deficit-

For decades haemodynamic management has remained central to treatment of DIND. Traditionally this has been administered as triple H therapy -raising systemic blood pressure and reducing blood viscosity. It was initiated in 1951. The practice, haemodilution, hypervolaemia and hypertension gained popularity in the 1970's and is now well established in the management of SAH after definitive treatment of the aneurysm. This therapy is recommended by Stroke AHA guidelines on management of SAH, the evidence to support triple-H therapy at best being Level B.

Systematic review failed to ascertain good quality evidence that prophylactic triple-H therapy improves outcome in the treatment of vasospasm secondary to SAH(Treggiari, 2003).

Evaluation of this therapy for treatment suffers a few limitations: the parameters that define DIND, that guide triple H therapy as well as the outcomes measured are not uniform. The role of each component of the therapy is unclear and the techniques and timing of institution of the therapy remain heterogenous. Moreover, numerous arbitrary values of circulating blood volume, systolic/mean blood pressure and hematocrit have been used as target parameters to direct triple H therapy. Without an insight into the impact on cerebral physiology, achieving these parameters has been a number chasing exercise. Even with administration of fluids, the attainment of hypervolaemia and adequate haemodilution is difficult. The sample size in most studies is small and there is a lack of control group, whereby, it is difficult to ascertain the effects of administering the therapy against the natural course of the disease. As such, the combined evidence from these studies suggests that triple H therapy is probably effective for treating DIND (Bederson, 2009).

The complications associated with this therapy are major, including worsening cerebral edema, haemorrhage into ischaemic brain, pulmonary edema and myocardial infarction; and are specific to the way the therapy is instituted. As such, further studies have explored effects of individual components of triple H on cerebral blood flow, tissue oxygen and metabolism.

A systematic review to assess studies evaluating individual component efficacy was recently undertaken(Dankbaar, 2010). This demonstrated that-

- Haemodiltion did not confer any physiological benefit in any study.

- In 1 of seven studies evaluating effects of therapeutic hypervolaemia, a significant improvement was noted in cerebral blood flow(Jost,2005). Largest RCT to study effect of normovolaemia v/s hypervolaemia during prophylaxis and treatment phases showed no symptomatic benefit. Prophylactic hypervolaemia increased cerebral blood flow but decreased tissue oxygenation.

-Hypertension has most consistently been associated with improvement in cerebral blood flow and oxygenation. 3 out of 6 studies evaluating hypertension with or without other components of triple H therapy observed benefit.

That hypertension is probably the most significant of the three H's, is also supported by physiological studies wherein induced hypertension has been shown to improve CBF and oxygenation (Treggiari, 2009).

Effects of triple H therapy on metabolism are less explored. In studies evaluating metabolism with cerebral microdialysis, while concomitant clinical features improved with the therapy; it did not cause any significant reversal of lactate values or lactate/pyruvate ratio (Sarrafzadeh, 2002).

Nevertheless, conducting a randomized controlled trial (RCT) to ascertain effectiveness of triple-H therapy is not a practical proposition. The ethical considerations of withholding such a well-established mode of treatment are multifaceted; no matter how inadequate the evidence.

Alternative treatments include cerebral angioplasty and/or intra-arterial vasodilator therapy. These treatments are supported by inferior level of evidence and as of yet, their use is restricted to triple-H non-responders. A randomized controlled trial is ongoing to compare primary angioplasty v/s triple-H therapy. Treatment with magnesium, statins and anti-inflammatory drugs like IL-1RA and autonomic block induced by stellate ganglion blockade are other alternatives that are still in research phase (Connolly, 2012).

1.7 Cognitive and Functional Outcome after SAH

Overview

In addition to physical disability, various studies have indicated that between 50% (Longstreth et al 1993) to 94.6% (Passier et al 2010), of aneurysmal subarachnoid haemorrhage (aSAH) patients are left with significant cognitive deficits. ASAH patients may experience deficits in verbal and non-verbal memory, psychomotor speed, executive function and visual-spatial function (Kreiter et al 2002). 50-60% of survivors who were in employment pre-haemorrhage, do not return to the same level of work (Buchanan et al 2000, Hackett et al 2000). It is unclear how these neuropsychological sequelae translate into substantive health outcomes for the patient such as health-related quality of life (HRQoL) and disability(Hackett and Anderson 2000)

Assessment of mild deficits after subarachnoid haemorrhage

Most studies in the field of aSAH and vasospasm are often restricted by limited outcome evaluation. The majority of studies and trials have utilized either the Glasgow outcome scale(GOS) or the modified Rankin score(MRS) to assess outcome. The former is a crude scale of 1 to 5 representing a spectrum from death to good outcome. Although the latter offers more categories of disability, it has been shown to give a disproportionate weighting to physical disability with inadequate sensitivity to detect the subtle cognitive deficits that are apparent following aSAH. (Kim et al 2005) Neuropsychological assessment following aSAH has been performed in small cohorts of patients. (Bellebaum et al 2004; Berry et al 1997; Fertl et al 1999; Hadjivassiliou et al 2001; Hutter and Gilsbach 1993; Hutter et al 1999) Although it is clear that neuropsychological impairment occurs following aSAH, no clear pattern of change has emerged and the deficits often vary considerably. Cognitive impairments have been observed for verbal and visual

memory. (Bellebaum et al 2004) There is controversy as to the type and extent of executive dysfunction that may occur. In particular, verbal fluency, concept formation, reasoning and cognitive estimation have been shown to be deficient by some authors but not by others. (Bellebaum et al 2004)

In a recent systematic review of most stroke trials and studies it has been shown that there is no consistency in the type and timing of outcome measures utilized. (Duncan et al 2000) It was thought that measures of impairment are often the best indicators of prognosis although primary outcome measures should always be measures of disability and activity (due to the patient's concern with activity). It was also noted that most outcome measures are not designed specifically for stroke victims. There have been numerous attempts to assess long-term outcome following ASAH. (Buchanan et al 2000; Dombovy et al 1998; Dunne and Besser 2005; Hackett and Anderson 2000; Hellawell et al 1999; Hop et al 1998; Kim et al 2005; Kreiter et al 2002; Longstreth et al 1993; McKenna et al 1989; Ogden et al 1993) Earlier studies have failed to highlight the significance of long-term neurocognitive deficits following aSAH. (McKenna et al 1989) Subsequent studies have since highlighted the importance and need for functional and neuropsychological outcome assessment following aSAH. (Dombovy et al 1998; Hop et al 1998)

1.8 Summary and aims

Whatever the mechanism- vasospasm, early brain injury, cortical spreading ischaemia, inflammation or microthrombosis, the impairment of cerebral blood flow is understood to be the primary pathophysiology leading up to ischaemic tissue damage. However, as seen above, studies of CBF reveal that low perfusion values are not by themselves sufficient to cause DIND and symptoms of DIND do occur with cerebral perfusion above ischaemic threshold. The values of tissue oxygenation change independent of CBF. Most importantly, energy metabolites do not follow CBF or oxygenation and these are most predictive of DIND. As a result of DIND, these patients are left with significant physical, cognitive and functional deficits. But, outcome assessment scales routinely used for aSAH (DIND) measure only physical disability at discharge or at best at 6 months.

Current literature lacks studies that concomitantly assess CBF, tissue oxygenation and metabolism in real time in awake patients so as to enable a clinical correlation of changes in cerebral pathophysiology in DIND. Current outcome measures used for this patient group are crude scales and do not give a full picture of subtle cognitive and functional deficits experienced by these patients that impede return to social and economic productivity.

Failure to understand pathophysiology of the condition and realize the full spectrum of disabilities experienced by these patients are responsible for the poor outcome in these patients despite technical advances. The aim of this work is to address these two issues.

-To elucidate physiological variables during course of DIND to explore the pathophysiology of the process

- To explore functional and cognitive deficits after aSAH by administering a battery of patient reported outcome scales, thereby better understand the correlation

between different components of health status in aSAH patients and to derive a set of tools that will help easy, uniform and early identification of subtle but clinically significant neuro-psycho-social deficits in this patient group to guide appropriate management and rehabilitation.

Chapter 2

Exploration of DIND Patho-physiology

This chapter describes the first part of my work. It elucidates the patho-physiology of DIND and assesses the effect of current therapy for DIND on cerebral physiology in patients with aSAH.

2.1 Introduction:

Cerebral physiology is a complex, delicately balanced web of interactions between blood flow, substrate availability, metabolic pathways and glio-neuronal activity. In this study we are focussing our efforts to identify patho-physiologic changes that lead up to DIND.

2.2 Methodology

The idea for this study grew from a lack of good evidence that the neurological deficit developing after SAH has an ischaemic basis. Put simply, the assumption in treating with triple-H therapy is that poor blood flow leads to decreased oxygen availability and anaerobic metabolism. This in turn leads to relative cellular ischaemia which manifests as DIND. To understand if this is what actually happens during DIND and thus prove/disprove current hypothesis, one would need to measure baseline blood flow, demonstrate a symptomatic decline in the baseline CBF, leading to a decline in oxygenation and a shift towards anaerobic metabolism; all of which should revert to baseline values with institution of effective therapy. In an ideal scenario, we would know the normal values of these parameters in awake patients, they would be more or less stable through the asymptomatic phase and clearly distinct from pathological values- which would also be known and whereby it would be easy to prove or disprove the current hypothesis by measuring these values in baseline and symptomatic patients as well as after institution of treatment through a study of continuous monitoring of all parameters. However, in reality, such clear transitions do not exist implying insufficient information on cerebral pathophysiology, including even normal levels, to draft a study with adequate sample size that can test the current hypothesis. So, we decided to use concurrent continuous monitoring of all cerebral physiological parameters in awake patients as a pilot study to try not only to decipher the inter-relationships of various physiological changes before, during and after DIND, but also to demonstrate the feasibility of making such measurements in awake patients, the recruitment rate for such studies and the level of between and within subject variability of various measurements made. Such monitoring will provide information on temporal changes in cerebral physiological parameters and interactions thereof with clinical correlation, thereby either

supporting the accepted hypothesis in causation of DIND or generating an alternative proposition.

Since DIND develops when the patient is already in hospital, such prospective observational study was possible. The monitoring was planned to cover time epochs- prior to onset of DIND, during symptomatic phase of DIND and with treatment. The tools chosen for monitoring were Hemedex (thermal diffusion probe) for CBF, Licox (Clark type electrode) for oxygenation and Microdialysis (CMA 100 probe) for metabolism. The mode of action of these tools is detailed in chapter 1. The reasons for tool selection are discussed under section 2.3.

The remaining part of this section describes an overview of the methodology employed for this work including details of location, research group, ethical approval, funding, recruitment- subjects, inclusion and exclusion criteria, standard operative procedures – protocol for management of aSAH patients, data collection, processing and analysis and a flow chart for the study group.

Location

This study took place in Leeds General Infirmary. The hospital is an acute teaching unit with close links to the University of Leeds and encompasses the regional neurosciences services for West Yorkshire serving a population of nearly 3.2 million people. A dedicated CT and MR scanner in addition to an angiography suite provide neuroimaging facilities for this patient population. The unit boasts a dedicated neuro-HDU and neuro-ITU which is where the aSAH patients are cared for in the acute phase. Neuro HDU and ITU were therefore the setting for this study. Advice and feedback was sought from ITU and HDU staff at various stages during the drafting of the study protocol. Prior to recruitment in the study, the medical and nursing staff on both these units were formally briefed and trained about the study including the care of and reading from monitors. The

author was responsible for any clinical/technical support needed regarding care of monitors and monitoring equipment.

Research Group

The research team for the study comprised of the Leeds Neurovascular Research Consortium. I was responsible for conduction and coordination of all aspects of the study. Supervision was provided by Dr. Audrey Quinn (Consultant Neuro-Anaesthesia and Neuro-Intensive Care) and Mr. Stuart A. Ross (Consultant Neurosurgeon and Principal Investigator). Help and advice was obtained from senior research fellow in the team, Mr. Al-Tamimi. Dr. Leong, research fellow at Imperial College London conducted the lab-based analysis for potassium ion concentration in microdialysate samples. Dr. Martyn Boutelle, Professor of Biomedical Sensors Engineering at Imperial College London, supervised this analysis.

Ethical Approval

Ethical approval was obtained from the Leeds (West) Research Ethics Committee. {REC reference number- 08/H1307/133}.

R&D approval and sponsorship was obtained from Leeds Teaching Hospitals NHS Trust. {LTHT R&D number- NS08/8757}.

Funding

Part funding in the form of 15 licox probes was obtained from Integra Neurosciences. They did not have any input or influence whatsoever in the preparation or dissemination of the study results.

Rest of the study was funded by the Neurosurgical Research Fund administered by the Leeds General Infirmary Trustees on behalf of the Neurosurgical department.

Recruitment

Subjects-

All patients admitted to the LGI were eligible for recruitment to this study if they were 17 years or over, with confirmed aneurysmal SAH within first 3 days of symptom onset. Complete eligibility criteria are detailed below:

Inclusion Criteria-

- Adult patient -17years and above, irrespective of sex and race
- Aneurysmal SAH confirmed on CT and CTA/DSA
- Recruitment prior to day 3 post haemorrhage, i.e., prior to onset of DIND
- Fisher Grade 3/4/3+4, poor WFNS grade, rebleed- implying high risk for developing DIND
- Written informed consent/assent

Exclusion criteria-

- Coagulation disorders- making patient likely to have complications with invasive monitoring
- History of pulmonary edema/congestive cardiac failure- making patient unsuitable for triple H therapy

Patient Identification and Enrolment-

Recruitment commenced in May 2009 and continued until July 2010. Patients with SAH were referred to neurosurgical registrar on-call at LGI either through LGI-A&E or from peripheral hospitals within West Yorkshire region. All such patients were admitted within 24 hours of initial referral, subject to bed availability.

All referrals were discussed at the neurosurgical referral review meeting next morning. The author attended these meetings and was thus alerted to all new referrals.

The cases were subsequently discussed with neuroradiologists to confirm the Fisher grade and presence and location of aneurysm as per CTA.

If the patient met all eligibility criteria, then he/she was approached by the research fellow to ask if they were interested in taking part in the study. If they expressed an interest, further details including purpose of study, what it entails and risks involved were discussed in detail. An information sheet with contact details for the research team was given to the patient and they were given time to consider the information and reach a decision. If the patient had altered consciousness, the patient's family were approached and similarly counseled for study participation.

In case a patient had a negative CTA and was proceeding for formal angiogram to confirm presence of aneurysm, they were approached and consented prior to DSA, as they would normally proceed to coiling in the same anaesthetic, with no time to consent in between. They were informed that they shall not be recruited if the DSA was negative.

Consent/Assent-

Patients willing to participate in the study were requested to confirm this in writing (patient information sheet and consent form attached).Written informed assent was sought from relatives in those cases where altered conscious state prevented consent being obtained from the patient. A copy of the consent form was given to patient, second copy filed in clinical case notes and third copy retained by the research fellow.

A screening-log was maintained that had records of all eligible patients and stated whether or not they were recruited with any reasons for exclusion.

Standard Operative Procedures

Diagnosis-

Since only high Fisher grade (see Appendix) patients were included in the study, the diagnosis of SAH was based on clinical presentation and confirmation of blood load on CT. The Fisher grade was decided in consultation with neuroradiology consultants and documented in the electronic case report forms. Aneurysm presence, site and size were confirmed based on CTA or DSA.

Hourly clinical assessments were performed throughout the study period. Diagnosis of DIND was clinical based on criteria mentioned in previous chapter, i.e.-

- Persistent (>1hr) drop in GCS by more than 2 points or development of new focal neurology not attributable to any other causes with or without development of hypodense areas on CT scan,
- Or in case of sedated patients, development of new hypodensity on CT scan not attributable to any acute cardiorespiratory event.

Acute deficits developing immediately following intervention or cardiorespiratory compromise were therefore defined and excluded as Acute Ischaemic Neurological Deficit (AIND).

Each episode of neurological deterioration was documented in electronic case report forms(CRF's).Every case with clinical deterioration suspicious of DIND was discussed with consultant neurosurgeon directly responsible for patient's care, independent of the study and any conflict of opinion regarding diagnosis was subsequently resolved following a discussion between the clinical and research teams. The final decision after this discussion was used to classify DIND and non-DIND patient groups in the study.

Surgical Management of aSAH patients

The first line management for aSAH patients in the LGI was endovascular coiling which was undertaken under the care of two experienced interventional neuroradiologists in a dedicated coiling suite. If this was not possible due to the location or shape of aneurysm, surgical clipping was carried out under care of experienced vascular neurosurgeons. Also, in cases deemed difficult for coiling, consultant neurosurgeon was available on standby. Both the procedures were carried out under general anaesthetic, postoperative care was carried out in HDU/ITU as considered appropriate.

Definitive management for aneurysm was undertaken as soon as possible after ictus and ideally within 24 hours of admission. Any treatment decisions were discussed in detail with patient and family and relevant consent/assent sought.

Study Intervention-

Once consented for participation in the study, the 3 monitors were inserted with full aseptic precautions at the time of coiling or clipping under general anaesthetic through separate frontal twist drill burr holes on the side of the aneurysm. In case of midline (A-Com) or posterior circulation aneurysms, monitors were placed on the right side. They were placed by the research fellow only, who had received training in placement and care of monitors at specific courses in Amsterdam and Berlin. Regular wound checks were done by research fellow daily to pick up any early signs of infection.

Institution of further therapy was similar whether or not patient was a part of the study and was standardised as per the unit protocol detailed below:-

Hospital protocol for medical management of aSAH patients-

Stage 1

- Cerebral vasospasm has been suspected or diagnosed clinically and/or radiologically
- Discuss with Intensive Care Unit if GCS ≤ 8
- Give supplemental oxygen therapy to achieve arterial saturation (SpO2) > 93%
- Ensure electrocardiography, SpO_2, blood pressure monitoring
- CT scan to exclude differential diagnosis e.g. hydrocephalus
- Check electrolytes, full blood count, blood glucose
- Ensure patient is receiving Nimodipine
- Document baseline mean arterial pressure (MAP) and central venous pressure (CVP)
- Paracetamol 1g, if pyrexial (max. 4g/24 hours)

Stage 2: Hypervolaemia

- Commence fluid balance chart. Ensure urinary catheterization has been performed.
- Ensure adequate hydration. Maintain CVP ≥8mmHg.
- Fluid replacement –

  -Use 0.9% saline 3L per day – consider 1.8% saline if serum Na low or low-normal

  -Give 250ml colloid boluses e.g. Voluven to achieve positive fluid balance.

  -Consider blood transfusion if Hb<10.
- Observe for clinical response. If no/incomplete response when patient's fluid status has been optimised commence hypertensive therapy (as detailed below).

Stage 3: Hypertension

- Insert arterial line. Check baseline MAP
- Commence Noradrenaline infusion at 2mcg/min.
- Titrate Noradrenaline to clinical response (up to 10mcg/min). Aim to increase MAP upto 120mm Hg initially. Watch for bradycardia.
- If no response after 2 hours (having achieved a MAP of 120mmHg) set target for increasing MAP upto 130mmHg. May have to consider additional agents and referral to Intensive Care Unit (ICU)
- If patient has a history of pulmonary oedema or cardiac failure, or is already bradycardic consider dobutamine (2.5 to 10 mcg/kg/min). Watch for tachycardia, arrhythmias. May be given via dedicated peripheral cannula. Discuss with ICU.

If the patient develops any cardiorespiratory compromise, during therapy, medical management shall be altered as per advice of the clinician incharge and therapy shall be modified accordingly. All record of such changes shall be kept and the patient shall continue to remain in the study.

Data/Sample Collection

Demographic details for all patients recruited to the study were recorded along with history of smoking, hypertension and family history of aneurysmal SAH. Alongside, a number of clinical assessments- including presenting GCS, WFNS score, other presenting features including but not restricted to loss of consciousness, headache, vomiting, meningism, weakness, presence of concomitant hydrocephalus and comorbidities were documented. The timing of ictus and the type and timing of any interventions were also documented as was the Fisher grade on CT. Subsequent hourly

assessments of the clinical parameters as detailed above was regularly undertaken and documented as standard.

Besides, specifically pertaining to the study, the baseline values for MAP, CVP, regional cerebral blood flow, brain tissue oxygenation and metabolism were obtained before the patient develops symptoms of DIND. Changes to these values were monitored with development of symptoms and the response to therapy noted with institution of hypervolaemia and hypertension in that order. Monitoring was discontinued once permanent symptomatic reversal was achieved or if there were signs of therapy failure. If no symptoms developed, monitoring was discontinued on the fifth day post probe insertion as these probes are validated for 5 day readings and the risk of infection escalates past this time. At any time the patients could withdraw from the study, in such an event, monitoring was to be discontinued, probes removed and further management continued unchanged.

Hourly recording for MAP, CVP, pTiO2, GCS, focal neurology and temperature was done by the nursing staff on the modified (with space for pTiO2 recording) standard observation sheets available in neuro HDU and neuro ITU. The author transferred data from the sheets to a secured trust computer at the end of each day.

Any volume replacement or inotrope administration was also recorded on these observation sheets.

The continuous rCBF data was automatically stored in the hemedex monitor.

Microdialysis was run at a flow rate of 3micromoles/min. The author changed the vials every 6 hours. The pooled 6 hour sample was labeled and stored in dry ice for transport and subsequently at -80 degree freezer at Leeds University LIMM lab.

Data Storage

The initial data entry was onto excel spreadsheets on a trust computer, a copy was stored on an encrypted memory stick which was in possession of the author.

Data/Sample Processing and Analysis

Sample Processing-

This was only required for microdialysate samples. The microdialysis machine can analyse a maximum of four substrates per sample. Glucose, lactate, pyruvate and glycerol were chosen for this study as they would give an idea of substrate availability, anaerobic and aerobic metabolism and cell death respectively. As the analyzer machine was on loan and shared between 2 research centres at Leeds and Manchester, analysis of the pooled samples was performed in 4 batches and not real time. This was adequate for this study as the readings were not intended to alter clinical management.

The microdialysate sample was also processed for potassium ion concentration. This facility is not available on the company analyzer and was only feasible for this study at the Imperial College London laboratory, which is where the samples were subsequently sent for this in airtight vials maintaining the cold chain.

Data Processing-

This was required for the Hemedex data. At the end of monitoring (per patient), the minute-to-minute data with half hourly calibration intervals stored in local monitor was transferred to central hemedex laboratory that returned the processed data (corrected for calibration drift) as excel spread sheets. Hourly average from these spread sheets was taken to standardize the monitoring interval for the study and entered onto the master spread sheets.

Data Analysis-

As the sample size was limited, descriptive analysis was undertaken using SPSS and LabPilot software. This is further detailed in the results section.

A flow chart for the study is presented as under-

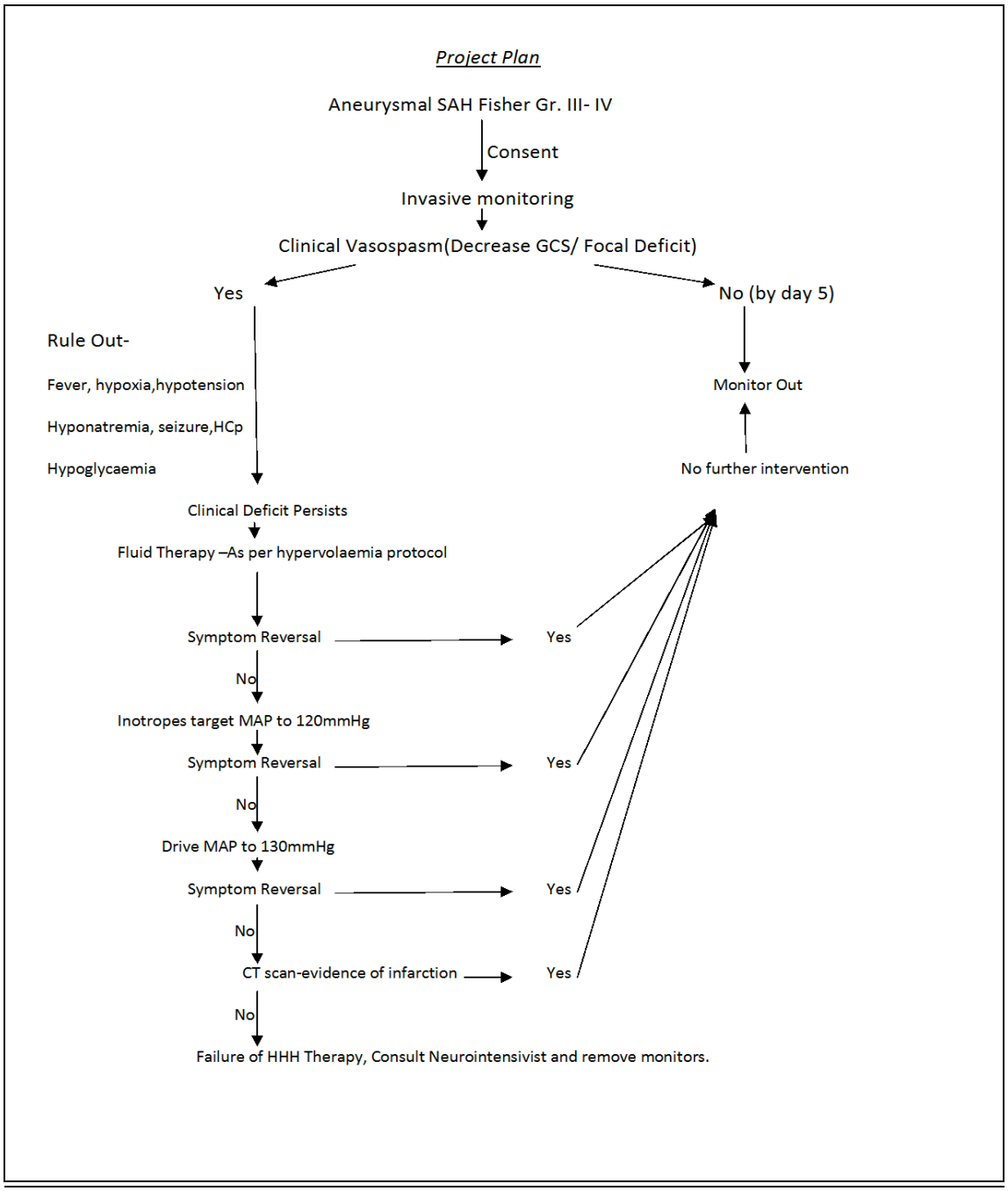


Fig.2.21:Flow chart showing patient pathway through the study

2.3 Results

Overview-

The pathophysiology study ran from May'09 to July'10. Of 43 eligible patients, 16 patients were recruited into this study. A site screening log is detailed as per table below.

Eligible patient serial number	Recruited	Reason
1	No	No catheters
2	Yes	
3	No	Another patient on trial- no monitors
4	Yes	
5	No	No consent
6	No	Haematoma –Fixed neurologic deficit
7	Yes	
8	Yes	
9	No	No catheters
10	Yes	
11	No	No consent
12	No	No consent
13	No	Another patient on trial- no monitors
14	Yes	
15	No	No consent
16	No	No consent
17	Yes- Cancelled	Unable to place catheter- LOTT
18	Yes	
19	No	No consent
20	No	No consent
21	Yes	
22	No	Consented for another study
23	No	No consent
24	Yes	
25	No	Another patient on trial- no monitors
26	No	Another patient on trial- no monitors
27	Yes- Cancelled	Unable to place catheter- LOTT
28	Yes	
29	No	Another patient on trial- no monitors
30	Yes	
31	No	No consent
32	No	No consent
33	Yes- Cancelled	Unable to place catheter- LOTT
34	No	No consent
35	No	No consent
36	Yes	
37	No	No consent
38	Yes	
39	Yes	
40	No	Another patient on trial- no monitors
41	No	No consent
42	Yes	
43	Yes	

Table 2.31: Site screening log DIND pathophysiology study(LOTT= Lack of theatre time)

Of 16, 2 patients died early, within hours of recruitment due to rebleed and no meaningful data was available. Of the 14 remaining 9 were females and 5 males. Mean age at presentation was 59.35 years with range from 47-76 years. 9 were anterior circulation aneurysms and 5 were posterior circulation. Of all locations A-com aneurysms were most common (5/14). 2 patients had incidental multiple aneurysms. Of this sample group only one aneurysm was clipped, one patient had clot evacuation followed by coiling and rest all were coiled. Placement of probe as discussed above in section 2.2 was done in the frontal lobe on the side of the lesion. If the lesion was midline or infratentorial, probes were placed on the right side. Thus we had 3 left sided and 11 right sided probes.

Symptomatically, one patient was sedated through the monitoring time epoch. Of the remaining 13, 7 developed DIND, 2 had AIND and 4 were asymptomatic. Apart from an inconsequential hematoma measuring 0.5×0.7cm, there was no significant morbidity associated with invasive multimodality neuromonitoring, which was well tolerated by awake, conscious patients.

Table 2.32 summarizes the demographic profile of the patients in this study:

Pt. no.	Age	Sex	WFNS	Fisher	Aneurysm location	Treatment	Placement of probe	Clinical outcome
1	52	F	1	3	Rt P-Com	Clipping	Rt Frontal	DIND Left MCA, Responded to T/T
2	69	F	2	3+4	Basilar tip	Coiled	Rt Frontal	DIND Diffuse*, Responded to T/T
3	76	F	2	3+4	Lt MCA	Coiled	Lt Frontal	Asymptomatic
4	55	M	2	3	A-Com	Coiled	Rt Frontal	DIND Diffuse +Rt MCA Responded to T/T
5	47	F	1	3	Lt. Term. Carotid	Coiled	Lt Frontal	Asymptomatic
6	72	F	2	3	A-Com	Coiled	Rt Frontal	DIND Diffuse + ACA's Responded to T/T
7⅄	56	F	2	3 + rebleed	A-Com	Coiled	Rt Frontal	AIND, diffuse + b/l ACA
8	48	F	2	3	Basilar tip	Coiled	Rt Frontal	DINDFluctuating, Responded to T/T
9✦	63	M	4	4	A-Com	Coiled	Rt Frontal	AIND, Fluctuating
10★	54	M	4	4	Rt MCA	Coiled	Rt Frontal	Sedated
11	66	M	4	3	Lt Vertebral	Coiled	Rt Frontal	DIND B/L ACA, Responded to T/T
12	60	M	5	3+4	A-Com	Coiled	Rt Frontal	DIND Rt ACA, Responded to T/T
13	65	F	2	3	Basilar Tip	Coiled	Rt Frontal	Asymptomatic
14	48	F	2	3+ Rebleed	Lt MCA	Coiled	Lt Frontal	Asymptomatic

Table 2.32: Patient demographics in pathophysiology study :
Total 14 patients; mean age 59 years; M:F=5:9; WFNS grades =1(2patients), 2(8patients), 4(3patients), 5(1patient); Fisher grades=3/4/3+4; 9 anterior circulation and 5 posterior circulation aneurysms; all except 1 treated by coiling; 11 right sided and 3 left sided probes; 7 patients developed DIND, 2 patients had AIND, 4 patients were asymptomatic, 1 patient remained sedated and hence could not be evaluated for symptoms during study period.
*DIND is labelled as diffuse when there is a general decline by more than 2 points on GCS, not associated with any localising signs/symptoms. In most cases this was associated with diffuse reversible ischaemic change on CTperfusion scan(CTP).
⅄Acute decline from pulmonary edema, Pt was sedated for bad chest, CTP showed diffuse ischaemia, no immediate response to treatment, MD picture typical of AIND, eventual recovery to obeying commands but severe weakness all 4 limbs.
✦Initial phase complicated by seizures and hydrocephalus. MD picture for this phase shows AIND type changes, gradual recovery after sedation hold after treatment for hydrocephalus, not on Triple H therapy
★Patient remained sedated throughout the course of monitoring, MD picture not showing any AIND/DIND type changes, CTP showed ischaemic areas in left MCA territory

Mean values for CVP, MAP, rCBF, pTiO2, metabolic parameters and potassium are detailed in the following section.

The averages for CVP, MAP, rCBF and pTiO2 are represented with graphs as temporal means.

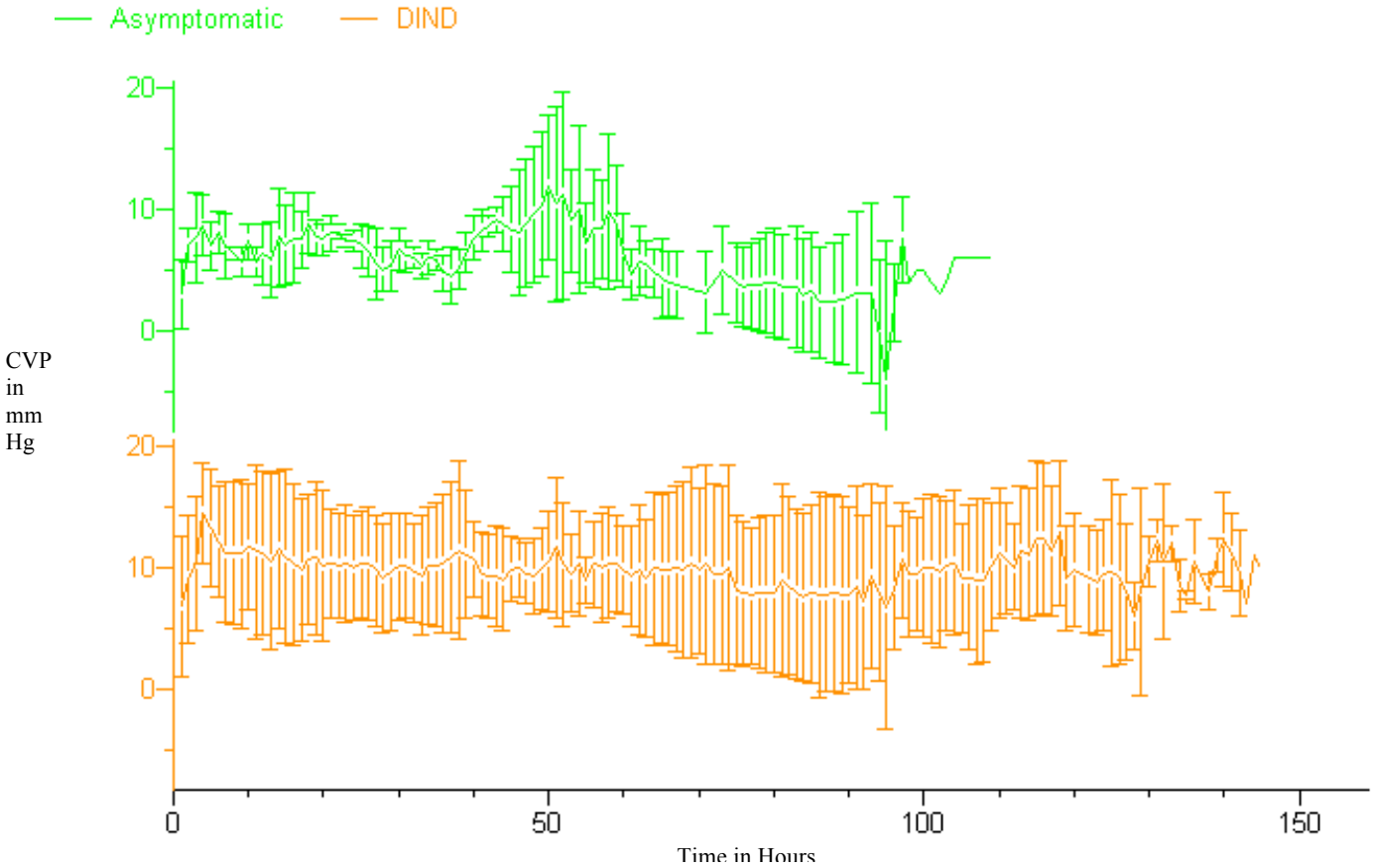


Fig. 2.31: Mean CVP Graph – X Axis is time in hours, Y axis is CVP in mmHg. The graph is a temporal mean i.e. a representation of hourly box plots. The bars on the graph represent upper and lower quartiles. Mean values for CVP as reflected above were around 8mmHg for asymptomatic patients and 9mmHg for DIND. Statistical analysis of the underlying data shows no significant difference between DIND and asymptomatic patients at equivalent time points (Student t-test)

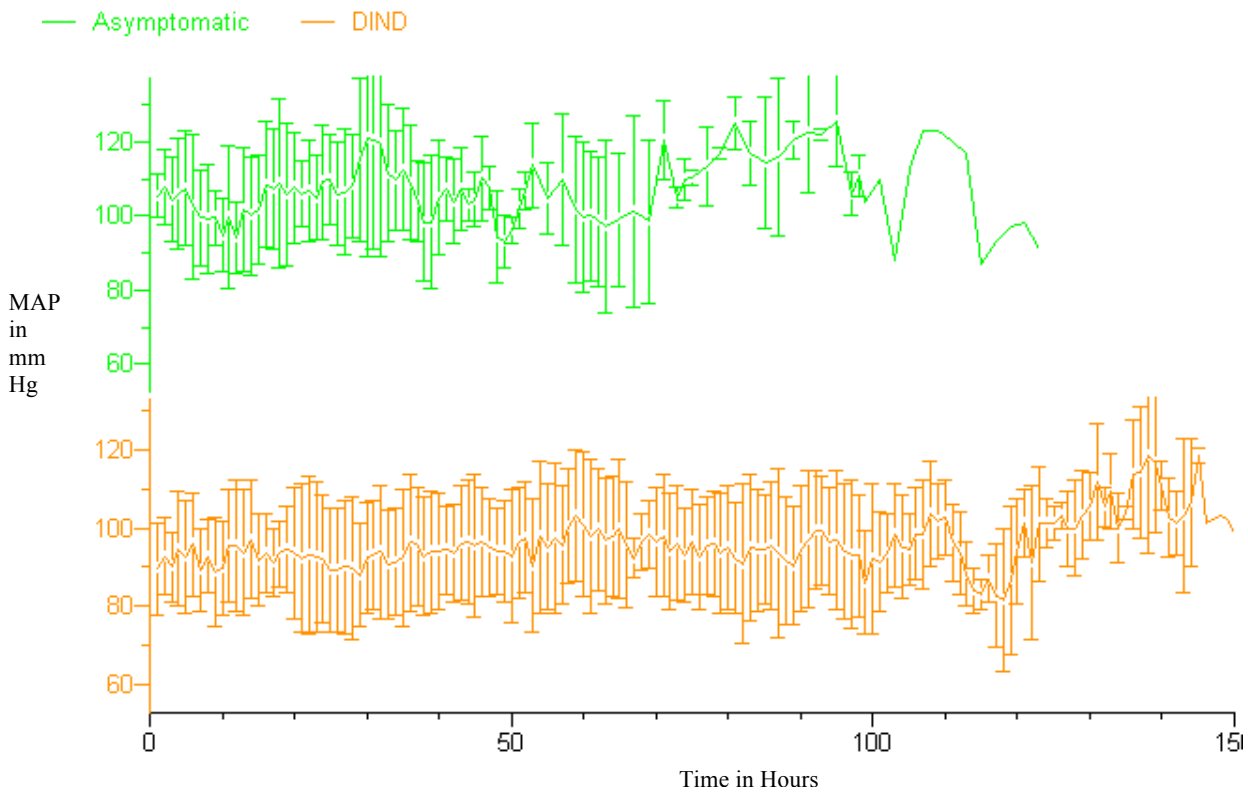


Fig. 2.32: Mean MAP Graph – X Axis is time in hours, Y axis is MAP in mmHg The graph is a temporal mean i.e. a representation of hourly box plots. Bars on the graph represent upper and lower quartiles. Mean MAP values were found to be 106mmHg for asymptomatic patients and 97mmHg for patients with DIND. Statistical analysis of underlying data showed no significant difference between DIND and asymptomatic patients, however, DIND patients were treated with triple H therapy, seen as a rise in MAP in the later hours.

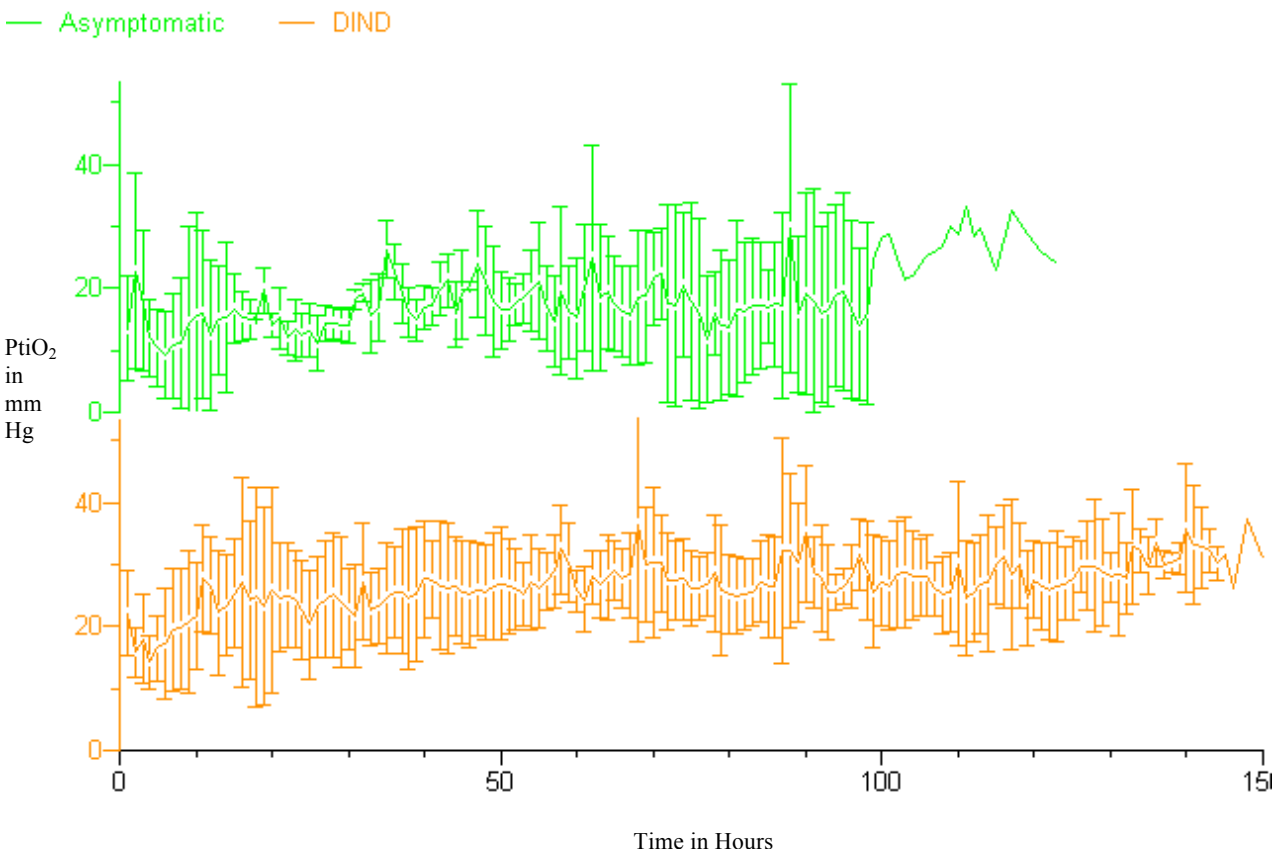


Fig.2.33: Mean Tissue Oxygenation Graph – X Axis is time in hours, Y axis is PtiO2 in mmHg. The graph is a temporal mean i.e. a representation of hourly box plots. The bars on the graph represent upper and lower quartiles. Mean values for asymptomatic patients was 19.80mmHg and for DIND patients 22mmHg. Again, no statistical difference was realized in PTiO2 values over time. There was no decline observed in DIND patients in association with symptoms.

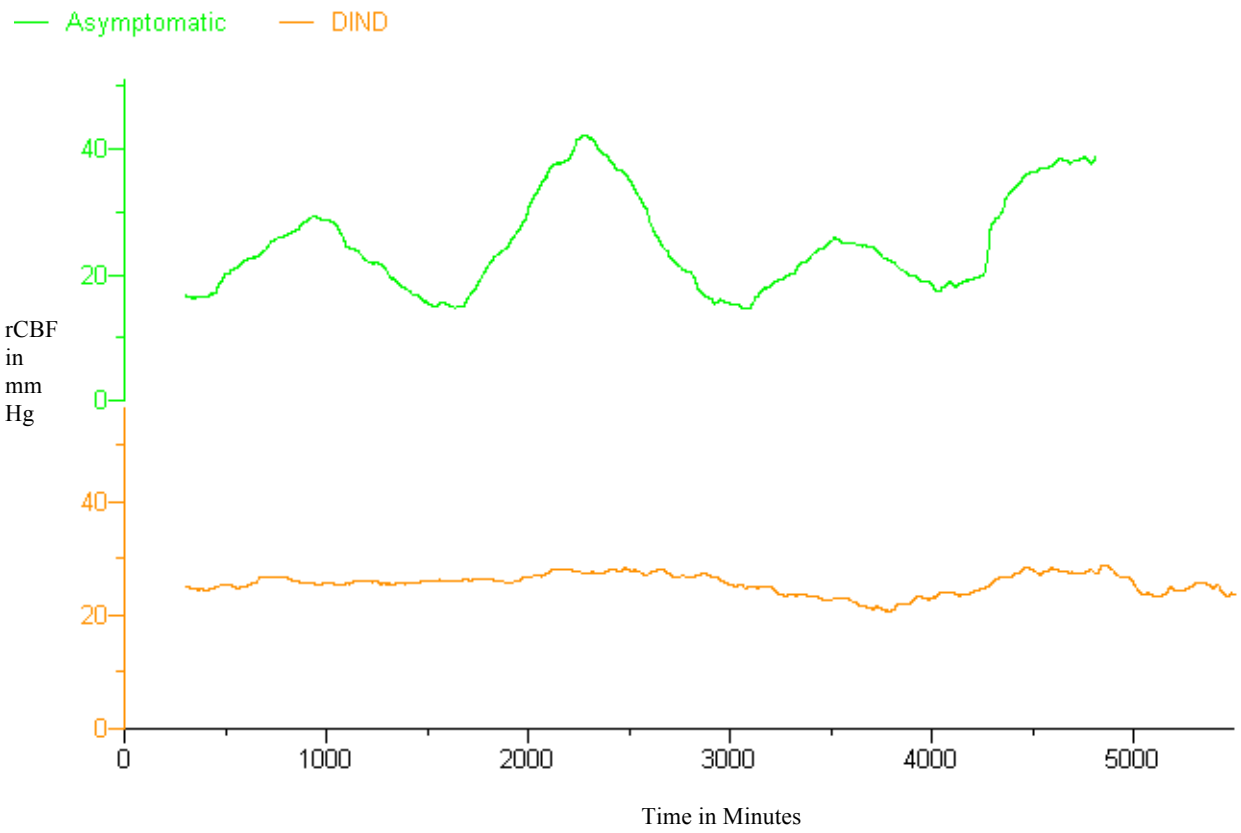


Fig. 2.34: Mean Perfusion Graph – X Axis is time in minutes, Y axis is regional cerebral perfusion in mmHg The graph is a temporal mean i.e. a representation of minute-to-minute box plots, the upper and lower quartiles have been left out of plots as that was making the graph very crowded. The mean values for asymptomatic patients were 26mmHg and that for DIND patients was 24.4mm Hg. Again the data revealed no statistically significant difference between DIND and asymptomatic patients. The baseline variability was higher in asymptomatic individuals but the significance of this finding is not understood. There was no significant decline observed in DIND patients in association with symptoms.

The values for metabolic parameters varied substantially with AIND/DIND ictus and hence a graphical temporal summation for mean was not informative in this respect. The average baseline values for the parameters in micromoles were- glucose- 1.3mM, lactate- 3.17mM, pyruvate- 89μM, glycerol- 94.4μM and potassium- 2.5mM. The average values for glycerol are relatively high because of the immediate post SAH spike noted in all patients.

Temporal Trends-

If the hypothesis that reduced cerebral blood flow leads to low oxygenation and anaerobic metabolism and cell death, then we should observe the following time trend-

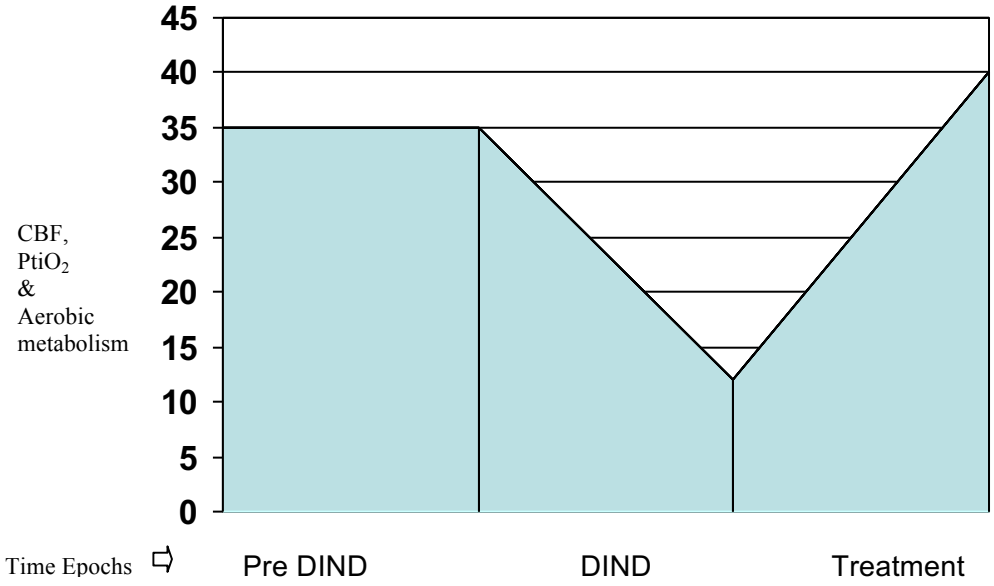


Fig.2.35: Hypothesis graph, detailing the expected trend of CBF, pTiO2 and aerobic metabolism as per current hypothesis: X axis represents symptomatic time-epochs, y axis represents arbitrary values for measured parameters. It describes that the values for perfusion followed by oxygenation and aerobic metabolism are likely to fall in DIND epoch leading to symptoms and then recover with institution of hyper dynamic therapy.

However, over the course of time these parameters followed one of three patterns -

AIND patients had classic drop in rCBF and pTiO2 and rise of lactate (and glycerol), without corresponding elevation of pyruvate at onset of symptoms. With correction of the hemodynamic parameters, there was delayed rise of pyruvate and reduction of lactate.

DIND patients had stable rCBF and pTiO2. They experienced simultaneous increase of lactate and pyruvate that corresponded to symptomatic phase. With commencement of Triple-H therapy and elevation of rCBF and pTiO2, metabolic picture did not change but symptoms improved.

Asymptomatic patients had well maintained metabolic ratios with spontaneous elevation of rCBF and pTiO2 to meet increasing metabolic demands.

Individual patient graphs below graphically demonstrate these findings-

In the graphs, X- axis shows time in hours, Y-axis shows measure of pTiO2 (Licox) and perfusion(perf) in mmHg and metabolite concentrations of lactate in millimoles and pyruvate in micromoles. Shaded area indicates the period of time when DIND/AIND was thought to be present clinically.

AIND

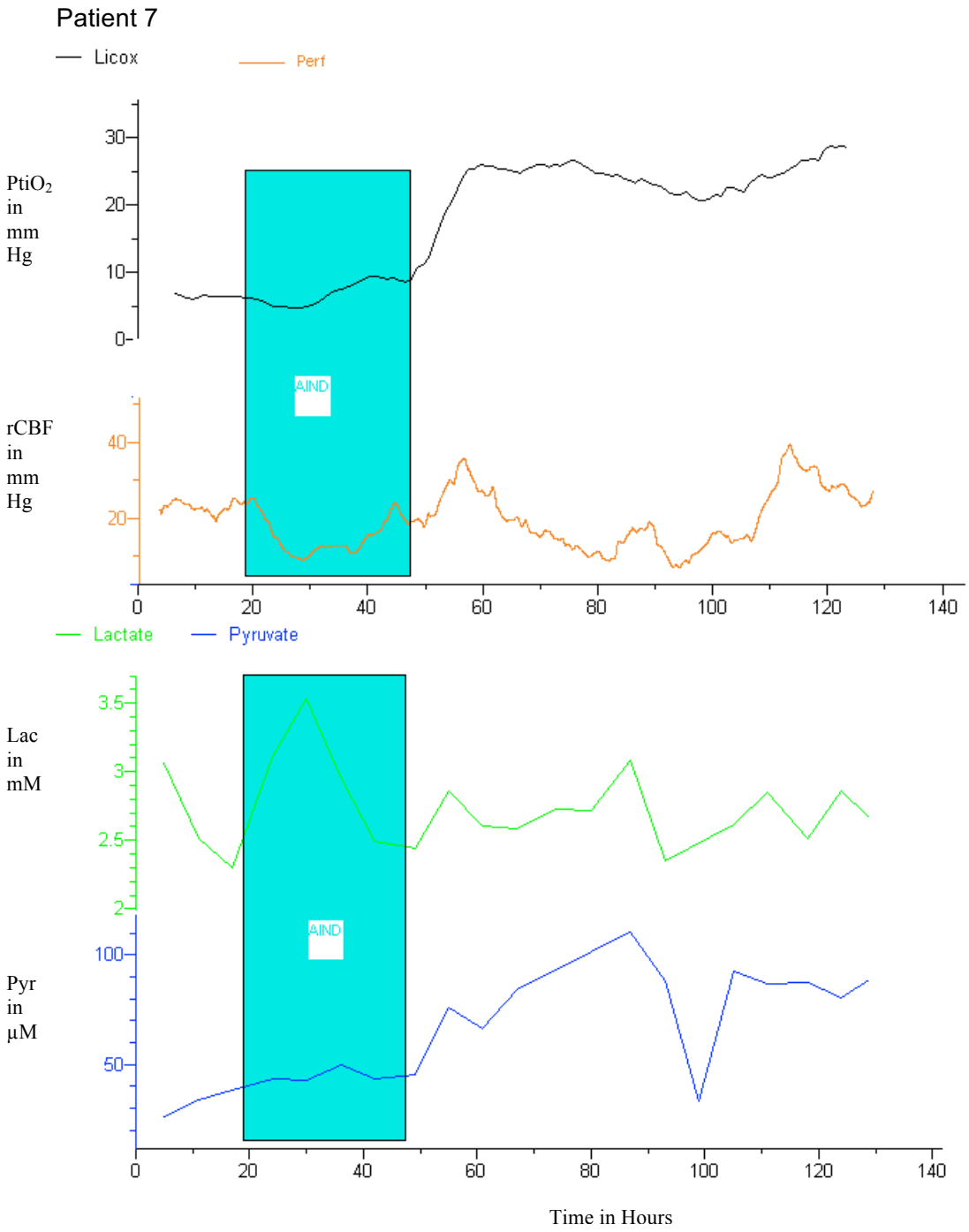


Fig. 2.36: Perfusion-Oxygenation-Metabolism-Symptoms correlation graph for patient 7: X- axis shows time in hours, Y-axis shows measure of pTiO2 (Licox) and perfusion(perf) in mmHg and metabolite concentrations of lactate in millimoles and pyruvate in micromoles. Graph demonstrates acute decline in GCS from pulmonary edema, represented as symptomatic phase (shaded area). Note associated decline in CBF and pTiO2 and corresponding rise in lactate and lactate pyruvate ratio.Patient was sedated for bad chest, CTP showed diffuse ischaemia, no immediate response to treatment, eventual recovery to obeying commands but severe weakness all 4 limbs.

AIND

Patient 9

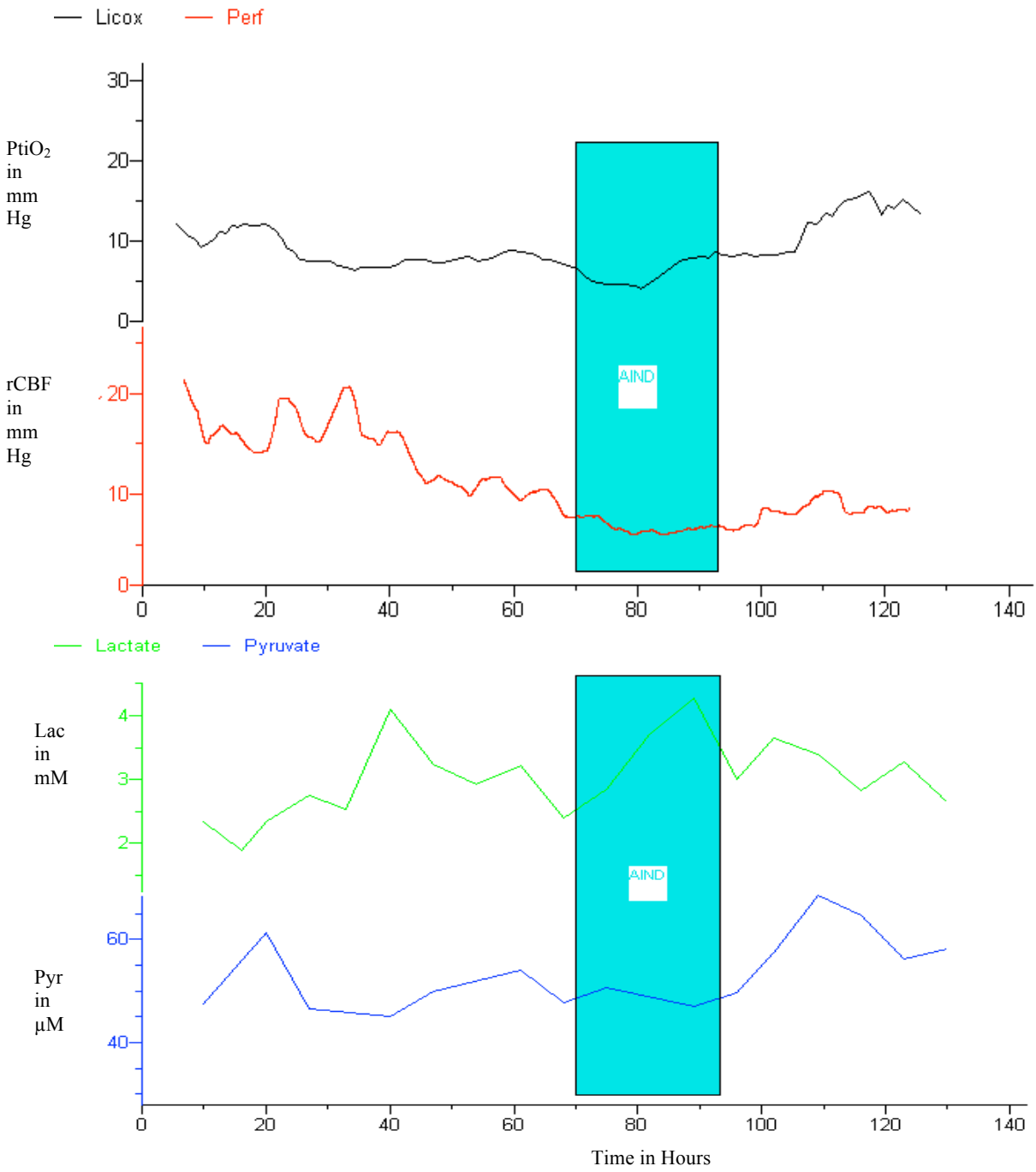


Fig. 2.37: Perfusion-Oxygenation-Metabolism-Symptoms correlation graph for patient 9: X- axis shows time in hours, Y-axis shows measure of pTiO2 (Licox) and perfusion(perf) in mmHg and metabolite concentrations of lactate in millimoles and pyruvate in micromoles. Graph demonstrates initial phase complicated by seizures and hydrocephalus. Symptomatic phase attributed to hydrocephalus marked by shaded area. Note decline in CBF and tissue oxygenation with corresponding increase in lactate pyruvate ratio and gradual recovery with resolution of hydrocephalus, not on Triple H therapy.

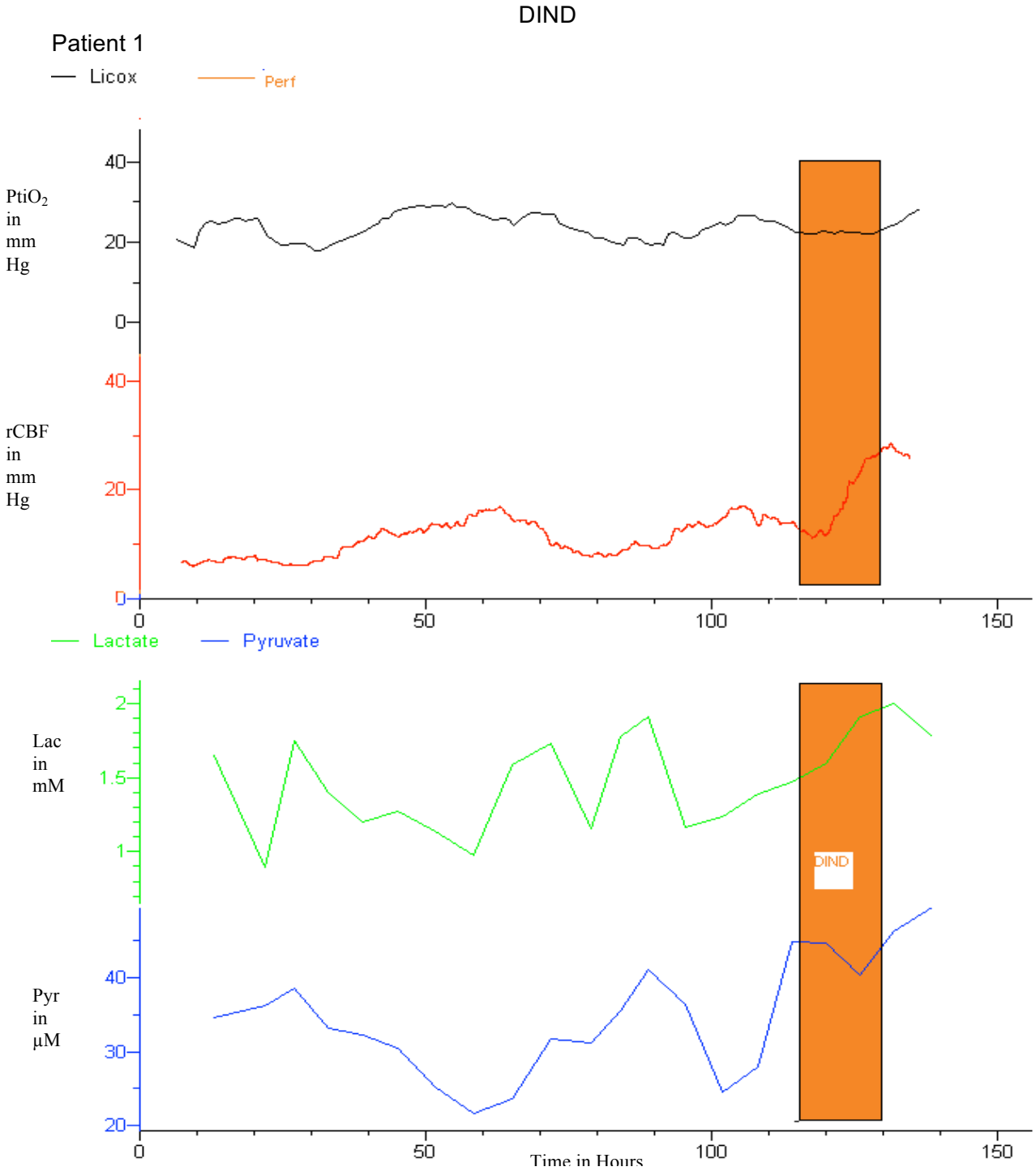


Fig. 2.38: Perfusion-Oxygenation-Metabolism-Symptoms correlation graph for patient 1: X- axis shows time in hours, Y-axis shows measure of pTiO2 (Licox) and perfusion(perf) in mmHg and metabolite concentrations of lactate in millimoles and pyruvate in micromoles. Graph demonstrates onset of right sided weakness and dysphasia in the shaded duration, full recovery with commencement of triple-H therapy. Of note, as seen above, there was no change in baseline CBF and pTiO2 with symptom onset, but simultaneously escalating lactate and pyruvate. CBF and pTiO2 improved with therapy, without change in metabolic parameters.

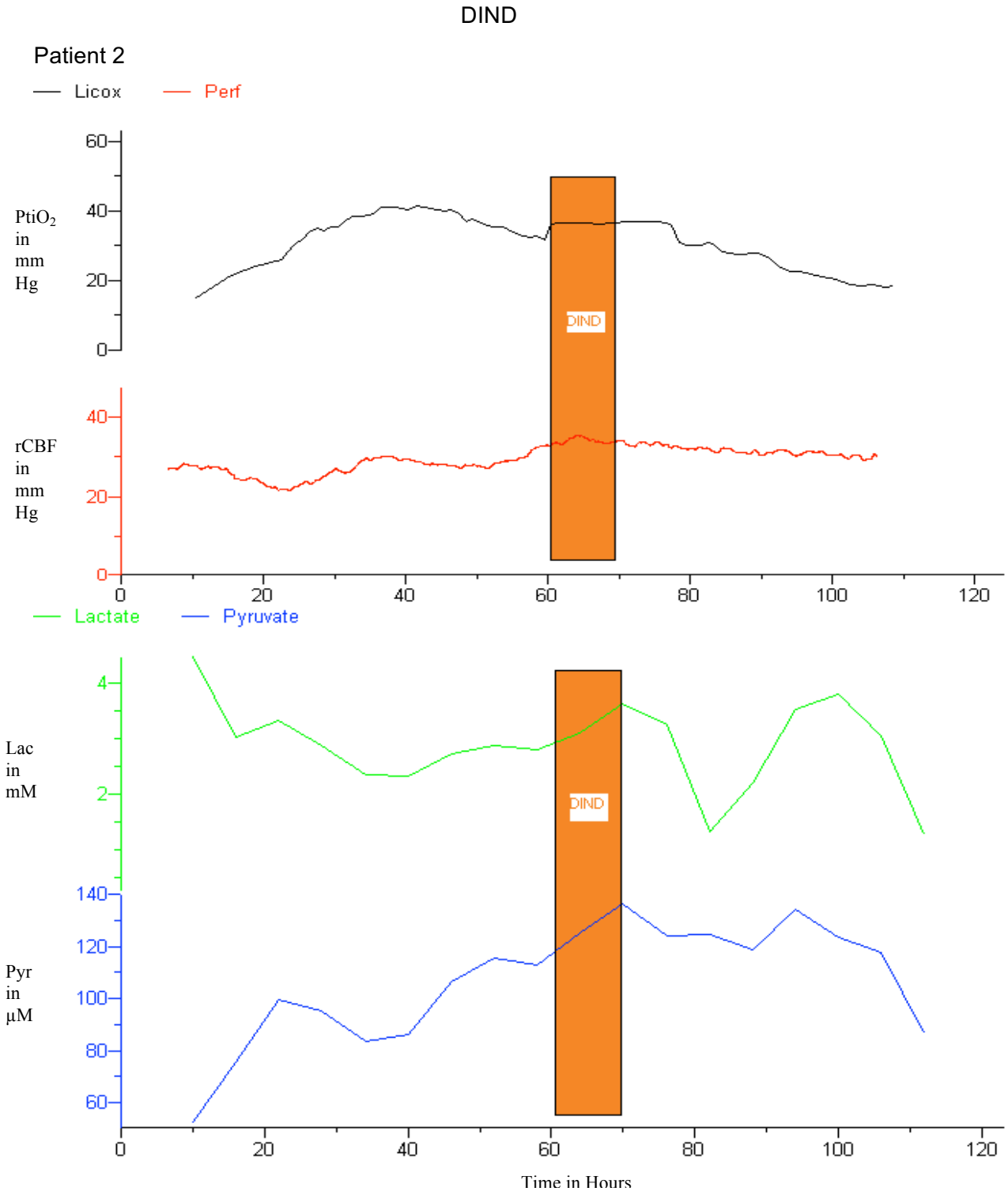


Fig. 2.39: Perfusion-Oxygenation-Metabolism-Symptoms correlation graph for patient 2: X- axis shows time in hours, Y-axis shows measure of pTiO2 (Licox) and perfusion(perf) in mmHg and metabolite concentrations of lactate in millimoles and pyruvate in micromoles. Graph demonstrates GCS 13= E3V4M6 in the shaded duration, no focal deficit, CTP showed diffuse ischaemia, full recovery with commencement of triple-H therapy. No change in baseline CBF and pTiO2 with symptom onset, but simultaneously escalating lactate and pyruvate. Improved CBF and pTiO2 with therapy, without change in metabolic parameters.

DIND

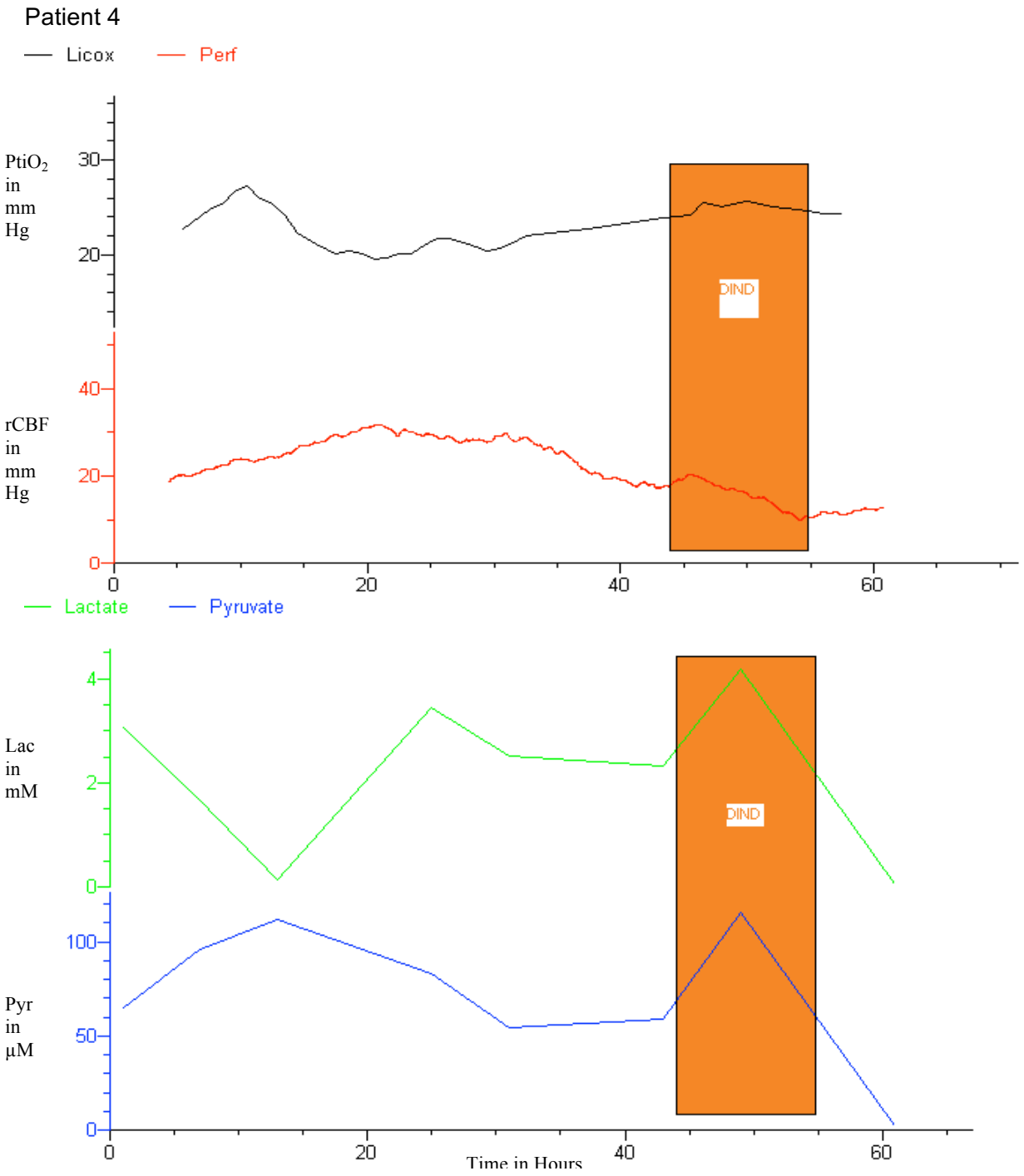


Fig. 2.310: Perfusion-Oxygenation-Metabolism-Symptoms correlation graph for patient 4: X- axis shows time in hours, Y-axis shows measure of pTiO2 (Licox) and perfusion(perf) in mmHg and metabolite concentrations of lactate in millimoles and pyruvate in micromoles. Graph demonstrates mild left hemiplegia in shaded phase, full recovery prior to commencement of triple H therapy. No change in baseline CBF and pTiO2 prior to symptom onset, deteriorating CBF with ongoing symptoms, simultaneously escalating lactate and pyruvate. Spontaneously improved metabolic parameters coinciding with symptomatic recovery without any change in CBF or pTiO2.

DIND

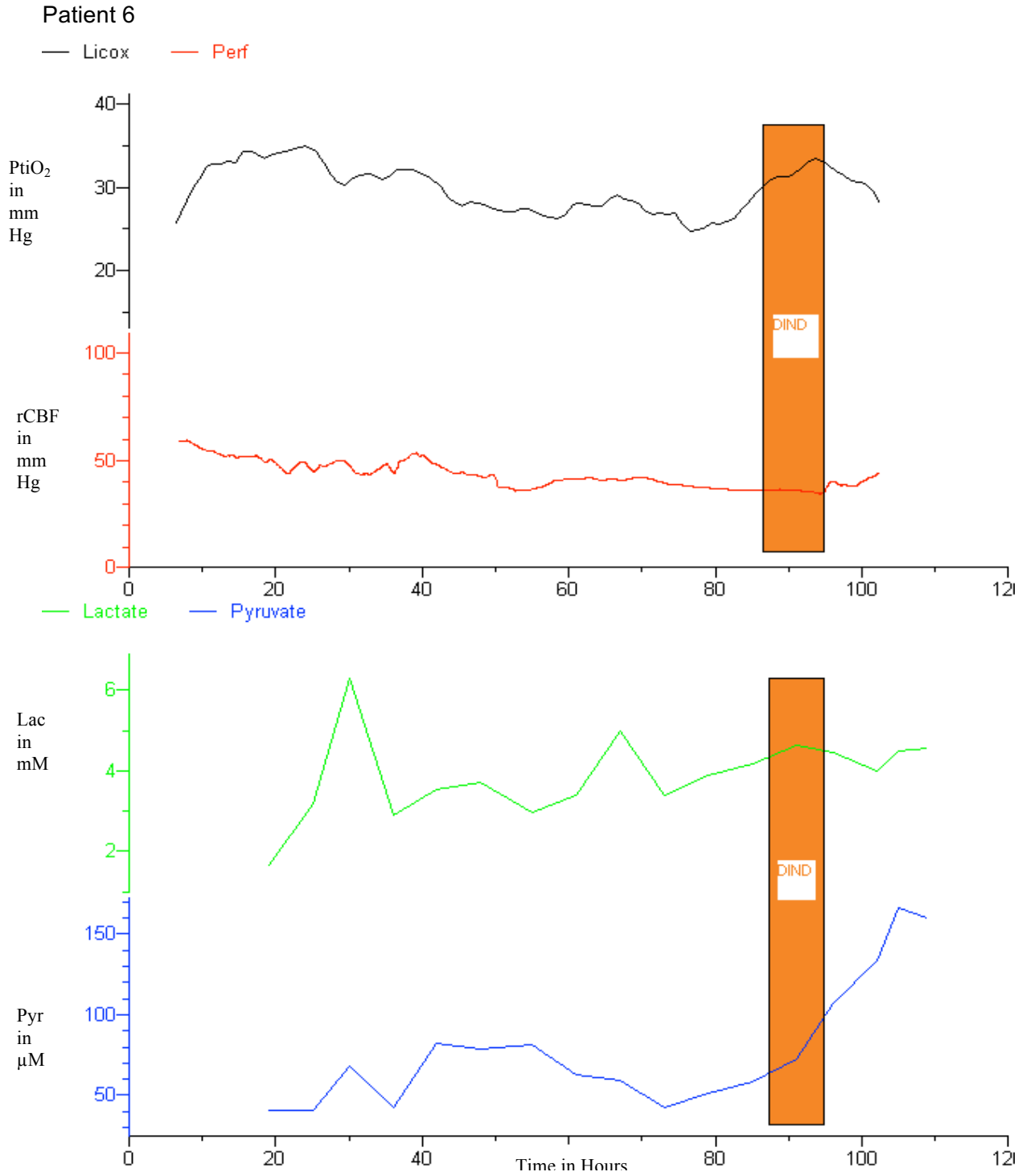


Fig. 2.311: Perfusion-Oxygenation-Metabolism-Symptoms correlation graph for patient 6: X- axis shows time in hours, Y-axis shows measure of pTiO2 (Licox) and perfusion(perf) in mmHg and metabolite concentrations of lactate in millimoles and pyruvate in micromoles. Graph demonstrates GCS= E3V3M6 in the shaded duration, full recovery with commencement of triple-H therapy. No change in baseline CBF and pTiO2 with symptom onset, escalating lactate and pyruvate, though not parallel. Improved CBF and pTiO2 with therapy, no change in metabolic parameters.

DIND

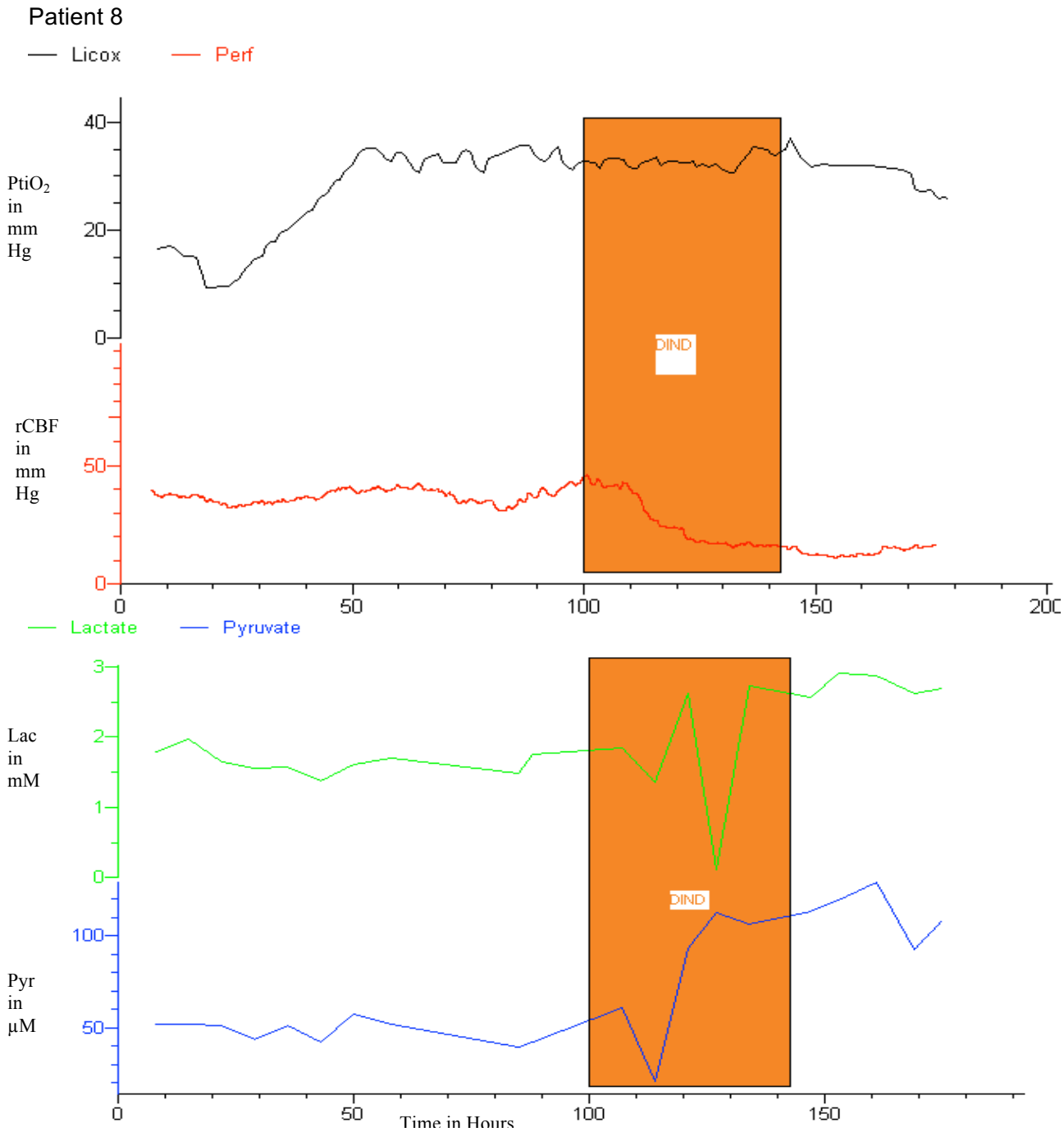


Fig. 2.312: Perfusion-Oxygenation-Metabolism-Symptoms correlation graph for patient 8: X- axis shows time in hours, Y-axis shows measure of pTiO2 (Licox) and perfusion(perf) in mmHg and metabolite concentrations of lactate in millimoles and pyruvate in micromoles. Graph demonstrates fluctuating GCS in the shaded duration, full recovery with commencement of triple-H therapy. No change in baseline CBF and pTiO2 with symptom onset, escalating lactate and pyruvate. Fall in CBF during symptomatic phase. Stable/slightly improved pTiO2 and no change in CBF with therapy, no change in metabolic parameters.

DIND

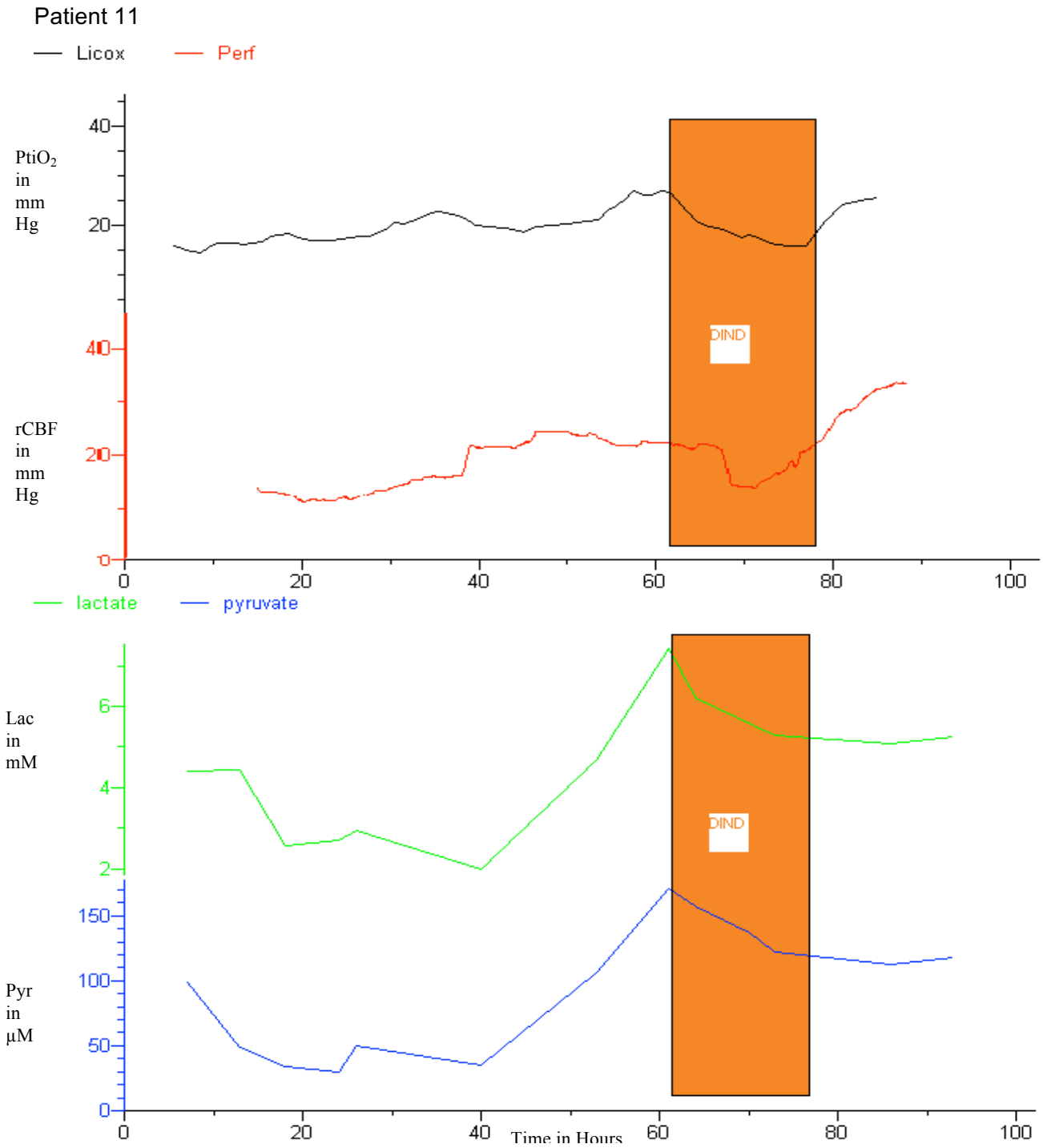


Fig. 2.313: Perfusion-Oxygenation-Metabolism-Symptoms correlation graph for patient 11: X- axis shows time in hours, Y-axis shows measure of pTiO2 (Licox) and perfusion(perf) in mmHg and metabolite concentrations of lactate in millimoles and pyruvate in micromoles. Graph demonstrates bilateral leg weakness in the shaded duration, full recovery of symptoms with commencement of treatment. No change in baseline CBF and pTiO2 with symptom onset, escalating lactate and pyruvate. Improved CBF and pTiO2 with treatment, no change in lactate/pyruvate.

DIND

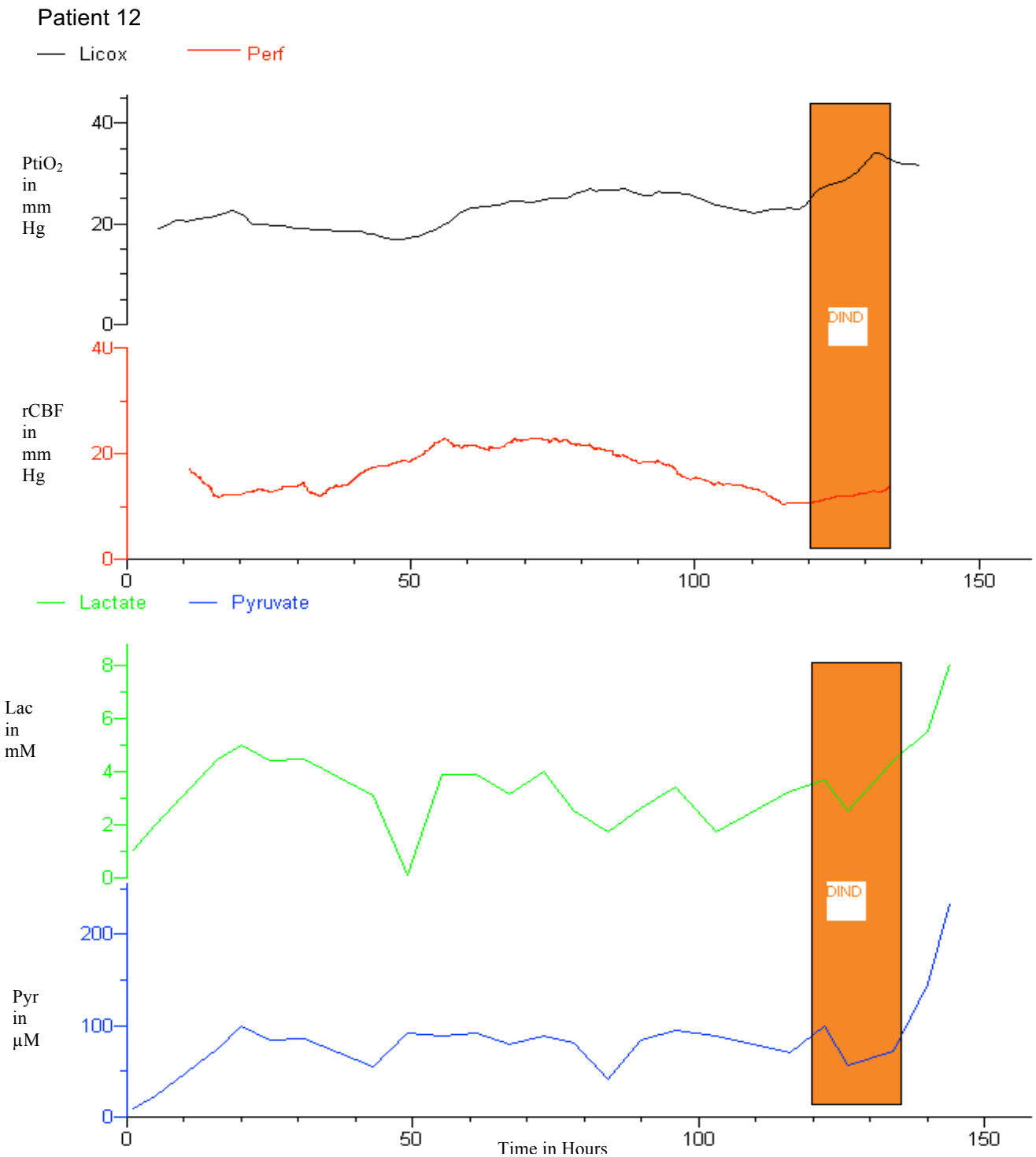


Fig. 2.314: Perfusion-Oxygenation-Metabolism-Symptoms correlation graph for patient 12: X- axis shows time in hours, Y-axis shows measure of pTiO2 (Licox) and perfusion(perf) in mmHg and metabolite concentrations of lactate in millimoles and pyruvate in micromoles. Graph demonstrates GCS=E2V4M6 in the shaded duration, full recovery with commencement of therapy. No change in baseline CBF and pTiO2 with symptom onset, escalating lactate and pyruvate during symptomatic phase. Improving CBF and pTiO2 with HHH therapy, no change in metabolic parameters.

Asymptomatic

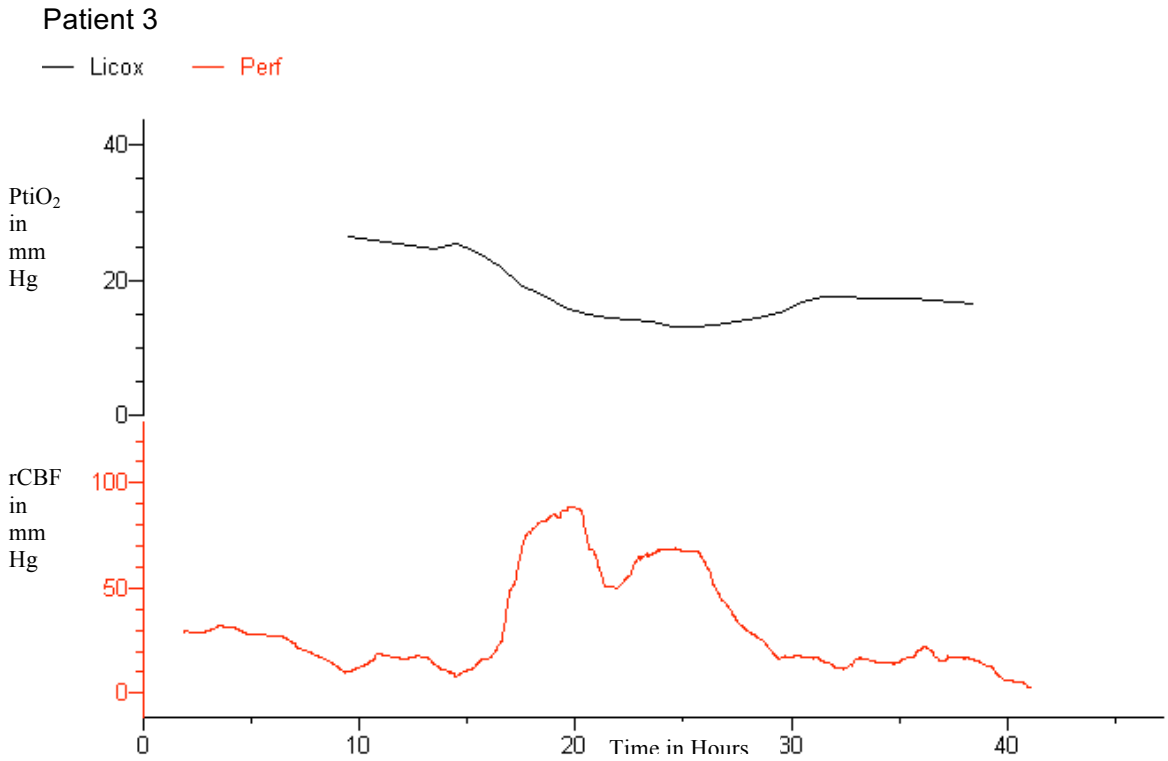


Fig. 2.315: Perfusion-Oxygenation-Symptoms correlation graph for patient 3: X- axis shows time in hours, Y-axis shows measure of pTiO2 (Licox) and perfusion(perf) in mmHg. For this asymptomatic patient microdialysis readings were not available as probe got caught and broke during transfer from coiling suite to the unit, hence removed for safety reasons, patient did not consent for placement of second probe. Graph demonstrates fluctuating baseline perfusion and gradual decline in oxygenation without any symptoms.

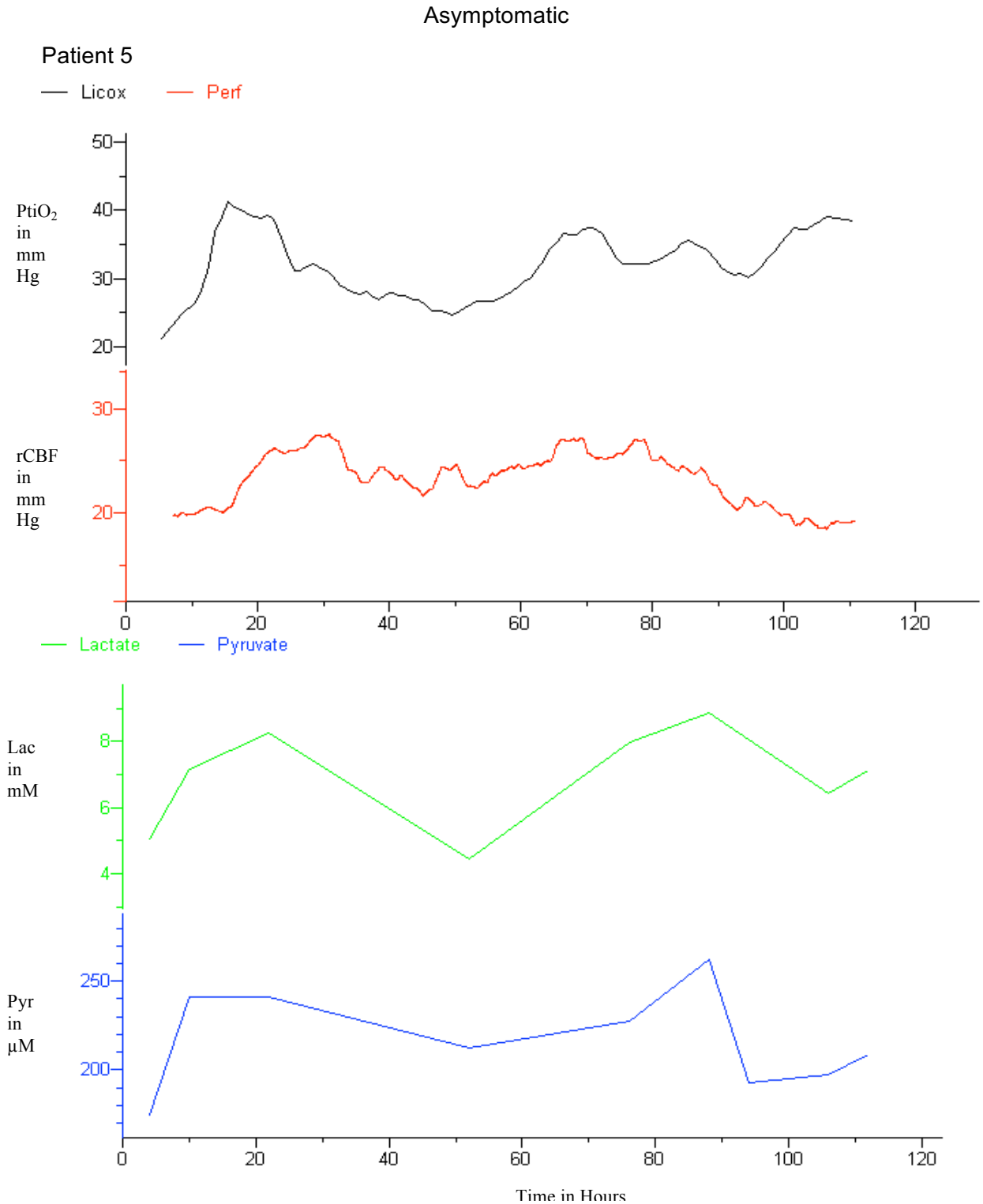


Fig. 2.316: Perfusion-Oxygenation-Metabolism-Symptoms correlation graph for patient 7: X- axis shows time in hours, Y-axis shows measure of pTiO2 (Licox) and perfusion(perf) in mmHg and metabolite concentrations of lactate in millimoles and pyruvate in micromoles. Graph demonstrates well matched escalation in all parameters with patient remaining asymptomatic

Asymptomatic

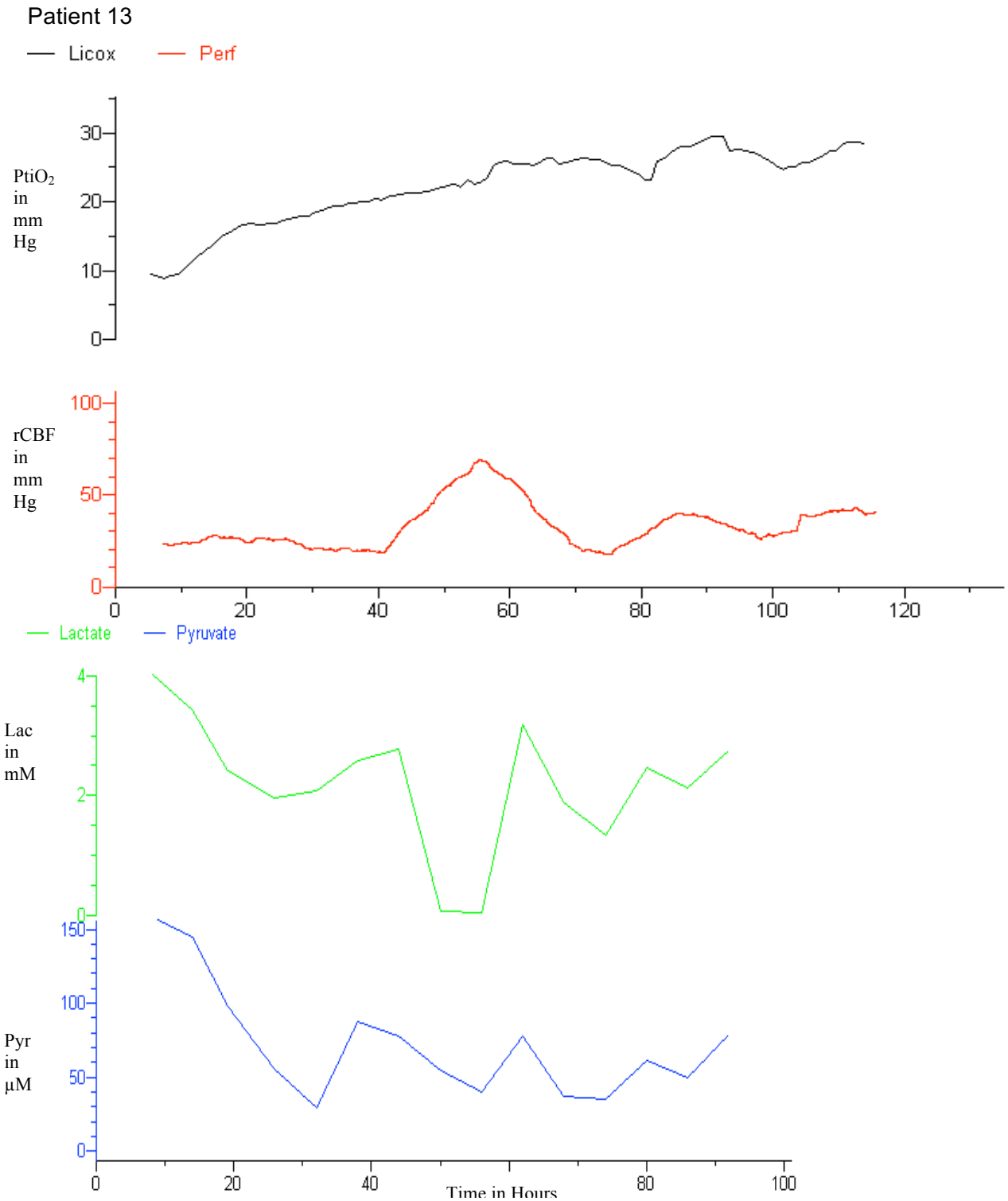


Fig. 2.317: Perfusion-Oxygenation-Metabolism-Symptoms correlation graph for patient 13: X- axis shows time in hours, Y-axis shows measure of pTiO2 (Licox) and perfusion(perf) in mmHg and metabolite concentrations of lactate in millimoles and pyruvate in micromoles. Graph demonstrates no change in baseline metabolic parameters,CBF. pTiO2 had general upward trend. Patient remained asymptomatic.

Asymptomatic

Patient 14

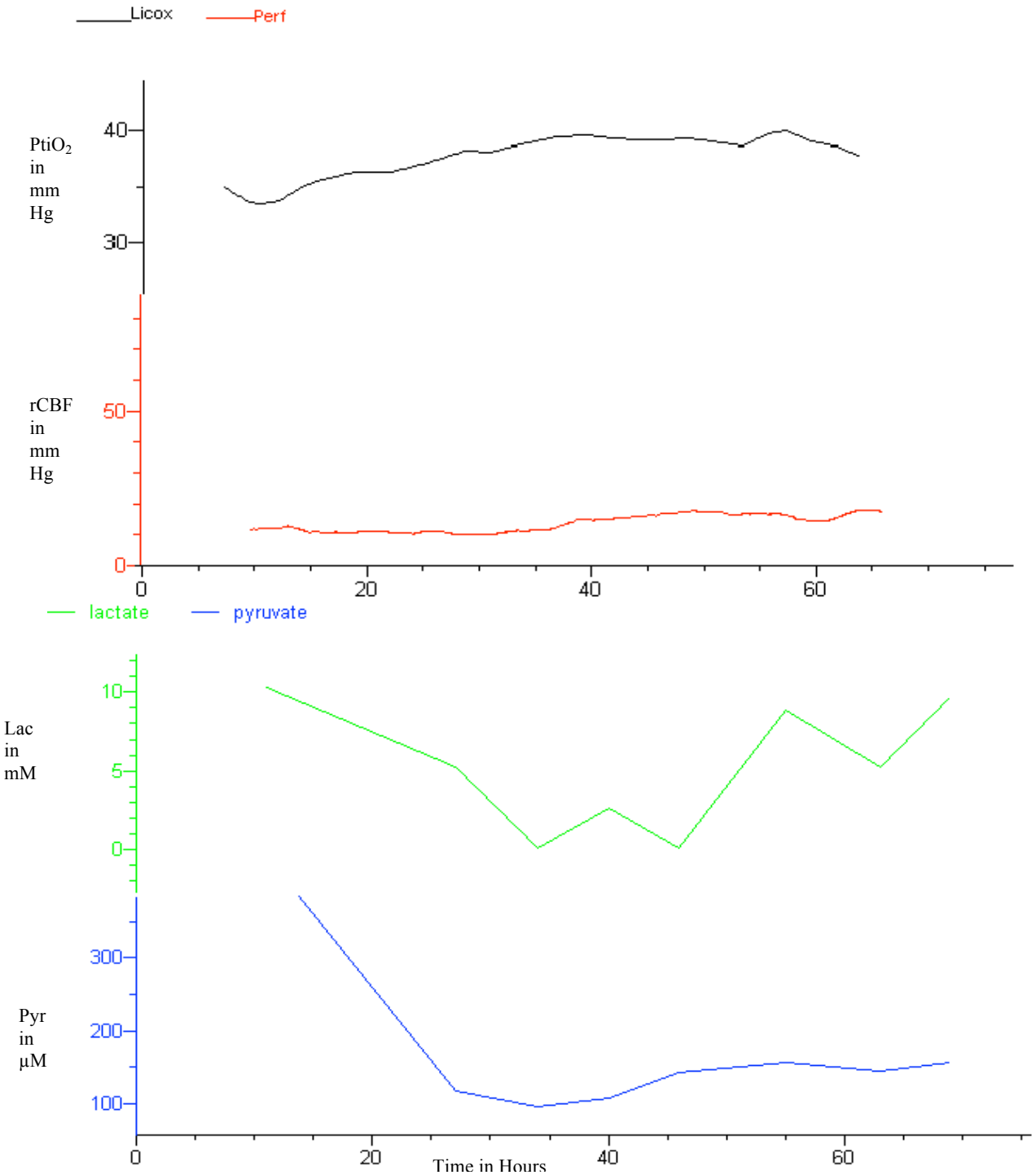


Fig. 2.318: Perfusion-Oxygenation-Metabolism-Symptoms correlation graph for patient 14: X- axis shows time in hours, Y-axis shows measure of pTiO2 (Licox) and perfusion(perf) in mmHg and metabolite concentrations of lactate in millimoles and pyruvate in micromoles. Graph demonstrates general upward trend in all parameters, patient remained asymptomatic.

The values of potassium were assessed in 6 patients- 4 DIND and 2 asymptomatic. In 4 patients- 3 DIND and 1 asymptomatic close association was noted between metabolism and potassium ion concentration as shown in the graph below.

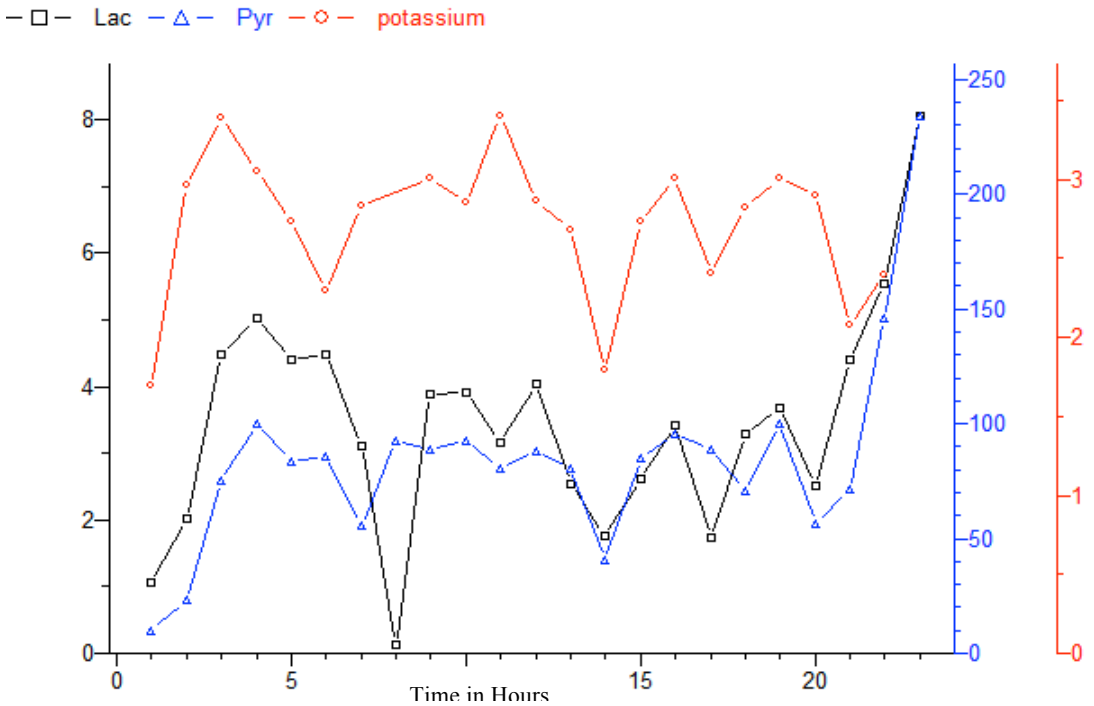


Fig. 2.319:Potassium-metabolite correlation graph pt12: X-axis is time, Y-axis shows lactate in millimoles, pyruvate in micromoles and potassium in milliEquivalents/litre. Graph demonstrates simultaneous trending of potassium with lactate and pyruvate.

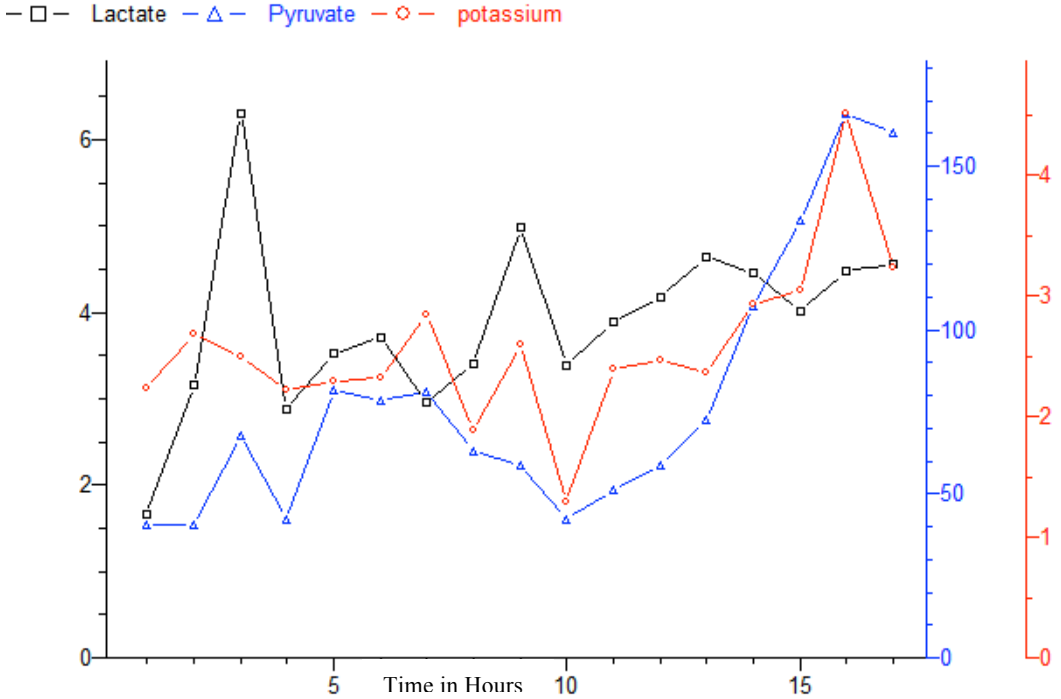


Fig. 2.320:Potassium-metabolite correlation graph pt6; X-axis shows time, Y-axis shows lactate in millimoles, pyruvate in micromoles and potassium in milliEquivalents/litre. Graph demonstrates simultaneous trending of potassium with lactate and pyruvate.

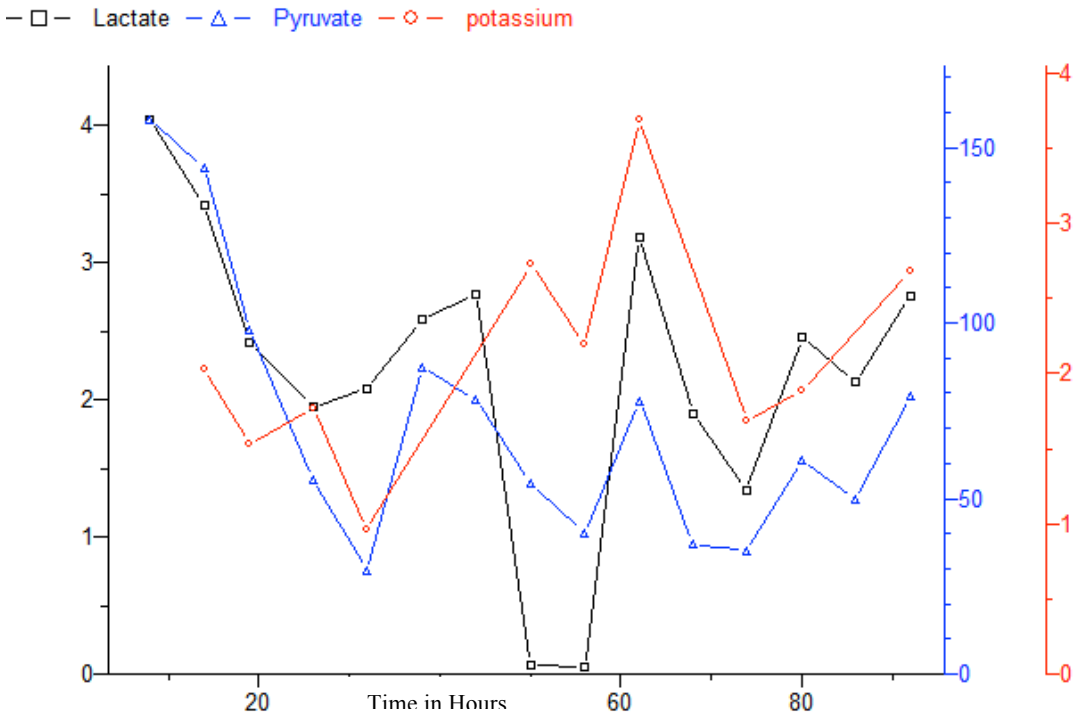


Fig. 2.321:Potassium-metabolite correlation graph pt13; X-axis is time, Y-axis shows lactate in millimoles, pyruvate in micromoles and potassium in milliEquivalents/litre. Graph demonstrates simultaneous trending of potassium with lactate and pyruvate.

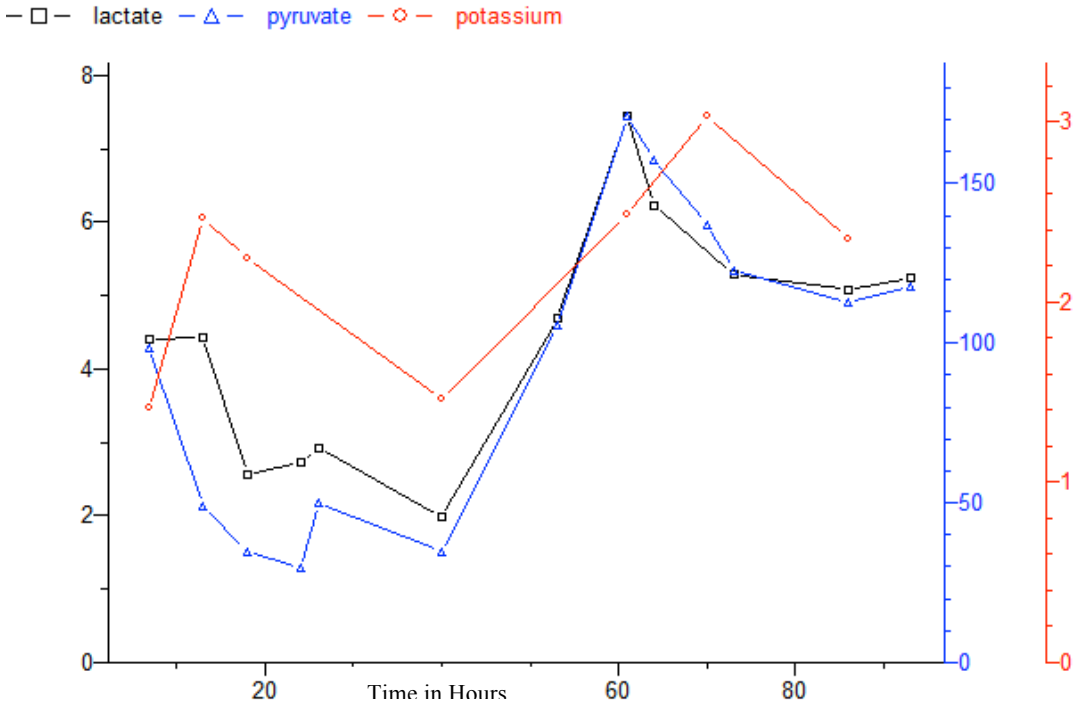


Fig. 2.322:Potassium-metabolite correlation graph pt11; X-axis shows time, Y-axis shows lactate in millimoles, pyruvate in micromoles and potassium in milliEquivalents/litre. Graph demonstrates simultaneous trending of potassium with lactate and pyruvate.

The potassium values in patients 12,6,13 and 11 respectively; closely paralleled metabolic trend.

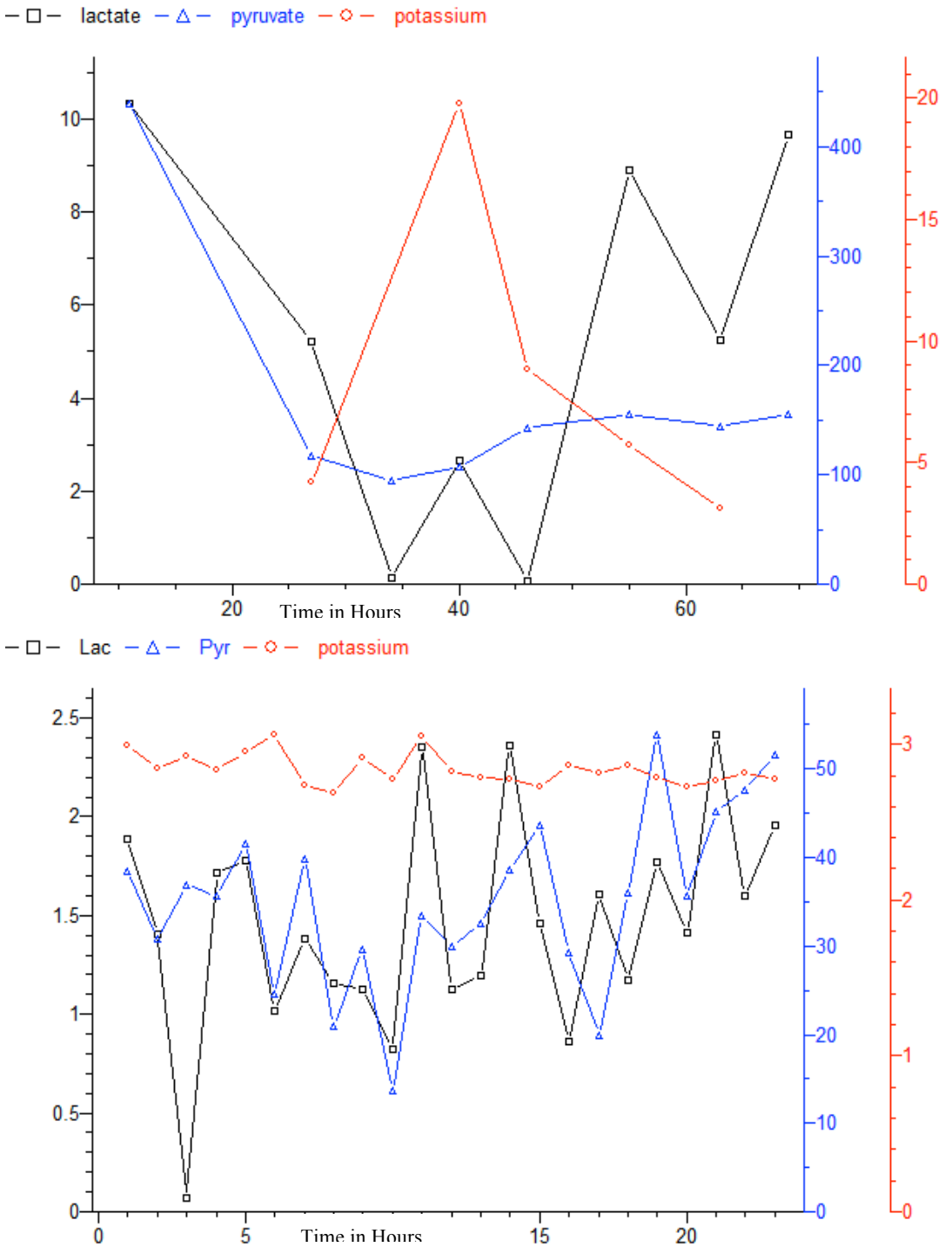


Fig. 2.323and 2.324:Potassium-metabolite correlation graphs for patients 14 and 1 respectively ; X-axis shows time, Y-axis shows lactate in millimoles, pyruvate in micromoles and potassium in milliEquivalents/litre. Graphs demonstrate no association of potassium with lactate and pyruvate values.

Potassium values in patients 14 and 1 respectively; not corroborating with lactate or pyruvate

Result Summary-

As previously stated 1 patient was not assessable. Of the remaining 13, 7 developed DIND, 2 had AIND and 4 were asymptomatic. 6/14 had reduced cerebral blood flow, of these, only 2 were symptomatic. Interestingly 6/7 patients with DIND had parallel elevation of lactate and pyruvate at time of symptoms, 4/5 asymptomatic patients did not (OR=24:1). Potassium levels parallelled metabolic rate. CBF/oxygenation and metabolism did not seem to bear any causal association in DIND patients. Triple H therapy increased CBF and oxygenation and symptoms improved, with no change in metabolic parameters. pTiO2 values had the closest association with MAP, with or without Triple H therapy.

2.4 Discussion

Choosing inclusion criteria

Fisher Grade:

As mentioned previously only Fisher grades 3/4/3+4 patients as well as those with rebleed were included, to increase the positive yield in an otherwise difficult to recruit study. The reason for this was that to date only blood load on the scan has proven to be a consistent predictor of the risk of DIND (English language literature review- 1996-2005; Harrod, 2005). The Fisher scale we used herein was the original scale (Appendix1). In 2006, Frontera and colleagues proposed the modified Fisher scale(Appendix1). This is supposed to predict the likelihood of DIND better than the original scale, however the main difference in the Odds Ratio for prediction of DIND in the two scales was between Fisher 3 and 4, and since both these high risk groups were in the inclusion criteria, it did not matter as far as this study was concerned. Also, as this was observational study we were only reflecting the routine practice in our unit which is to measure blood load as per the original Fisher scale, thereby adding to the consistency of results by minimising any interobserver variation brought in by introduction of a new scale.

Timing:

We only recruited patients within the first three days of ictus. This was to be able to get a baseline value for physiological parameters before the clinical signs and symptoms of DIND set in. 14/16 patients were recruited on day 1, only 2 patients were recruited on day 2. We understand that any delay in recruitment post ictus will lead to missing some Early Brain injury data. But, logistically, it was only possible to recruit the patients at the time of coiling or clipping to avoid a further anaesthetic. Also, we could only keep in the monitors for 5-7 days with an acceptable low infection risk and reliability of readings.

Since the main aim was to capture physiological changes surrounding DIND symptoms, we accepted the trade-off.

Monitoring awake patients:

Most monitoring in neurosurgery is currently utilised for comatose patients. However, we decided to include awake, good WFNS grade patients for the following reasons-

Clinical benefit- DIND is a clinical diagnosis. Direct clinical correlation provides the most accurate and sensitive tool for diagnosing caseness.

Although ischaemia on scanning after ruling out other causes is a specific tool, by the time of radiological ischaemic change, the damage is believed to have sufficiently progressed. Early reversible stages of DIND may not be associated with any hypodense lesions on scanning, as is the case with a lot of follow-up scans we see in patients who have recovered from DIND. As such there is no sensitive tool to pick up DIND in comatose patients.

Academic benefit-There is large baseline variability in the regional cerebral blood flow, oxygenation and metabolic readings as detailed earlier. Since there is a lack of clinical correlation, it is hard to decide what values are physiological and what are pathological. Most previous work on SAH neuromonitoring has been in comatose patients whereby it is assumed that if the CBF is low on monitors, the patient must be experiencing DIND. As the aim of this work was to obtain a pathophysiological correlate for DIND, such an assumption was not safe. In fact, our results indicate that patients with CBF in ranges diagnostic of ischaemia based on previous data, were well enough reading a newspaper and discussing football scores!

Ethical issues- As similar probes (ICP for diagnosing benign intracranial hypertension and for picking up signs of over or under-drainage in patients with headache who have a shunt in situ) are routinely used in awake neurosurgical patients and are well tolerated,

this endeavour was considered acceptable. Wherever, awake patients were recruited, a fully informed consent was obtained and patients/relatives were free to withdraw from the study if the monitoring seemed to compromise their care or comfort in any way. All awake patients in the study tolerated the monitoring very well and no probes had to be removed prematurely.

Diagnosis of DIND

While in many studies, besides clinical deterioration, either TCD or radiographic evidence was required to diagnose clinical vasospasm aka DIND, there has been a recent change in the understanding of what should be called delayed ischaemic neurological deficit. As mentioned in chapter 1, vasospasm is no longer believed to have a full causal association with DIND. While radiological evidence of infarction in absence of other causes is the only reliable way to detect DIND in comatose patients, clinical deterioration due to DIND is now being recognised as a separate entity.

Both these criteria were employed to diagnose DIND in this study.

For comatose patients, DIND was defined as the presence of new hypodensities on CT that could not be attributed to any other cause, and,

For awake patients, we defined DIND as clinical deterioration (2 point drop in GCS or new focal neurology) in the absence of any other explanations for the same, persistent for at least 1 hour.

Inter-observer variability has been a major criticism of using a purely clinical definition for DIND in previous studies. To ensure consistency in what was called DIND, all patients in this study were reviewed by the researcher at the time of deterioration, who was alerted to any change in clinical condition of the patient upon hourly monitoring by the nursing staff in N-ITU/ N-HDU.

Neuromonitoring: Validity, acceptability and generalisability of these results

Regional v/s global monitoring:

All probes used in this study are validated tools for bedside regional monitoring and the trade-off is that they do not necessarily reflect global changes. We have seen in previous studies (chapter 1) that focal changes relate better to symptoms in DIND yet DIND is a diffuse process. Previous researchers (Muench et al, 2007) have placed four regional monitors in different locations in SAH patients and in-vivo monitoring did not reveal any significant differences by location. Besides, all of these tools have the advantage of providing continuous real time monitoring as opposed to snap-shot views provided by most global techniques.

Monitoring the at-risk territory v/s frontal monitoring:

Again as cited above, researchers have shown little difference in values recorded at four different monitors in the same patient, nevertheless, there are obvious advantages in monitoring the area undergoing pathophysiological change during development of DIND. The main problem is defining this at-risk territory. A recent study by Miller, 2011 revealed that unilateral aneurysms lead to DIND symptoms in the ipsilateral hemisphere in 90% cases, nearly 80% are in same vascular territory and only about 70% probes that are 100% sensitive will pick up the change even if placed in the MCA territory with its attendant risks.

The midline aneurysms are even more variable, with most anterior circulation midline lesions causing ACA territorial infarcts, and the highest variability is seen in posterior circulation lesions.

With the limitaions regarding patient numbers and available time, it was not possible to be superselective in the inclusion criteria with the location of aneurysms and even so, there would be no guarantee that the probe would be in the infarct/periinfarct zone.

Secondly this was an observational study and it has been noted that it is relatively safer in the event of a probe related haemorrhage to put neuro-monitoring probes in the frontal lobe.

As such we chose to put the monitors in the frontal lobes, preferably on the side of aneurysm in supratentorial non midline aneurysms and in the right frontal lobe in all others.

Potential flaws due to the monitoring technique used

As detailed previously, thermo-diffusion probe (HEMEDEX) was chosen for monitoring cerebral blood flow, Clark type electrode (LICOX) for tissue oxygen concentration and CMA 100 for microdialysis.

The mechanism of action of these tools is detailed in the introduction(chapter 1). The potential flaws introduced by these techniques are discussed in this section.

The thermo- diffusion probe works by creating a temperature gradient of 2 degrees above body temperature. If the patient is pyrexial, raising temperature further is not safe and hence the probe stops heating above 39 degrees centigrade and consequentially stops measuring CBF values in pyrexia. Both ‘central’ and inflammatory rises in temperature are often seen in aSAH patients. If the pyrexia persists for long duration, the CBF recording may thus be jeopardised, making interpretation of other parameters difficult too. other alternatives for continuous bed side measurement of CBF are not so well established and available and have their own pitfalls as detailed in chapter 1. Fortunately, persistent pyrexia was not a problem in the patients recruited for this study.

The other issue was that the probe recalibrates itself after every 30 minutes. After each recalibration there is possibility of drift. With prolonged monitoring for >7 days, the drift becomes significant. As such the monitoring period was restricted to 5-7 days. Still, however, some amount of drift would be present. Therefore we decided to concentrate

on trend of CBF rather than actual values which had large baseline variation between patients anyway, to assess whether or not CBF was decreasing with DIND and reversing with Triple H. Due to this drift issue, it was not sensible to calculate area under the curve for statistical analysis and we had to restrict it to descriptive analysis.

Overall, thermal diffusion with all the above potential flaws is currently the standard tool for monitoring CBF in other studies as well, and hence offers the benefit of comparability to other works in literature.

The Clark type electrode has the drawback that it measures the redox state in the tissue, to measure oxygen concentration. As previously mentioned, the redox state could be altered after aSAH. However, this is a theoretical concern and has not been a practical issue in any of previous studies. As noted in the results of this study, the Licox values paralleled those of MAP throughout the monitoring period in all patients. This would not have happened if the values were in fact influenced by a changing redox state. Again as the Hemedex, Licox probe is widely used, it offers the benefit of comparability with literature.

Lastly, the microdialysis probe has only one issue- that of simultaneous use with thermo-diffusion probes. The thermo diffusion probe only heats up the immediate vicinity and, as advised in the literature of two probes, placing them a centimetre apart in the white matter resolved this issue. The values for the parameters monitored –glucose, glycerol, lactate and pyruvate in this study were in similar range to values observed in studies using microdialysis independently.

Another consideration was that these are all invasive tools, however the safety of these tools has been well established in previous studies (Sarrafzadeh, 2000; Muench 2007).

Triple H therapy

Application: 1H, 2H or all 3:

The pros and cons of the three elements of Triple H: hypertension, haemodilution and hypervolaemia have been previously discussed in chapter 1. As such, for the purpose of this study, although being conventionally called 'Triple-H', it was actually hyperdynamic therapy with fluid induced hypervolaemia and hypertension and drug induced hypertension being administered as per the unit protocol detailed in the methodology section of this chapter.

Trigger and target: numbers or deficit?

Prophylactic Triple H has no role in management of DIND as such. The trigger for starting treatment was clinical deficit, the exception being in comatose patients, where hyperdynamic therapy was commenced if the MAP values were very low or patient was in negative balance. The target, however, was still numbers (thresholds), meaning that the target end-point was an arbitrary figure – not tailored to the individual nor reflecting clinical parameters. Yet the therapy was considered successful and often curtailed if the clinical deterioration was reversed. As detailed before, the idea was to achieve a positive fluid balance with CVP reflecting a well filled state and if there was still no clinical improvement, to commence drug induced hypertension. The target for hypertension was again numbers, and one might argue that elevating MAP by a certain percentage above baseline might have been a better way than trying to achieve a set value in all patients. However, this was an observational study documenting the routine practice in the unit.

Deviations in this study

When these probes were inserted, patients were informed that these were just for observation but, should the clinician in charge wish to use these values to guide therapy,

we would not intervene in the matter. In 1 comatose patient, there was an acute drop in LICOX values, which triggered commencement of hyperdynamic therapy. However, this was later found to be secondary to pulmonary edema and the patient had developed AIND as evidenced on subsequent scan.

Interpretation of Results

There was a huge baseline variation in the readings of rCBF, both mean and range, between patients, which makes it difficult to set a threshold for tissue ischaemia with regards to rCBF measurement alone. Previous studies which set threshold values have done so on basis of animal studies or readings in comatose individuals. However, as demonstrated clearly in the chart below, 6/14 awake patients had values well below the ischaemic threshold which is based on the above mentioned studies and were completely asymptomatic. The equipment was well calibrated. The observed measurements in these patients trended as expected raising doubts over accepted threshold for normal rCBF values. While based on 14 patients, it is not possible to conclude on range of CBF levels considered normal, this finding signifies the importance of trends over arbitrary thresholds.

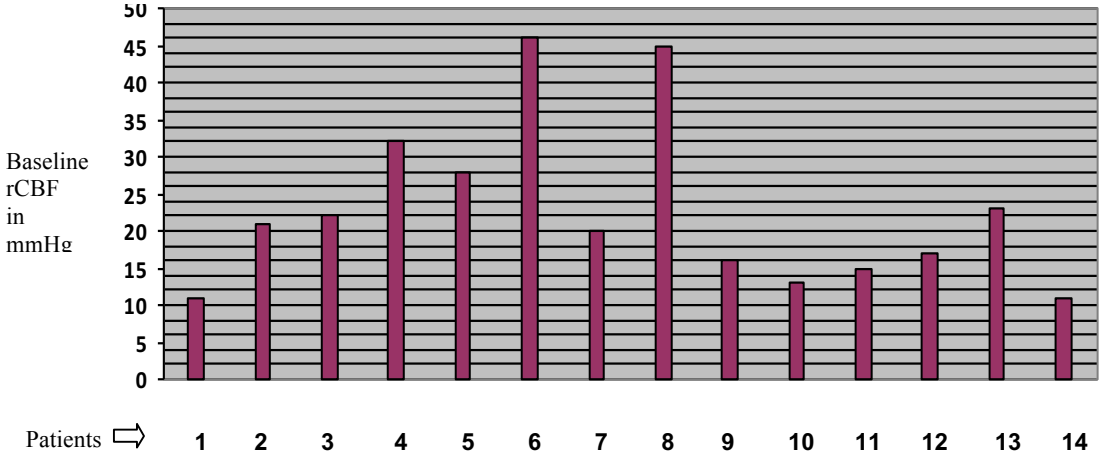


Fig. 2.41:The graph depicts mean baseline perfusion values i.e. average CBF values in pre-symptomatic phase with exclusion of immediate post probe insertion values. Y axis reads CBF in mls/100g/min. Each bar on X axis represents a single patient.

The oxygenation values also had similar variation with respect to numbers but pTiO2 graphs did parallel MAP graphs. This can be explained as the dissolved tissue oxygen being measured here may be directly affected by transarterial pressure gradient. This finding is supported by recent work by Woitzik, 2012, which states that pTiO2 values parallel CPP. While ICP remains constant after the bleed in SAH patient, CPP will be directly proportional to MAP. This finding further supports that pTiO2 numbers recorded were correct and trends over time were more informative than isolated values.
The mean values for CVP, MAP, rCBF and pTiO2 did not differ between asymptomatic, DIND and AIND patients and there was no change in the trend on rCBF or pTiO2 graphs in symptomatic patients contrary to what one would expect from the current hypothesis (please refer graphs in results section).

Values of Microdialysis parameters best correlated with symptoms, consistent with previous studies (Sarrafzadeh, 2002). Interestingly, the pattern of microdialysate changes was different in our patient population, compared to Sarrafzadeh study.
The changes of rising lactate alone with resultant raised lactate pyruvate ratio were only seen in patients who clinically had AIND, either secondary to vessel occlusion post coiling/clipping or secondary to acute cardorespiratory compromise. This was associated with a rise in glycerol in cases with established infarcts on CT. In patients with DIND and in asymptomatic individuals a simultaneous rise in both lactate and pyruvate was seen around day 5. In symptomatic individuals, this concurred with onset of DIND.

In order to interpret these changes correctly, we first have to understand what is meant by raised lactate what is lactate/pyruvate ratio, brain basal metabolism and how it changes with increased need.

With reference to processes explained in chapter 1, at basal metabolic rate, the respiratory quotient(RQ=Carbondioxide(CO2) produced per mole of Oxygen(O_2)+ substrate burnt) of brain is 1, indicating that carbohydrates are main energy substrates and are fully metabolised to CO_2 and water. Amongst physiologically tested carbohydrates glucose is the only one that can sustain normal brain function. Lactate and pyruvate can sustain synaptic function but they cannot cross blood brain barrier and have to be produced within the brain parenchyma. Glycolysis is the metabolism of glucose to lactate and pyruvate, producing 2 mol ATP and reducing equivalents. Pyruvate can further enter tricarboxylic acid (TCA)cycle to produce 30 mol ATP. Estimates of enzyme capacity reveal that oxidative phosphorylation of glucose operates at maximal strength at basal rate. Any increase in demand has therefore to be met by glycolysis. Studies of activation in animal models and humans confirm increased lactate in the brain parenchyma with increasing demand. However the RQ for the whole brain remains 1 even in situations of increased demand. This can be explained by metabolic trafficking between glial cells and neurons. The increased energy need is primarily met by glial glycolysis. The lactate and pyruvate so produced are released in the interstitium which is taken up by neurons for further metabolism through TCA cycle. If TCA cycle is operational, lactate will get converted to pyruvate and enter TCA cycle, lactate-pyruvate thus remaining in equilibrium. If TCA cycle is hampered (lack of O_2) lactate alone shall rise. Immunohistochemical and cytological studies support this view.

That elevation of lactate due to increased glycolysis by glial cells and elevation of pyruvate due to increased aerobic respiration by neurons is the plausible clinical picture in SAH, is further supported by A-VdO_2 studies. At basal rate the arterio-venous difference of Oxygen (A-VdO_2) is 50%. In SAH this has been noted to variously increase, remain same or decrease, irrespective of vasospasm. Outcome is better in patients with unperturbed A-VdO_2 (Pereira RS, 1997). If whole metabolic rate goes up, A-VdO_2 will

remain unchanged with intact flow-metabolic coupling or can increase if the CBF fails to catch up to the increased demand. If glycolysis was separately meeting immediate energy needs, then only A-VdO_2 will be expected to decrease, unless the tissue was infarcted and being bypassed.

Coming to metabolites, isolated rise in lactate would thus suggest impairment of oxidative phosphorylation which may be due to hypoxia or evidence of neuronal death. While, increased lactate and pyruvate in the interstitium, where these are measured by microdialysis, mean increased demand.

An alternative view to the current hypothesis would be that it was rise in the metabolic rate rather than shift to anaerobic respiration that secondarily led to lack of metabolic substrate and cellular ischaemia of DIND or in other words primary outstripping of supply due to increased demand rather than a primary supply problem.

The findings of this study are further consistent with what might be the expected metabolic picture in a case of cortical spreading depolarisation(CSD) seen with aSAH. With CSD it is seen that the metabolic rate goes up. It is noted that in aSAH due to constant potassium load and presence of nitric oxide scavengers from the subarachnoid blood, the perfusion response to CSD changes from hyperaemia to ischaemia. As a result, intermediate recovery/intermediate depolarisation is seen. This leads to a prolonged slow potential change in the ecf. This prolonged slow potential change noted in aSAH patients in CSD studies agrees well with the slow global change in microdialysate (potassium and metabolites) observed in this study which appears to become symptomatic at a point where there is imbalance of supply and demand as against the acute ischaemic rise of lactate noted in individuals with onset of symptoms more typical of AIND.

Reasons for the discrepancy from previous studies-

Previous studies have looked for evidence to support the traditional hypothesis and confirm whether or not lactate and lactate/pyruvate ratio were elevated in DIND. While lactate and lactate/pyruvate ratio was found to be raised in DIND, this was not significantly different from the asymptomatic patients. Also these studies have not reported on a rise in pyruvate. The rise in lactate was more specific than lactate/pyruvate ratio in preceding DIND features; which could be explained by a possible simultaneous rise of pyruvate.

The microdialysate analysis of this study may be flawed, accounting for parallel changes in lactate and pyruvate but if this were true changes in glucose and glycerol should parallel lactate and pyruvate too, which was not the case. In a majority of cases, glucose declined with rising lactate and pyruvate or remained constant. Glycerol did not rise in any of the DIND patients.

Potential explanation for rising metabolic rate-

Previous work has informed us that cerebral metabolic rate drops acutely after aSAH. This elevated rate might represent a return to basal level. However, this explanation seems less likely as the stop-flow phenomenon and resultant metabolic depression is likely to be short lived. If the initial readings in fact represent a suppressed metabolism, one would not expect patients to be cognitively intact. Lastly, the values measured in the initial asymptomatic phase in this patient group are similar to those in healthy individuals (Tisdall, 2006).

One of the reasons for the secondary rise in lactate and pyruvate at day 3+ in these patients could be as a response to rising extracellular potassium concentration.

Glial metabolism accounts for majority of cerebral metabolism measured with microdialysis. Glia are responsible for mopping up excess glutamate and potassium

(both raised in these patients). This is an energy consuming process resulting in overall raised metabolic rate.

Also, the larger the red cell load, the larger the rise in ECF potassium from red cell break down, and the larger the glial and neuronal need for a metabolic rise to maintain intra and extracellular ion differentials and consequentially larger the risk of developing DIND. To date, the amount of blood load is the only factor that consistently predicts the likelihood of DIND, which also lends some support to this proposition.

Trend of potassium-

In this study we measured potassium ion concentration in the microdialysate and found it to parallel lactate and pyruvate changes. The potassium levels observed here were in range comparable to other studies (Bhatia, PhD thesis London 2010 -unpublished).

In the current study the samples were pooled samples for 6 hours. Hence, it was not possible to ascertain whether changes in potassium pre-empt metabolic changes. Theoretically, as detailed above potassium rise could be occurring first followed by increased requirement of energy for driving sodium potassium pump to maintain cellular integrity, thus leading to increased metabolic rate. Equally, it could be that ischaemic change manifesting at this time was leading to neuronal breakdown and subsequent release of potassium ions. However, if this was to be true, then potassium should parallel glycerol trend and this was not what was observed.

Certainly having 6 hourly data is a shortcoming of this study and in future studies online microdialysate analysis alongside potassium flowcell would enable to better decipher this picture.

Response to Triple H-

Consistent with the findings of previous studies, we did not see any change in metabolic profile but symptoms improved with administration of hyperdynamic therapy. This was associated with an improvement in MAP, CBF and pTiO2.

In the traditional DIND hypothesis, this improvement was expected, but then there should have been reversal of the lactate rise and lactate/pyruvate ratio.

With the alternate hypothesis suggested by this study, the findings represent restoration of demand-supply balance and hence symptom reversal with persistent rise in metabolic rate.

Also, as discussed above, only Double H (hypervolaemia and hypertension) were used in this study as per unit protocol. Change in MAP was probably the most important factor, but we did not have very accurate tools i.e. pulmonary capillary wedge pressure, body weight etc. to measure volume changes, which might therefore underrate the effects of volume alterations on symptoms.

Difficulties encountered

Consent – This was a difficult study to obtain patients' consent as there was no direct patient benefit from an invasive monitoring process. Besides there was a limited time window to discuss and explain a rather complex disease.

Logistics – Availability of theatre time was a major logistics issue. At least 20 minutes were needed for monitor placement and cleaning up under GA prior to coiling in an interventional radiology suite. In a busy radiology department time pressures often led to prioritisation of clinical need over research activity. The cooperation of non-research staff was paramount and not always forthcoming.

We lost three consented patients from the study due to inability to place monitors due to lack of theatre time. These were not sicker patients, the reason for lack of theatre time were more number of patients that needed endovascular procedure on the given day.

Funds – All neuromonitoring is expensive, with probes costing between 250-1000 GBP. We accepted free probes from Licox to help with the funding. Being a small research unit we could not afford research nurses and were short on manpower. We could not afford the online microdialysis machine and had to share it with another centre. Also, the monitoring frequency for Microdialysis had to be curtailed to 6 hourly rather than hourly which we would have preferred. This was to ensure the researcher could change the vials and put them for storage round the clock for 5 days. SAH patients come in batches, with well accepted SAH season. We had monitoring equipments only able to accommodate 1 patient at a time. So, if a patient was recruited, none others could be recruited for 5 days. We did manage to loan extra equipments on a couple of occasions but timely supply of the same cannot be relied upon. As such 6 eligible patients could not be recruited into the study. Better funding might thus have improved the study by addressing these shortcomings.

Limitations: As explained before, this is a pilot study and due to limited numbers, the results cannot be used to prove or disprove any hypothesis, but serve to give directions to future work. Current approach was most practically feasible but we could have improved the accuracy of results with online microdialysis, and minute to minute monitoring of oxygenation as against hourly readings. One of the other major flaws is that we are not necessarily in the territory of the aneurysmal bleed, and all these findings need to be interpreted in the light that DIND is a global process, manifesting specific symptoms in regions where matters are worst. Of course this supposition could be

wrong and this might just represent epiphenomenon of increased metabolism in normal brain tissue while some parts of brain are suffering ischaemic damage. However, if CBF-metabolic coupling was responsible for this increase, then we should see a rise in rCBF readings, which was not the case in this study. Last but not the least, in future studies, incorporation of monitoring of cerebral electrical activity should accompany CBF, oxygenation and MD.

Chapter 3

Exploration of long term cognitive and functional outcome after aSAH

This chapter describes the second part of my work. It elucidates the long term cognitive and functional difficulties encountered by these patients. It also explores the interactions between physical and cognitive deficits, mood disorder and patient outcome to enable better detection, assessment and management of these problems in rehabilitation.

3.1 Introduction:

As per the literature detailed in Chapter 1, as well as a recent systematic review thereof (Al-Khindi, 2010), we know-

- Long term outcome of aSAH patients is associated with significant cognitive and functional deficits compromising return to social and economic productivity even in wake of good outcome as measured on the physical scales- Glasgow Outcome Scale(GOS) or Modified Rankin Scale(MRS).
- Studies exploring these deficits lack consistency with respect to- patient groups assessed (with or without controls, severity of deficits by GOS or MRS categories included in the study), methods chosen (objective or subjective), assessment tools or scales chosen with variable cut-offs therein for identifying and classifying pertinence, time to follow-up and associations of cognitive and functional deficits with clinical aspects.
- Consequently, there is limited understanding of how these deficits may interact to result in a quality of life for a given patient and there are no measures of assessment or management of these problems in day to day practice.

In this work, the aim was to explore functional and cognitive deficits after aSAH by administering a battery of patient reported outcome scales and thereby better understand the correlation between different components of health status in aSAH patients and to derive a set of tools that will help easy, uniform and early identification of subtle but clinically significant neuro-psycho-social deficits in this patient group to guide appropriate management / rehabilitation.

3.2 Methods :

In order to achieve the above aim, we first needed to identify deficits. This could either be done through objective clinical assessment or subjective evaluation. The objective route would offer more reliable and uniform assessment but at the same time would fail to measure the patient's perspective of the disease and its impact. Hence, we chose to abide by subjective route. Again we had a choice of semi structured interviews v/s structured self reported scales. The former needed a great number of resources, time and expertise, at the same time it did not meet our objective that the assessment offered should be quick, easy and universally available to ensure its applicability on a wide scale in treatment and rehabilitation. Therefore we chose to administer a battery of well known validated patient reported outcome measures. The scales chosen had been used variably in SAH or in patients with other forms of stroke and covered all deficits and disabilities that had been reported in SAH patients. Descriptive analysis of the results was very valuable. But to understand the interactions between different factors further statistical tests - logistic regression and structural equation modelling(SEM) were applied. The reasons for this choice are detailed later in this chapter in section 3.4.

The rest of this section details the methodology used in this study enlisting the Research Group, Ethical Approval, Study Design, Patient Selection and Data Analysis.

Research Group

The research team for the study comprised of the Leeds Neurovascular Research Consortium. The study took place in two cohorts. The first cohort covered patients from 1998 to 2003. The second cohort ran from 2004 to 2008. Research fellows Mr. Hall and Mr. Al-Tamimi with the then research nurses in the Department of Neurosurgery at Leeds General Infirmary were mainly responsible for the data collection in first cohort. I was responsible for data collection for the second cohort and for data analysis for the whole study. Ms. Vicky Lane, secretary in Department of Rehabilitation Medicine, University of Leeds, helped with printing and postage of questionnaires. Supervision was provided by Dr. Audrey Quinn (Consultant Neuro-Anaesthesia and Neuro-Intensive Care), Mr. Stuart A. Ross (Consultant Neurosurgeon and Principal Investigator) and Prof. Alan Tenant (Consultant Rehabilitation Medicine, University of Leeds).

Ethical Approval:

The study was approved by the West and Central Yorkshire ethics committee (Ref 08/H1313/95).

R&D approval and sponsorship was obtained from Leeds Teaching Hospitals NHS Trust.

Patient Selection:

All patients admitted to the neurosurgical department at LGI are routinely entered onto a neurosurgical database. This database was accessed and all cases with a diagnosis of aSAH were selected. The NHS Patient Administration System database was then used to identify and exclude any deceased patients. Using this database, 376 surviving patients were identified. Two patient cohorts were selected between 1998 and 2008. The second cohort straddled the introduction of coiling procedures to the unit.

Postal Questionnaires with covering letters were sent out to the patients. All patients who did not respond were sent a follow up reminder letter.

As these were self reported outcomes, it was important that the patients understand the questionnaire and hence all participants who failed the short-sentences test were excluded from the analysis.

Questionnaires were only sent out to patients who were at least 12 months following their aSAH.

Study Design and Statistical Analysis:

This was a questionnaire based survey, incorporating patient reported outcome measure (PROM) scales that investigate known aspects of neuro-psycho-social deficits. The scales were validated in stroke patients including those presenting with SAH and included- AKC short sentences test- in the first place to assess if the patient could understand the questionnaire, Everyday Memory Questionnaire (EMQ)- to assess memory and concentration, Dysexecutive (DEX) Questionnaire- to interrogate the complexities of social interaction and structured thinking, Barthel Index- to detect physical disability, Stroke symptom checklist- to give an overall assessment, Stroke QOL- a quality of life measure and Wimbledon self-report scale (WSRS)- to assess mood. Postal versions of the questionnaires were selected. Only free or those 'licensed for use by University of Leeds' questionnaires were included. Fortunately, we did not have to exclude any desired scales. Alongside, the clinical and demographic data for these patients was also retrieved including age, sex, clinical features at presentation, severity of bleed, management and mRS at the time of follow-up.

Table 3.21 gives further details on the battery of questionnaires:

Table 3.21

Questionnaires

AKC Short Sentences Test. A simple 10-point test to confirm that the patient is able to read and understand the booklet. Scores range from 0 to 10.

The Postal Barthel Index (BI). A 10-item list that measures physical ability by assessing various aspects of mobility and activities. The patient rates their level of independence in each of the activities according to specified criteria. Scores range from 0 to 100.

The Self-Report Dysexecutive (DEX) Questionnaire. The DEX questionnaire is a standardised self-report measure of behavioural difficulties associated with executive functioning such as impulsivity, inhibition control, monitoring and planning. Here the patient rates the frequency of difficulties with emotions or personality, motivation, behaviour and cognitive problems on a 5-point scale ranging from never to very often. Scores range from 0 to 80.

The Everyday Memory Questionnaire (EMQ). A 35-item questionnaire assessing the incidence of memory failures based on different everyday errors. For each of these errors, the patient rates the frequency of these errors ranging from ‘never’ (score of 0) to ‘all the time’ (score of 4). This has originally been described following head injury.

Stroke Symptom Checklist (SSC). An informal checklist of 12 common symptoms (including effects of mood, cognition and physical problems) that are associated with

brain injury. Patients score a point if symptoms are worse now than prior to their illness. Scores range from 0 to 12.

Wimbledon Self-Report Scale (WSRS). The Wimbledon Self-Report Scale was originally standardised on a hospital population with predominantly neurological disorders. It provides a general appraisal of mood rather than being limited to specific symptoms of anxiety or depression. The patient has to rate the frequency with which 30 emotions occur on a 4 point scale ranging from most of the time to not all. Using the original dichotomised scoring system of 1100, scores of 0-7 are considered normal, 8-10 are borderline and 11-30 represent clinically significant mood disturbance.

Modified Rankin Score (mRS). The MRS has been widely adopted in Stroke research as the primary clinical endpoint in most trials. It is a 6-point scale of independence and difficulties with activities of daily living, ranging from needing constant care to complete independence.

A needs-based Stroke-Specific Quality of Life scale (Stroke-QoL) was introduced for Cohort 2. This is a new holistic scale potentially appropriate for this diagnosis, as some of the original qualitative work was undertaken including those with ASAH. Comprising 30 dichotomous items, a high score represents a poor quality of life.

The idea was to filter which PROMs were most relevant for this patient group, understand their interaction so as to achieve a conceptual model like the one proposed below and to contribute to the development of condition specific PROMs for aSAH-

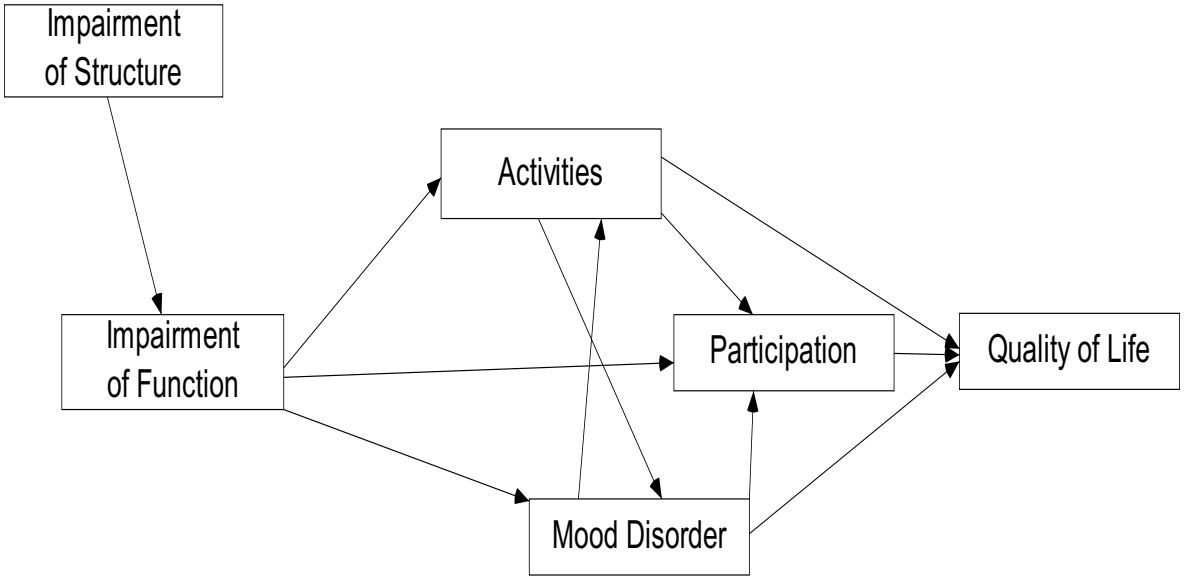


Fig.3.21: Conceptual bio-psycho-social model for SAH depicting impairment of function due to haemorrhage leading to deficits in physical, psychological and social abilities which interact with each other to result in a specific overall quality of life for the individual patient.

The data was first processed via exploratory factor analysis and rasch analysis (both detailed in section 3.3) to ascertain validity of the scales used in this patient group. It was then entered onto SPSS version 17 for a descriptive and comparative analysis and backward logistic regression. Further processing in AMOS was done for structural equation modelling. The basic concepts of these statistical techniques are detailed later in this section. The reasons for this statistical tool selection with their pros and cons are further detailed in section 3.4.

Outcome Measures:

Results for all the scales were analysed with respect to three outcome measures- for factors affecting return to work, quality of life and MRS at follow-up.

The main idea of the work was to assess the neuropsychosocial impairment and hence return to work, that offers a holistic objective assessment of back to normalcy for the individual, was chosen as the outcome measure. The second outcome measure was the new quality of life scale. This aims to directly measure up what we would infer from return to work. However, this scale was only available for half the patients (cohort 2) and is not well established in SAH patient group as yet. Therefore, lastly, to maintain uniformity and comparability with literature, MRS was chosen as last but not the least of the outcome measures.

Statistical Tools:

Descriptive analysis: This was used for exploring demographic details of our patient population and to explore what deficits are found and how commonly in aSAH patients.

Comparative analysis: This analysis used Chi squared tests to compare proportions in coiled and clipped patients.

Logistic regression: Logistic regression analysis is a statistical test that helps to find out which independent variables presented simultaneously predict a given outcome when the dependent or outcome variable is dichotomous. It generates the probability of a given outcome with each set of predictor variables. We used a modification- backward logistic regression in this study. In this, factor that least predicts the outcome is removed first and so on until only factors that significantly predict outcome are left. The cut-off for probability is chosen at a significance level of .05 in most cases and this cut-off was adhered to in this study to assess what predictors (PROMs) significantly predicted likelihood of return to work and quality of life respectively. The benefit of logistic

regression is that it is exploratory. The down side is that it does not tell us about any indirect effects or interactions between predictors and if two predictors are closely associated to each other one of them is removed.

SEM: Structural equation modelling is an extension of linear regression. The difference is that this is confirmatory and not exploratory i.e. we have to put in predictor and outcome variables by constructing a plausible hypothesis based on prior knowledge and the test tells us how the predictors affect outcome. It will test the goodness of fit of the proposed model to our data and if the goodness of fit is adequate, it argues for plausibility of the proposed interrelations amongst variables. It addresses the shortcoming of regression by finding associations between different predictor variables and thus fully exploring their direct and indirect effects on outcome variable. It can also asses effects of independent contextual variables on the predictor-outcome relationship. Downside is that this can only work like linear regression and not assess binary outcomes. We used SEM to find causal associations between patient deficits as measured on PROMs and patient assessed MRS as outcome variable.

3.3 Results :

Response Rates and Patient Characteristics

97 patients from the first cohort and 117 from the second cohort returned completed questionnaires thereby achieving an overall response rate of 214/376 i.e. 57%. Analysis for non-response bias revealed no significant difference for age (t=0.838; p=0.403), gender (Chi-Square 0.902; p= 0.376) or WFNS on admission (t=0.811; p=0.418) between responders and non-responders.

The mean age of the responders was 56.6 years (SD10.7). 68% of these were females. Most patients (76%) had presented with a WFNS grade 1 or 2 subarachnoid haemorrhage.

70% patients had anterior circulation aneurysms (where P-Com's are classed as posterior circulation), of which A-Com was the most frequent location.

As per the two cohorts, 41.3% patients of cohort 2 had been coiled.

There was no significant difference for age – mean age 55.5 (SD 12.37) for cohort 1 and 57.40 (SD 9.12) for cohort 2 (t=1.254; p=0.225) or gender 62% females in cohort 1 and 73% in cohort 2 (Chi-Square 3.3; p=0.79) between the 2 cohorts(Table 3.31 and 3.32, respectively).

They were similar in presenting WFNS and Fisher grades and had no difference in outcome as measured on MRS (Table 3.33) or employment status Pre (Table 3.34) or Post (table 3.35) aSAH.

		N	Mean age in years
Cohort	1	97	55.5521
	2	117	57.4017

Table 3.31: Distribution of cohorts by age: statistical analysis of data showed no significant difference(Students' T test p=.225)

		Gender	
		Males	Females
Cohort	1	37 (38.1%)	60 (61.9%)
	2	31 (26.5%)	86 (73.5%)

Table 3.32: Distribution of cohorts by gender: statistical analysis of data showed no significant difference(Chi^2 test p=.79)

		Rankin Scores		
		Gr I (MRS=0-1)	Gr II (MRS=2-3)	Gr III (MRS=4-5)
Cohort	1	37 (53.6%)	23 (33.3%)	9 (13%)
	2	49 (45%)	38 (34.9%)	22 (20.2%)

Table3.33: Distribution of cohorts by outcome (MRS): statistical analysis of data showed no significant difference(Chi^2 test)

		Employment status before SAH	
		Unemployed	Employed
Cohort	1	35 (36.1%)	62 (63.9%)
	2	42 (35.9%)	75 (64.1%)

Table3.34: Distribution of cohorts by employment status before SAH: statistical analysis of data showed no significant difference (Chi^2 test)

		Employment status after SAH	
		Unemployed	Employed
Cohort	1	63 (64.9%)	34 (35.1%)
	2	80 (68.4%)	37 (31.6%)

Table3.35: Distribution of Cohorts by Employment Status after SAH: statistical analysis of data showed no significant difference(Chi^2 test)

As such, for further analysis, the two cohorts were treated as one single group.

Data Validity and Suitability

Before feeding the data for further analysis, we wanted to test if it was valid and suitable to use. As discussed before, all the scales used were well established for use in stroke patients. So, we just had to –

- test the construct validity of these scales with the data we obtained,
- check that the data so obtained were normally distributed across patients thus meeting assumptions for the tests we planned to undertake.

Construct validity defines how well a scale measures what it is supposed to measure- eg. A scale designed to measure mathematical skills must only measure that and not closely related items like IQ or language skills. We used Scree test, a part of factor analysis to assess this. The Scree plot graphically shows the additional variance of each item on a given scale to test if all items are measuring one thing or different things. Scree plots were constructed for all scales we used and we found that all scales loaded on to single factor implying the validity of our measurements. An example of result for DEX scale is given as under-

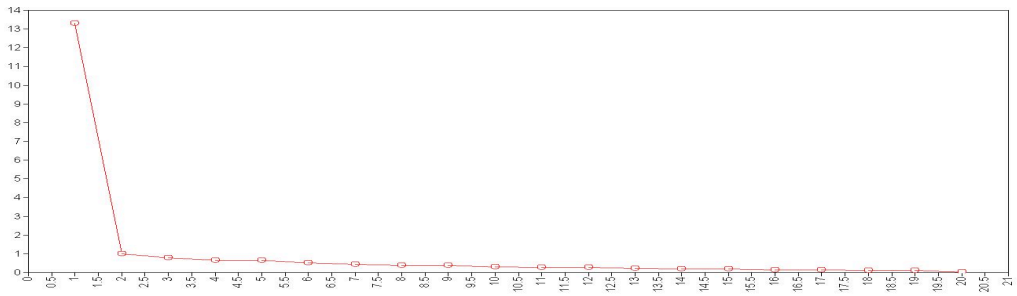


Fig.3.31: Scree Plot for DEX scale from Exploratory Factor Analysis of MPLUS (statistical software) : Scree plots check additional variance of each factor in the test to see if all factor s are measuring the same entity. The graph above demonstrates-

- Root Mean Square Residual of 0.057 is suggestive of a single domain. (recommended level < 0.05)
- All variables loaded on single factor at .7 and above.
- Scree plot indictative of a single factor

To assess distribution of factors measured across patients, we constructed rasch person-item threshold distribution maps for all scales and found expected bell shaped distribution curve for both persons showing normal distribution of person ability and items showing normal distribution of item difficulty as evaluated by these persons(patients). As an example, the model for DEX scale is given as under:

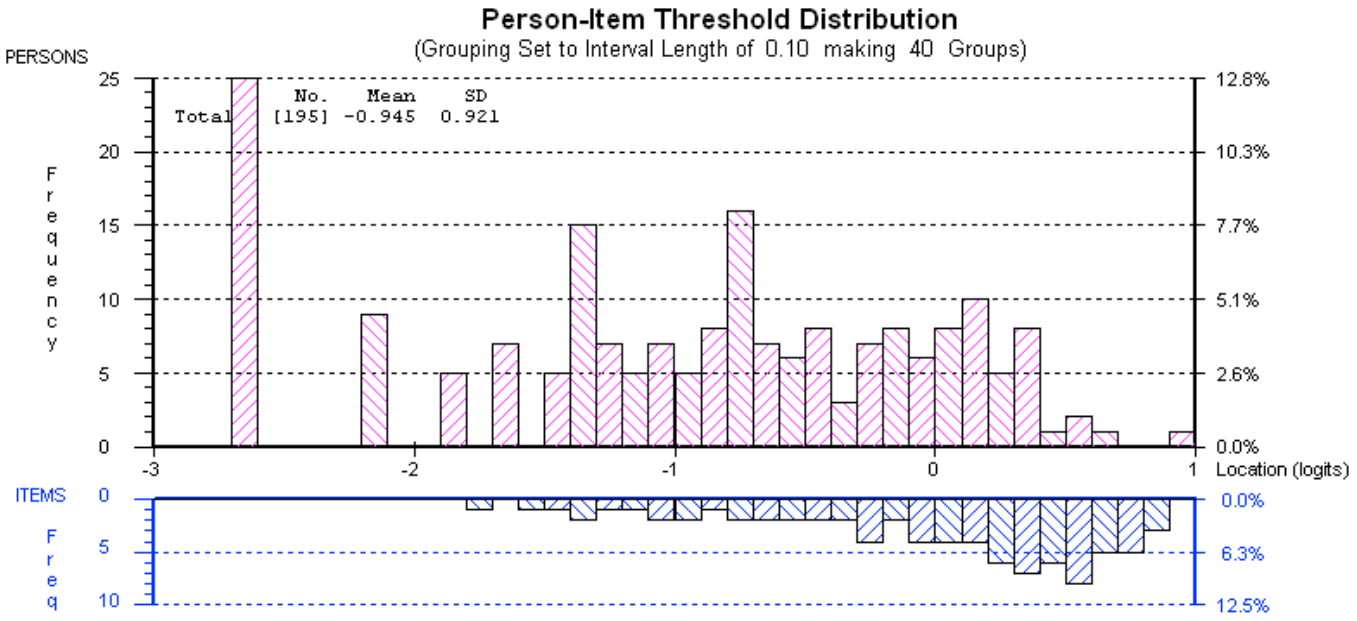


Fig. 3.32: Person-Item distribution threshold for DEX scale.The x-axis demarcates level of ability on person scale(top) and item difficulty on item scale(bottom), y-axis shows person and item frequency respectively for the top and bottom graphs. The graph demonstrates Fit of DEX data to Rasch Model: Mean Item residual -0.079; SD 0.073; Chi Square p=0.25; $\alpha = 0.93$ In plain words, it shows that people who answered the questionnaire had a normal distribution of ability(or so to say disability), negative values corresponding to lesser ability; and normal distribution of item difficulty encountered by these patients, thus making the scale suitable for further analysis.

Thus, our data was found to be valid and suitable for further analysis.

Descriptive results

Table 3.36 shows the responses to the various questionnaires, including the median and inter-quartile range for each scale.

Scale	Minimum	Maximum	Median	Inter-Quartile Range	N.
AKC	7	10	10	10-10	206
Rankin	0	5	1	0-2	178
Barthel Index	27	100	100	95-100	160
Stroke Symptom Checklist	0	12	7	3.5-10	189
DEX	0	76	12	4-26	195
Everyday Memory					
• Speech	0	52	11	4-24	205
• Reading	0	16	2	0-7	208
• Face recognition	0	24	2	1-6	203
• Actions	0	24	2	0-9	209
• Learning	0	23	4	1-9	203
Wimbledon Mood	0	83	18.5	6-38	196
Stroke – QoL	0	29	9.3	2.6-17.0	113

Table 3.36: Responses to PROM questionnaires: Median and inter-quartile range of health status instruments showing good ability to understand questionnaires (AKC), higher independence with activities of daily living(MRS), good physical ability(BI), significant impairment of cognition(DEX), memory(EMQ) and mood(WSRS) in a substantial minority, and lastly, high prevalence of residual symptoms (Stroke-QOL).

The response to the AKC Short Sentences Test indicated that the majority of those who responded to the follow-up were able to read and understand the booklet. Nine-out-of-ten scored a maximum on the test, with only 6 patients (2.9%) scoring 7 or 8/10.

At follow-up, over four in five (82.6%) were 0-2 on the modified self reported Rankin scale, corresponding to a good outcome on the GOS. The majority of those responding also had a maximum, or near maximum score of the Barthel Index with just 20 patients (12.5%) scoring below 80 suggesting, as did the Rankin, that there was little residual physical dependency.

Despite this, a median of 7 symptoms were reported from the Stroke Symptom Check list. Less than one-in-five (19.2%) reported no symptoms. The most common symptom reported was irritability (57.9%), closely followed by anxiety (57.5%). Other symptoms such as headaches or blurred vision were reported by approximately half of patients.

The extent of dysexecutive function indicated that while most patients displayed few signs of impairment of this function, there was a minority who did so (Figure 1). With a median score of 12, one-quarter of patients scored above 26. Likewise problems with everyday memory were absent for the majority, although a significant minority displayed some impairment associated with speech.

A third (33%) displayed borderline/caseness for significant mood disorder on the Wimbledon scale.

Comparative results

In cohort 2 (n=117) where additional clinical information was obtained, there was no association between Fisher grade and the MRS (Chi-Square 3.266; p= 0.195). Neither was there any association between Fisher Grade and type of surgery (Chi-Square 0.212; p= 0.693). Within cohort 2 almost three in five (58.7%) were clipped. There was no significant difference in age (t= .762; p >0.448) and gender (Chi Square 2.164, p=0.112) by type of intervention. Likewise there was no significant difference in the Fisher grade by intervention (Chi-Square 2.854; p= 0.415) or WFNS level (Chi-Square 0.601; p=0.438). Outcomes, including return to work among those previously employed (Chi-Square 0.061; p= 0.806) also showed no difference by type of surgery. However, over half (55.8%) of those coiled were graded as a Rankin score of zero, compared to just under a third (32.8%) of those clipped (Chi-Square 5.48; p= 0.027). Furthermore,

patients who had been coiled reported better levels of mood on the Wimbledon (Mann Whitney U, p 0.037), and a better quality of life on the new Stroke-QoL scale, than those clipped (median 12.7)(Mann Whitney U, p 0.028) (Table 3.37).

	Surgery	N	Mean	Std. Deviation	Std. Error Mean
Qol	Coil	42	8.6194	8.51216	1.31345
	Clip	58	12.2469	8.48338	1.11392
Akctotal	Coil	41	9.8537	.57276	.08945
	Clip	152	9.8553	.45175	.03664
Dextotal	Coil	40	15.7750	18.21170	2.87952
	Clip	142	16.9577	15.70692	1.31810
Barthel	Coil	34	95.9706	7.52565	1.29064
	Clip	118	92.1949	16.66526	1.53416
Speech	Coil	41	14.2439	12.96492	2.02478
	Clip	151	15.5497	14.03600	1.14223
Reading	Coil	43	3.6512	4.09345	.62425
	Clip	152	4.0658	4.48348	.36366
Faces	Coil	43	4.4419	6.00517	.91578
	Clip	147	3.9184	4.87165	.40181
Actions	Coil	42	5.5476	6.48902	1.00128
	Clip	154	5.0584	6.09965	.49152
Learning	Coil	42	6.0476	5.68246	.87682
	Clip	148	5.5338	5.33429	.43848
SSC	Coil	41	5.0976	3.74035	.58415
	Clip	135	7.2148	3.71842	.32003
Wimb	Coil	41	68.0976	22.06446	3.44589
	Clip	142	65.4789	19.81250	1.66263

Table 3.37: Questionnaire responses by type of surgery showing significantly better quality of life, independence with daily activities and mood (Chi^2 test p values0.028, 0.027 and 0.037 respectively for coiled patients; no difference was noted in other scales.

Outcome Measures1- Return to Work (RTW)

For sake of this study, employment included full or partial return to same or different job thereby implying reintegration into social and economic productivity. Within the constraints of the study, we did not have a finer understanding of reintegration of patients who were not in employment prior to SAH.

Associations with return to work

Almost two-thirds of those responding were in work previously, but only one-third (33.1%) at follow-up (Table 3.38). Thus of those previously in full or part-time employment, 48.9% were unemployed at follow-up. To complete the picture, just one patient not previously in work reported full time employment at follow-up.

	Unemployed after SAH	Employed after SAH
Unemployed before SAH (77)	76 (98.7%)	1 (1.3%)
Employed before SAH (137)	67 (48.9%)	70 (51.1%)

Table 3.38: Return to work by prior employment status in SAH patients showing that almost half of those in employment before SAH did not return to work.

Several factors had strong associations with return to work within this previously employed group. For example, those returning to work were significantly younger at a mean age of 51.0 years, as compared to those who did not return, at 56.7 years (t= 4.091; P <0.001) (Table 3.39).

		RTW in previously employed	
		Working	Not working
Agegrp	<51	36 (78.3%)	10 (21.7%)
	51-57	18 (47.4%)	20 (52.6%)
	58-64	13 (30.2%)	30 (69.8%)
	64<	3 (30.0%)	7 (70.0%)

Table 3.39 Return to work in previously employed patients (RTW) by age-group showed that those returning to work were significantly younger than those that did not.

Of those in work previously, and considered to have made a full recovery with a Modified Rankin Score of zero, almost one third (32.8%) had not been able to return to work (Table 3.310).

		RTW in previously employed	
		Not working	Working
Rankin Groups	***I (MRS=0-1)***	***19 (32.8%)***	39 (67.2%)
	II (MRS=2-3)	24 (52.2%)	22 (47.8%)
	III (MRS=4-5)	11 (100%)	0 (0%)

Table 3.310 : Return to work by final Rankin scores . The three groups in each are Rankin 0-1=I, Rankin 2-3=II and Rankin 4-5=III. Rankin scores significantly affected post SAH employment status, however the importance of this table is to show that nearly a third of those previously employed with good MRS did not manage to return to work(highlighted).

One half (50.78%) of those not returning to work were borderline or case for mood disorder, compared to just less than one-in-six (15.7%) of those who had returned to work (Chi-Square 19.05; $p<0.001$) (Table 3.311).

		RTW in previously employed	
		Working	Not working
WSRS Caseness	Normal	59 (64.1%)	33 (35.9%)
	Borderline/case	11 (24.4%)	34 (75.6%)

Table 3.311: Return to work by mood as per Wimbledon Self Report Scale (WSRS) showed significantly lower RTW rate in patients with low mood

As we had collected dichotomous outcome data for return to work, this could not be used for structural equation modelling. A backwards logistic regression was undertaken to identify those factors, which appear to be associated with the ability to return to work, having been previously employed. For this group, age was significantly associated with return to work, as were physical dependency expressed by a Barthel Index score of less than 80, a score of greater than zero on the Rankin, and memory deficits associated with speech (Table 3.312). Thus older people, those with residual physical disability, and

those experiencing memory problems were less likely to have returned to work. The model is adequate with a Hosmer-Lemeshow Goodness of fit test of 0.244, a Nagelkerke R Square of 0.396, and overall correct classification of 73.6%. Although on descriptive analysis mood appears to be affecting return to work, it did not factor in the logistic regression. This might mean either mood disorder may not be affecting return to work, or the effect size may have been small, or that people with speech problems; which correlated with cognitive dysfunction; also affected mood and because of the close association mood did not independently appear as a factor in logistic regression analysis. Also, as a majority of these patients were females, it is possible that any effect of gender was underestimated.

	Beta	Exp	CI	Sig.
Age	-0.116	0.891	0.840-0.945	<0.001
Barthel Index	-0.965	0.381	0.158-0.918	0.032
Speech	-0.715	0.489	0.312-0.767	0.002
Rank (0;1+)	-1.155	0.315	0.130-0.764	0.011

Table 3.312. Backwards logistic regression predicting return to work showing older people with residual physical disabilities and memory problems are less likely to return to work

Outcome Measure 2- Quality of Life (QOL)

There were indications of a considerable impact upon the ability to meet needs as expressed by the needs-based QoL scale. The scale was only used in cohort 2, and patient numbers were not sufficient to use this for modelling.

Associations with QOL-

Splitting the scale at the median value, a logistic regression identified that memory impairment affecting actions (e.g. starting something, then forgetting what it is you wanted to do) is associated with a significantly poorer reported quality of life. Likewise a Barthel Index score less than 80, and significant mood disorder, although with only marginal significance (Table 3.313).

	Beta	Exp	CI	Sig.
Barthel < 80	2.562	12.967	2.933-57.320	0.001
Mood Borderline/case	2.716	12.763	0.903-8.167	0.075
Functional Memory	2.547	12.763	3.586-45.430	<0.001

Table 3.313: Backward Logistic Regression for Quality of Life showing patients with residual physical disability, low mood and memory deficits are likely to have a poor quality of life.

Outcome Measure 3- MRS

With logistic regression for both return to work and quality of life, it was obvious that demographic profile, physical, cognitive and mood disability had a significant impact on outcome. The next goal was to try and understand both manifest and latent relationships amongst these variables that will help to predict the outcome in a given patient. This was achieved through Structural equation modelling (SEM). Because MRS was an ordinal outcome measure with sufficient sample size, it was well suited to be used for such modelling.

With SEM we specially wanted to explore the knitty-gritty of relationships between cognitive functions, affect and outcome as a third of patients with minimal physical disability were still unable to return to productive social life. Thus, physical disability scale was left out of the model.

For carrying out SEM analysis assumptions for multivariate normality were met (Rasch models as described above).

This model informed that cognitive deficits as measured by Dysexecutive index and mood disorder on Wimbledon scale explained a third of variance in outcome measured by self assessed Rankin.

While cognitive deficits and mood disorder directly affect Rankin, cognitive problems lead to mood problems as well causing indirect effect on outcome.

Age does not factor-in in this model, nor does Fisher or WFNS grade. Gender acts as significant independent contextual variable.

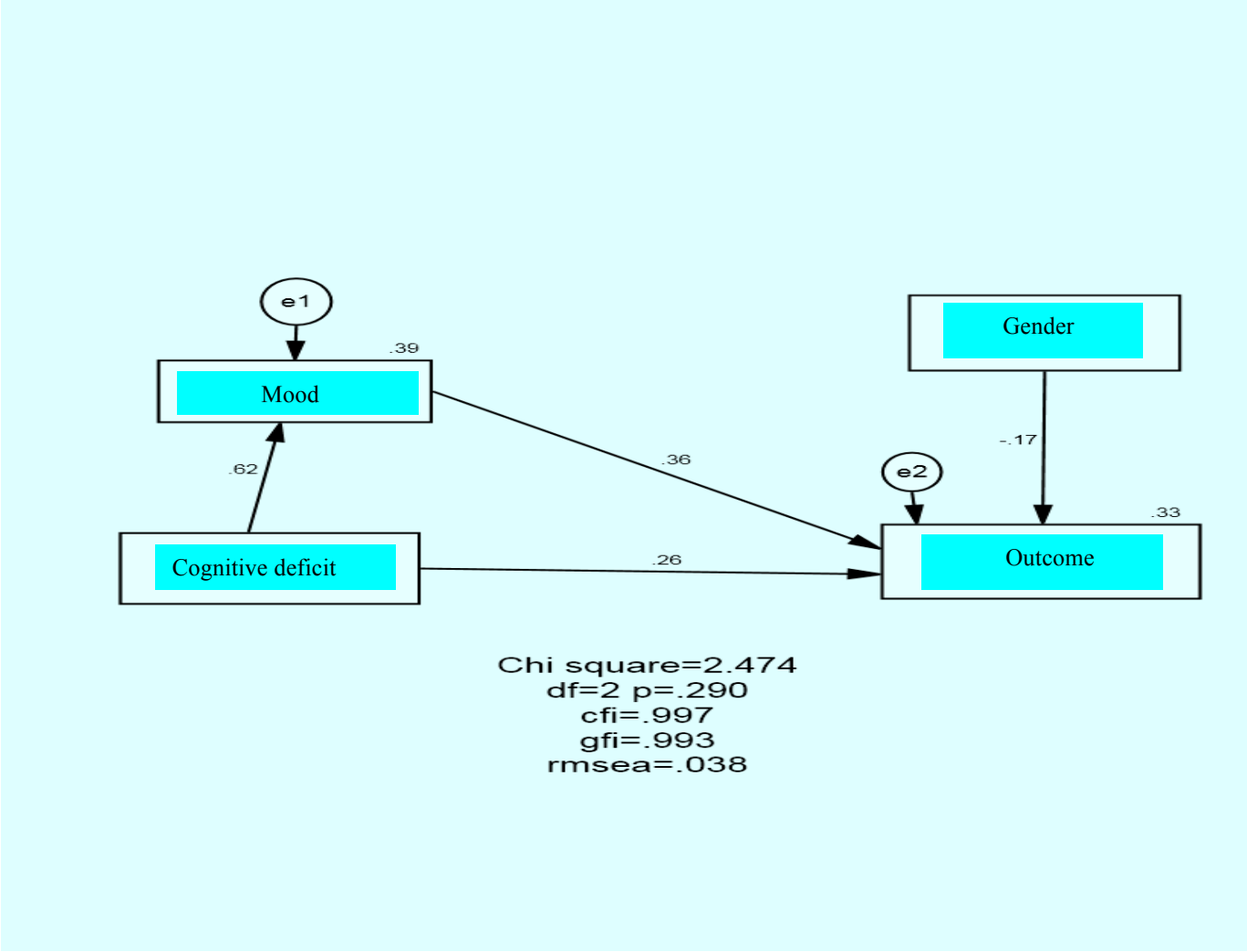


Fig. 3.33:SEM model for SAH, MRS as outcome measure: The model shows a plausible relationship of cognitive deficits, mood and patient's perceived outcome on MRS in context of patient's gender.(Fisher scale, WFNS scale and age were put into the equation but did not show any association, hence not seen in the model). The values on the arrows show weighting/bearing of each item, e1 and e2 represent that inherent errors in measurement have been taken into account. It shows that cognitive deficits and mood disorder in context of patients' gender explain a third of variance in patient reported disability (MRS). Cognitive deficits have direct as well as indirect effect by affecting mood. The indices listed indicate goodness of fit for the model comparing difference between hypothesised and observed model. Chi-square values close to 0 indicate good model fit, these can be influenced by sample size. RMSEA(root mean square error of approximation) avoids issues of sample size, values range from 0-1 smaller values indicate better model fit. Goodness of Fit Index (GFI) and Comparative Fit Index(CFI) are similar indices, values range from 0-1, values exceeding 0.9 indicate a good model fit.

3.4 Discussion :

Patient Profile:

In the United Kingdom over 6000 people are admitted to hospital annually with aSAH, almost two thirds of whom are female, and with a mean age (in 2010-11) of 59 years(Table 3.4a).

Table 3.41: UK Hospital admissions for Subarachnoid Haemhhorage (I60).

Year	Admissions	% Male	Average Stay (Days)
2010-11	6166	37.8	16.7
2009-10	6333	36.7	16.9
2008-9	6278	39.8	16.7
2007-8	6460	36.9	17.6
2006-7	6560	38.3	16.2
2000-1	6631	37.7	14.5

As per literature (Greenberg), 85-95% aneurysms occur in the carotid system, with anterior communicating artery aneurysms (single most common), accounting for 30% of all aneurysms. The posterior communicating artery aneurysms 25% and middle cerebral artery aneurysms 20%. 5-15% aneurysms arise in posterior circulation (vertebro-basilar). Thus the demographic profile of patients in this study and aneurysm location was representative of the general UK aSAH population.

Response Rate and Selection Bias:

Good response rates for questionnaire based studies in UK population are considered to be between 70-80% (Togerson, University of York). We expect the response rates to be lower for more complex patient populations like the SAH group and also as the length of questionnaire increases.The response rate for the first cohort in our study was 54% and

for the second cohort 60%. The questionnaires in the second cohort were accompanied by a cover letter about the study and the potential benefits of the information obtained, a self addressed reply envelope was included and the patients who did not respond to the questionnaires within 3 weeks were sent a reminder to increase the response rates. Calling the non-responders could have been one of the options to address any queries directly and increase the response, however, this was considered to be intrusive without previous consent as discussed in the Ethics Committee and the idea was dropped. It was also discussed at Ethics Committee whether responding to a disability questionnaire might increase the stress levels in individual patients with significant mood disorder and as such the cover letter was worded to say that “some of the questions might be disturbing and please ignore this questionnaire if you are feeling particularly low”. The response rates thus achieved were lower than what we expected but we were able to show that no bias existed for age, gender and GCS level. Nevertheless, it is possible that those who would have scored much lower on the AKC Short Sentences Test, indicating problems understanding the questions, chose not to respond. Equally those with significant depression are less likely to have responded. If this were the case, then the study would understate the true impact of aSAH upon peoples’ lives as a result of systematic selection bias. This might also be the reason why our MRS outcomes were better than other studies.

Duration of follow up

The time course of recovery for cognitive and functional deficits seems to be longer than physical symptoms. While some authors suggest that cognitive symptoms are present well beyond 3.5 years (Ljunggren, 1985), others suggest an improvement between 3 and 12 months in about 30% of those affected (Powell -2002, Springer -2009). Some previous studies have covered a minimum of 6 months period of follow up. However, in

view of the above, in order to assess long-term cognitive and functional deficits, a minimum of 1 year follow up was chosen for this study.

Choice of Assessment Method and Assessment tools:

Assessment Method

In this study we used Self Reported Outcome as the assessment tool. An alternative objective structured clinical assessments / qualitative approach would be possible, however, that would be more time consuming, costly and not achieve the same goal. Our approach allowed for patient involvement in larger numbers and solved the purpose of teasing out relevant information from multiple scales for formulation of a simple assessment tool that could be similarly administered for future monitoring.

The downside of Self Reported Outcomes as discussed previously is the systematic selection bias due to non-response and missing values in the questionnaire. To deal with these issues, the responders and non-responders were compared for demographic profile to rule out significant selection bias. The missing values were imputed using rasch latent estimates.

Assessment Tools

The assessment tools were selected to cover physical, cognitive, affective and functional aspects of patient's health. All questionnaires used in the study had been validated for this patient group and for postal administration. At time of use the questionnaires were freely available, however, subsequently DEX questionnaire needs licensing, which might affect its use in future studies. We found that Speech scores on the Everyday Memory Questionnaire parallel DEX scores in this study and subject to confirmation in other studies, this might offer a surrogate tool where DEX cannot be used for lack of resources.

Outcome Measures chosen:

SAH itself is not a single disease entity but a heterogeneous constellation of clinical manifestations after bleeding in the subarachnoid space depending on the location of aneurysm, severity of bleed and post haemorrhagic complications- hence finding one outcome or test to assess outcome in all patients is a holy grail.

We chose to use three outcome measures – return to work, modified Rankin score and quality of life in this study. The results obtained for each individual PROM scale were tested for association with all of these outcome measures.

Return to work is the most objective assessment of impairments and disabilities or in short 'real-world functioning' of an individual. We used it for picking up return to social productivity. However, since return to work was a dichotomous outcome, we could not use SEM analysis for this and logistic regression had to be done. In hindsight, we could have further improved the sensitivity of this measure by grading it as return to same level /full time work or another/part time work.

MRS is a measure that assesses activities of daily living (ADL). It thus provides only a broad discontinuous ordinal assessment of patient's ability. In this sense it is weak outcome measure. However, assessing MRS offers better comparability of results to literature, as this is the most widely used tool to assess patient outcome in aSAH. Being ordinal meant that it could be used as an outcome measure for structural equation modelling.

Third measure was QoL, the locally developed Stroke QoL tool was used for this. QoL tool gives most holistic picture of patient experience. Unfortunately, we did not have sufficient patient numbers on QoL scale and it is not previously validated in this patient group to be used as the sole outcome measure in this study.

Statistical Tools used:

Descriptive analysis: This gave an overview of our sample population and the deficits experienced by them, thereby enhancing our understanding of the nature and extent of problems and enabling comparisons to similar works in literature.

Comparative analysis: There is not much concrete knowledge about the differences in neuropsychosocial outcomes between patients treated with clipping or coiling. Comparative analysis of PROMs with respect to this subject added further to the current limited evidence base.

Logistic regression: Logistic regression analysis as discussed before in section 3.2 is the only way to explore associations with binary outcome variables like return to work, thus this was chosen. It is exploratory and not confirmatory, thus can only show associations. We were aiming to measure more or less the same thing i.e. back to normality with both return to work and quality of life as outcomes. Apart from age, that is expected to affect return to work; corroboration of predictor variables for both these outcomes lends credence to the findings of our study. Added benefit of doing logistic regression was that in conjunction with previous literature we could use these results from logistic regression to inform our structural equation model.

SEM: Structural Equation Modelling was chosen as it is the sole confirmatory tool to assess relationships in multivariate setting with linear outcome variable like MRS. It also met our aim of being able to decipher the inter-relationships of various health statistics and construct a simple model to inform further assessments and interventions in this group of patients.

Our SEM Model Justification:

From previous studies and logistic regression for return to work in this study we knew that physical deficits as measured on Barthel Index affect the disability as perceived on Modified Rankin Scale. However, in this study it was noted that even good grade patients i.e. with minimal physical disability find it difficult to return to social and economic productivity. We also know that cognitive deficits and low mood affect outcome. We wanted to get a feel for other important factors besides physical disability, explore relationship between these factors and outcome and knowing that poor cognition can affect mood we chose to use this simplistic model (figure 3.33). Other factors that were considered in this model were age, gender, WFNS and Fisher scores. Only gender affected outcome by acting as an independent contextual variable, i.e. the relationship between cognition, mood and outcome varied depending on patient's gender. Factors that were not included in the model were ethnicity and level of education and if I had a chance to do this study again, I will include these factors.

What does the SEM model add to our understanding- SEM is better than logistic regression. Using SEM to assess relationships instead of linear regression, we found that cognitive deficit is acting behind the scene. Without SEM, the regression model would have put more weight on mood, but with this model we understand that poor cognition accounts for a lot of variance in mood and so directing our intervention to address cognitive disability is equally important (figure 3.33) as efforts to improve mood.

Relationship between EMQ and DEX: EMQ is an assessment of functional memory while DEX is indicative of overall cognitive functionality. In this study speech on DEX and EMQ related to poor outcome and were closely associated to each other. Since DEX is a paid test, we could substitute EMQ for DEX.

Gender as independent contextual variable- Since early days in SAH studies it is known that gender affects incidence, severity and prognosis, even affects outcome- probably as this depends on male and female perception of deficits and disabilities, expectations and their coping strategies.

Results in comparison to literature

Patient demographics, overall rates of cognitive and functional impairment in specific domains in our study were compatible with outcomes expected as per literature, as were the outcome measures of return to work rate and MRS, thus reinforcing the comparability of our patient population and validity of data collected.

Factor analysis of individual scales further supported their validity in this cohort. Furthermore, there was a hierarchical ordering of items in frequency of reporting implying that the scales worked well in assessing patients recovering from subarachnoid haemorrhage.

The following paragraphs discuss points of interest relevant to individual scales as well as overall results.

MRS- In the current study a large proportion of patients had a good (0-2) Modified Rankin Score at follow-up. Results from the International Subarachnoid Aneurysm Trial (ISAT) demonstrated that at one-year follow-up 69.1% and 76.5% of patients in the surgical and endovascular group respectively had a Modified Rankin Score of 0-2. With 82% achieving this grade in the current study Modified Rankin Scores are better than those demonstrated in the ISAT study for patients in the surgical arm. This may be secondary to a longer follow-up for some patients in this study (range of up to 400 days follow-up and therefore continued improvement noted after one year). This may also be

due to the effects of a single centre with specialist experience at offering predominantly surgical aneurysm treatment.

Barthel Index- The high median Barthel Index score again indicated that patients required minimal assistance with activities of daily living. In another cross-sectional study of 40 ASAH survivors originally categorised as independent, it was shown that only 5 (12.5%) patients scored less than 100 in the Barthel Index (range from 70 to 95 in this subgroup).

Despite an exceptional MRS and BI score the inability of a significant proportion to return to work indicated that there were other significant contributors to the patient's well being besides physical ability.

DEX- One fourth of patients in this study displayed significant dysexecutive function. The Dex scores in the current study are comparable to another recent study investigating cognitive deficit in a small cohort of clipped and coiled ASAH patients (mean Dex score 19.4 and 15.4 in clipped and coiled patients respectively) (Bellebaum, 2004). The cognitive dysfunction as measured on DEX scale directly affected the outcome as measured on MRS but also through affecting mood indirectly.

EMQ- The results of the Everyday Memory Questionnaire demonstrate that 40% patients post SAH exhibit some detectable memory deficits, particularly in the speech which, in the current study, has been shown to influence return to work and in actions which influences perceived quality of life. It also affects MRS in a way similar to DEX.

WSRS- The results of the WSRS indicate that a substantial minority (33%) had a clinically relevant mood disorder. This is similar to a study of total brain injury patients

utilising the WSRS, in which it was demonstrated that 38% of patients had a clinically significant mood disorder at six-months post injury and 35% at one-year post injury (Bowen 1998, 99) In this cohort the WSRS had a significant impact on return to work independent of the MRS grade of the patient.

Return to Work- Almost half of the patients in the current study who were previously employed, were unemployed at follow up. In a recent Australian study, two-thirds of patients who were in pre-haemorrhage employment, returned to full-wage employment at 1-year following haemorrhage(Hackett, 2000). This was noted to be higher than previously reported (Hop 1998, Hellawell 1999) and much higher than the employment level noted in the current study. We did not specifically ask about why our patients did not return to work and accept this could have been out of choice or if the patient was of retirement age. The difference could also be due to better rehabilitation facilities in Australia.

Clinical indicators of poor outcome:

Factors previously thought to be associated with persistence of impairment were older age, less education, non-white race, fever, poor initial grade, hyperglycaemia and delayed cerebral ischaemia. In the current study the aim was to see if any of the factors known at admission will help predict final outcome so this could be used for advising patient and relatives and influence decision-making on aggressiveness of treatment and rehabilitation strategies. This study showed no association between patient age, sex and WFNS or Fisher grade with outcome. The only thing that was associated with a trend towards better cognitive and functional outcome was treatment option i.e. coiling. Again with this the difference on all scales showed a trend but was insignificant apart from stroke symptom checklist. This finding is surprising. It is plausible that cognitive

problems exist separately from physical problems (that we understand relate to age and WFNS), so that causative factors are different. Also, secondary injury and perturbation of cerebral neurophysiology is likely to be greater with clipping which may entail increased neurocognitive deficits not measureable on crude scales like the mRS.

Limitations:

Selection bias, missing values and lack of control group were the main limitations of this work. Efforts to deal with selection bias have already been discussed. To deal with missing values, imputation of RASCH latent estimates would be required. We did not have statistical expertise to do this for present study but this can be addressed in future work. Also, more details on subsequent inpatient clinical course of these patients would have helped to relate deficits to DIND. However, as this was retrospective data, the documentation of DIND, with variable criteria used to diagnose DIND over the course of the study, was not reliably present in the case records and as such this analysis could not be undertaken. Data for future studies could be improved by prospective collection. To improve quality of retrospective data, we are introducing SAH guidelines so that clinical details are recorded as per a set format and management standardised further.

Chapter 4

Conclusion

This chapter summarizes this work and gives implications for future work in this area.

4.1 Summary, Clinical Implications and Future Directions:

Clinically, delayed neurological deficit is akin to “neuronal stunning” or “functional stand-still without structural damage” or “reversible injury” that may progress to irreversible injury if the cellular milieu is not corrected. In an excitable tissue, the increase in extracellular potassium as is common after SAH, offers a very plausible explanation for such a state. The increase in potassium extracellularly will depolarise the membranes, implying inability to fire while maintaining structural integrity. Cells will have to spend more energy on the sodium-potassium pump to maintain the cellular integrity, which means the metabolic rate will go up. If this is matched by a corresponding increase in supply of oxygen and glucose, a full recovery will follow; if not, the cell will swell up and the calcium-dependent cascade of cell death will begin. If this were to be true, in a symptomatic patient, we should observe a rise in potassium with an escalation of both lactate and pyruvate and a decline in glucose despite normal cerebral blood flow and tissue oxygen concentration, albeit in the initial phase the tissue oxygen extraction should go up. With escalation of CBF and pTiO2, the symptoms should correct but not the metabolic picture. This is exactly what we observe in current study.

Thus within the constraints of a small pilot work, this study raises an interesting issue. It argues that at the cellular level, besides primary ischaemia as suggested by the current hypothesis, increasing metabolic rate outstripping the available supply induces relative ischaemia leading to signs and symptoms of DIND. Thereby, it opens other avenues for investigation and lays framework for future studies.

Recent in-vitro studies(Bhatia, 2010) and COSBID data lend support to this proposition. This picture observed in our work could well be the metabolic signature of cortical

spreading depolarisation. However, one glaring difference that comes into view is that symptoms develop when the metabolic ratio (concentration of lactate and pyruvate/availability of oxygen) gradually reaches a threshold and not in an instant manner as would be expected in relation to an event (CSD). It may be that such a threshold happens when the frequency of CSD's reaches a point where the increased demand can no longer be matched with energy supply. This could also be other way round that as metabolic failure begins, more and more cortical depolarisations are observed and thus cortical spreading depolarisation may be the epiphenomenon of this ongoing metabolic failure. Equally it is possible that the frequently occurring CSD's and CSI's, and vasospasm, etc., worsen this background disturbance and thus make symptoms worse. Recent studies from the COSBID group have shown that the surface electroencephalogram can mimic changes on electrocorticogram. The logical next step that follows these findings should be the multimodal monitoring of aSAH patients with continuous electroencephalograms, microdialysis, pTiO2 and CBF monitors. Correlates of metabolites and potassium from microdialysis and lumbar drain fluid need to be established to see if less invasive ways can help monitor and guide treatment.

Since it's the metabolic ratio that seems to determine symptoms rather than isolated values of CBF, pTiO2, lactate or pyruvate, pTiO2 might be a better indicator of clinical picture as it gives an idea of demand-supply rather than supply alone (CBF). As pTiO2 values parallel MAP, it might be sensible to offer MAP-guided therapy once symptoms commence in areas where there are not enough resources to do the full invasive neuromonitoring. MAP guided hypertensive therapy has been found to be the most significant H of the triple H anyway, lending further support to this proposition.

Suppression of neuronal metabolic demand might be another treatment avenue- perhaps inducing burst suppression as we do for head injury patients with rising ICP's. This is much more aggressive treatment but can be attempted in patients who fail to respond to conventional management.

Another important finding from this study is that the neurophysiology is disturbed globally- near or away from the aneurysmal territory in all aSAH patients to variable extent, whether or not it accounts for overt symptoms of DIND.

Lastly, the results of this study demonstrate that multimodal neuromonitoring is the way forward in centres that have the capability. It is relatively safe and gives a lot of information even with limited patient numbers. It is quite feasible in awake patients. As there is a large baseline inter and intra-subject variability, following trends in individual patients and correlation of clinical features with neuromonitoring data is crucial for formulation of a safe, tailored, proactive intervention plan. Overall data acquisition can be improved by better research support infrastructure and eventually incorporation of neuromonitoring into clinical patient pathway.

Current outcome measures- MRS and GOS classify patients in broad categories of recovery from physical dependency perspective. While this is important information, it masks the severity of functional deficits that some of these patients experience. The data from our outcome study shows that >80% aSAH survivors have a "good outcome", a third of patients assigned in the good outcome category do not return to work. A significant proportion of these have deficits in executive functioning and caseness for mood disorder which is significantly associated with their return to normalcy. Thereby it is crucial to employ more sensitive outcome measures to identify these deficits,

especially in the good physical outcome group, to help effective rehabilitation. PROM's can be used to screen these patients. Incorporation of Neuropsychology services in routine SAH follow up will ensure timely identification, cognitive and psychological rehabilitation of these individuals.

Currently, we do not fully understand why some patients have these deficits and some do not, despite similar clinical characteristics- age, sex, WFNS/Fisher grades. There is some evidence to suggest that DIND, fever; i.e. things that affect neurophysiology, might be associated with worse cognitive outcome.

In future studies incorporating neuromonitoring as detailed above, it will be important to include outcome measures that look at cognitive and functional outcome. This will help to get a handle on prediction of extent of neurocognitive deficit likely in a given patient with a known extent of deranged physiology and will help to gauge effectiveness of treatment for neurophysiological derangement through long term neurocognitive outcome measures. We have seen that this can be reliably and economically achieved through administration of PROM's.

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Appendix 1

Fisher Scale

The Fisher Grade classifies the appearance of subarachnoid hemorrhage on CT scan.

Grade	Appearance of hemorrhage
1	None evident
2	Less than 1 mm thick
3	More than 1 mm thick
4	Diffuse or none with intraventricular hemorrhage or parenchymal extension

This scale has been modified by Claassen and coworkers, reflecting the additive risk from SAH size and accompanying intraventricular hemorrhage (0 - none; 1 - minimal SAH w/o IVH; 2 - minimal SAH with IVH; 3 - thick SAH w/o IVH; 4 - thick SAH with IVH)

Modified Rankin Scale

The scale runs from 0-6, running from perfect health without symptoms to death.

- 0 - No symptoms.
- 1 - No significant disability. Able to carry out all usual activities, despite some symptoms.
- 2 - Slight disability. Able to look after own affairs without assistance, but unable to carry out all previous activities.
- 3 - Moderate disability. Requires some help, but able to walk unassisted.
- 4 - Moderately severe disability. Unable to attend to own bodily needs without assistance, and unable to walk unassisted.
- 5 - Severe disability. Requires constant nursing care and attention, bedridden, incontinent.
- 6 - Dead.

WFNS Scale

The World Federation of Neurosurgeons (WFNS) classification uses Glasgow coma score (GCS) and focal neurological deficit to gauge severity of symptoms.

Grade	GCS	Focal neurological deficit
1	15	Absent
2	13–14	Absent
3	13–14	Present
4	7–12	Present or absent
5	<7	Present or absent

Glasgow Outcome Scale

The Glasgow Outcome Scale is a 5-level score:

1. Dead
2. Vegetative State (meaning the patient is unresponsive, but alive; a "vegetable" in lay language)
3. Severely Disabled (conscious but the patient requires others for daily support due to disability)
4. Moderately Disabled (the patient is independent but disabled)
5. Good Recovery (the patient has resumed most normal activities but may have minor residual problems)

The Extended GOS, or GOS-E, has extended the scale to an 8-level score:

1. Dead
2. Vegetative State
3. Lower Severe Disability
4. Upper Severe Disability
5. Lower Moderate Disability
6. Upper Moderate Disability
7. Lower Good Recovery
8. Upper Good Recovery

The Leeds Teaching Hospitals NHS
NHS Trust

Follow Up After Haemorrhagic Stroke

Patient's Booklet

First Name

Surname _____ Mr/Mrs/Ms

Date of Birth

Day	Day	Month	Month	Year	Year	Year	Year

Marital Status

Married	
Lives with Partner	
Separated/Divorced	
Widow(er)ed	
Never Married	

Do you live alone? Yes No

Please (circle) your response.

Are you happy for us to inform your GP that you are participating in this survey? Yes No

Please (circle) your response.

Patient signature _____

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AKC Short Sentences Test

Would you please read each item and do what it says:

1. Put a circle around the name of a fruit in the words below

   butter lemon basket slipper

2. Put a circle around the third word in the words below

   four break hammer stop

3. Put a circle around the thing which you cannot eat

   coal fish ice-cream sandwich

4. Put a circle around the word that means the same as “select”

   help pick throw dust

5. Put a circle around the word that means the opposite of “pleased”

   calm ready angry common

6. Put a circle around the animal with black and yellow stripes

   rabbit wolf shark tiger

7. Put a circle around the highest of these numbers

   fifty-nine ten sixty-one eighteen

8. Put a circle around the place you would go to if you wanted to send a letter to America

   police station garage London post office

9. Put a circle around the person whose job involves travelling around the world

   sailor artist dentist postman

10. Put a circle around the smallest of these things

    desk spoon door horse

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The Barthel Index

These are some questions about your ability to look after yourself. They may not seem to apply to you. Please answer them all

Circle one response to each question only

1. **Bathing**

   In the bath or shower, do you

   0 Manage on your own
   1 Need help getting in and out
   2 Need other help
   3 Never have a bath or shower
   4 Need to be washed in bed

2. **Stairs**

   Do you climb stairs at home

   0 Without any help
   1 With minimal assistance
   2 With someone encouraging you
   3 With physical help
   4 Not at all
   5 Don't have stairs

3. **Dressing**

   Do you get dressed

   0 Without any help
   1 Just with help with fastenings e.g. buttons/zips
   2 With someone helping me most of the time

4. **Mobility**

   Do you walk indoors

   0 Without any help apart from a frame
   1 With one person watching over me
   2 With one person helping me
   3 With more than one person helping
   4 Not at all
   5 Or do you use a wheelchair independently even around corners

Page 3...continue

5. **Transfer**
   Do you move from bed to chair
   0 On your own
   1 With a little help from one person
   2 With a lot of help from one or more people
   3 Not at all

6. **Feeding**
   Do you eat food
   0 Without any help
   1 With help cutting food or spreading butter
   2 With more help

7. **Toilet use**
   Do you use the toilet or commode
   0 Without any help
   1 With some help
   2 With quite a lot of help

8. **Grooming**
   Do you brush your hair and teeth, wash your face and groom
   0 Without any help
   1 With help

9. **Bladder**
   Are you incontinent of urine
   0 Never
   1 Less than once a week
   2 Less than once a day
   3 More often
   4 Do you have a catheter managed by someone

10. **Bowels**
    Do you soil yourself
    0 Never
    1 Occasional accident
    2 All the time
    3 Do you need someone to give you an enema

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Dex Questionnaire

This questionnaire looks at some of the difficulties that people sometimes experience. We would like you to read the following statements and rate them on a five-point scale according to your own experience. Circle the response option which applies to you.

1. **I have problems understanding what other people mean unless they keep things simple and straightforward**
   0 Never
   1 Occasionally
   2 Sometimes
   3 Fairly Often
   4 Very Often

2. **I act without thinking, doing the first thing that comes to mind**
   0 Never
   1 Occasionally
   2 Sometimes
   3 Fairly Often
   4 Very Often

3. **I sometimes talk about events or details that never actually happened, but I believe did happen**
   0 Never
   1 Occasionally
   2 Sometimes
   3 Fairly Often
   4 Very Often

4. **I have difficulty thinking ahead or planning for the future**
   0 Never
   1 Occasionally
   2 Sometimes
   3 Fairly Often
   4 Very Often

5. **I sometimes get over-excited about things and can be a bit over the top at times**
   0 Never
   1 Occasionally
   2 Sometimes
   3 Fairly Often
   4 Very Often

6. **I get events mixed up with each other, and get confused about the correct order of events**
   0 Never
   1 Occasionally
   2 Sometimes
   3 Fairly Often
   4 Very Often

Page 5...continue

7. **I have difficulty realizing the extent of my problems and am unrealistic about the future**
   0 Never
   1 Occasionally
   2 Sometimes
   3 Fairly Often
   4 Very Often

8. **I am lethargic, or unenthusiastic about things**
   0 Never
   1 Occasionally
   2 Sometimes
   3 Fairly Often
   4 Very Often

9. **I do or say embarrassing things when in the company of others**
   0 Never
   1 Occasionally
   2 Sometimes
   3 Fairly Often
   4 Very Often

10. **I really want to do something one minute, but couldn't care less about it the next**
    0 Never
    1 Occasionally
    2 Sometimes
    3 Fairly Often
    4 Very Often

11. **I have difficulty showing emotion**
    0 Never
    1 Occasionally
    2 Sometimes
    3 Fairly Often
    4 Very Often

12. **I lose my temper at the slightest thing**
    0 Never
    1 Occasionally
    2 Sometimes
    3 Fairly Often
    4 Very Often

13. **I am unconcerned about how I should behave in certain situations**
    0 Never
    1 Occasionally
    2 Sometimes
    3 Fairly Often
    4 Very Often

14. **I find it hard to stop repeating, saying or doing things once I've started**
    0 Never
    1 Occasionally
    2 Sometimes
    3 Fairly Often
    4 Very Often

Page 6...continue

Dex Questionnaire continued: This questionnaire looks at some of the difficulties that people sometimes experience. We would like you to read the following statements and rate them on a five-point scale according to your own experience. Circle the response option which applies to you.

15. **I tend to be very restless, and can't sit still for any length of time**
    0 Never
    1 Occasionally
    2 Sometimes
    3 Fairly Often
    4 Very Often

16. **I find it difficult to stop myself from doing something even if I know I shouldn't**
    0 Never
    1 Occasionally
    2 Sometimes
    3 Fairly Often
    4 Very Often

17. **I will say one thing but will do something different**
    0 Never
    1 Occasionally
    2 Sometimes
    3 Fairly Often
    4 Very Often

18. **I find it difficult to keep my mind on something, and am easily distracted**
    0 Never
    1 Occasionally
    2 Sometimes
    3 Fairly Often
    4 Very Often

19. **I have trouble making decisions or deciding what I want to do**
    0 Never
    1 Occasionally
    2 Sometimes
    3 Fairly Often
    4 Very Often

20. **I am unaware of, or unconcerned about how others feel about my behaviour**
    0 Never
    1 Occasionally
    2 Sometimes
    3 Fairly Often
    4 Very Often

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Everyday Memory Questionnaire

Please circle the appropriate response. How often **in the last week** did you find you were.

A. Speech

1. **Forgetting the names of friends or relatives or calling them by the wrong names**
   0 Never
   1 Less than once a week
   2 Once or twice in a wee
   3 About once each day
   4 Several times in a day

2. **Forgetting the names of common things or using the wrong names**
   0 Never
   1 Less than once a week
   2 Once or twice in a week
   3 About once each day
   4 Several times in a day

3. **Finding that a word is 'on the tip of your tongue'. You know what it is but can't quite find it.**
   0 Never
   1 Less than once a week
   2 Once or twice in a week
   3 About once each day
   4 Several times in a day

4. **Forgetting something you were told a few minutes ago. Perhaps something your partner or a friend has just said**
   0 Never
   1 Less than once a week
   2 Once or twice in a wee
   3 About once each day
   4 Several times in a day

5. **Forgetting something you were told yesterday or a few days ago**
   0 Never
   1 Less than once a week
   2 Once or twice in a week
   3 About once each day
   4 Several times in a day

6. **Repeating something you have just said or asking the same question several times**
   0 Never
   1 Less than once a week
   2 Once or twice in a week
   3 About once each day
   4 Several times in a day

Page 8...continue

Everyday Memory Questionnaire continued: Please circle the appropriate response. How often **in the last week** did you find you were.

7. **Forgetting what you have just said. Maybe saying 'What was I talking about?'**
   0 Never
   1 Less than once a week
   2 Once or twice in a wee
   3 About once each day
   4 Several times in a day

8. **Loosing track of what someone is trying to tell you. Unable to follow the thread of their conversation.**
   0 Never
   1 Less than once a week
   2 Once or twice in a week
   3 About once each day
   4 Several times in a day

9. **Starting to say something, then forgetting what it was that you wanted to speak about**
   0 Never
   1 Less than once a week
   2 Once or twice in a week
   3 About once each day
   4 Several times in a day

10. **Letting yourself ramble on to speak about unimportant or irrelevant things**
    0 Never
    1 Less than once a week
    2 Once or twice in a week
    3 About once each day
    4 Several times in a day

11. **Forgetting to tell somebody something important. Perhaps forgetting to pass on a message or remind someone of something**
    0 Never
    1 Less than once a week
    2 Once or twice in a wee
    3 About once each day
    4 Several times in a day

12. **Getting the details of what someone has told you mixed up and confused**
    0 Never
    1 Less than once a week
    2 Once or twice in a week
    3 About once each day
    4 Several times in a day

Page 9...continue

Everyday Memory Questionnaire continued: Please circle the appropriate response. How often **in the last week** did you find you were.

13. Repeating a story or joke you have already told

0 Never
1 Less than once a week
2 Once or twice in a week
3 About once each day
4 Several times in a day

B. Reading and Writing

14. Forgetting the meanings of unusual words

0 Never
1 Less than once a week
2 Once or twice in a week
3 About once each day
4 Several times in a day

15. Forgetting what the sentence you have just read was about and having to re-read it

0 Never
1 Less than once a week
2 Once or twice in a wee
3 About once each day
4 Several times in a day

16. Unable to follow the thread of a story. Loose track of what it is about

0 Never
1 Less than once a week
2 Once or twice in a week
3 About once each day
4 Several times in a day

17. Forgetting how to spell words

0 Never
1 Less than once a week
2 Once or twice in a week
3 About once each day
4 Several times in a day

C. Faces and Places

18. Forgetting where you have put something. Loosing things around the house

0 Never
1 Less than once a week
2 Once or twice in a week
3 About once each day
4 Several times in a day

Page 10...continue

Everyday Memory Questionnaire continued: Please circle the appropriate response. How often **in the last week** did you find you were.

19. Failing to recognise friends or relatives by sight

0 Never
1 Less than once a week
2 Once or twice in a wee
3 About once each day
4 Several times in a day

20. Failing to recognise television characters or other famous people by sight

0 Never
1 Less than once a week
2 Once or twice in a week
3 About once each day
4 Several times in a day

21. Getting lost or turning in the wrong direction on a journey or walk you have often been on

0 Never
1 Less than once a week
2 Once or twice in a week
3 About once each day
4 Several times in a day

22. Failing to recognise places you are told you've often been to before

0 Never
1 Less than once a week
2 Once or twice in a week
3 About once each day
4 Several times in a day

23. Finding television stories difficult to follow

0 Never
1 Less than once a week
2 Once or twice in a wee
3 About once each day
4 Several times in a day

D. Actions

24. Forgetting to do some routine things which you would normally do once or twice in a day.

0 Never
1 Less than once a week
2 Once or twice in a week
3 About once each day
4 Several times in a day

Page 11...continue

Everyday Memory Questionnaire continued: Please circle the appropriate response. How often **in the last week** did you find you were.

25. Discovering that you have done some routine thing twice by mistake

0 Never
1 Less than once a week
2 Once or twice in a week
3 About once each day
4 Several times in a day

26. Having to go around checking whether you have done everything you meant to do

0 Never
1 Less than once a week
2 Once or twice in a week
3 About once each day
4 Several times in a day

27. Forgetting what you did yesterday or getting the details of what happened mixed up and confused

0 Never
1 Less than once a week
2 Once or twice in a wee
3 About once each day
4 Several times in a day

28. Starting to do something, then forgetting what it is you wanted to do. Maybe saying 'What am I doing?'

0 Never
1 Less than once a week
2 Once or twice in a week
3 About once each day
4 Several times in a day

29. Being absent minded. Doing something which you didn't really intend to do

0 Never
1 Less than once a week
2 Once or twice in a week
3 About once each day
4 Several times in a day

E. Learning New Things

30. Unable to remember the name of someone you met for the first time recently

0 Never
1 Very rarely
2 Only sometimes
3 On every other occasion
4 On every occasion

Page 12...continue

Everyday Memory Questionnaire continued: Please circle the appropriate response. How often **in the last week** did you find you were.

31. Failing to recognise someone you met for the first time recently

0 Never
1 Very rarely
2 Only sometimes
3 On every other occasion
4 On every occasion

32. Getting lost on a journey or walk which you've only been on once or twice before to do

0 Never
1 Very rarely
2 Only sometimes
3 On every other occasion
4 On every occasion

33. Unable to pick up a new skill such as a game or working some new gadget after you have practised once or twice

0 Never
1 Very rarely
2 Only sometimes
3 On every other occasion
4 On every occasion

34. Unable to cope with a change in your daily routine. Following your old routine by mistake

0 Never
1 Very rarely
2 Only sometimes
3 On every other occasion
4 On every occasion

35. Forgetting to keep an appointment

0 Never
1 Very rarely
2 Only sometimes
3 On every other occasion
4 On every occasion

Page 13...continue

Stroke Symptom Checklist

Over the past few weeks have you had the following symptoms more often than before your stroke? Circle the appropriate answer

1. Headaches
   1 Yes
   0 No

2. Fatigue
   1 Yes
   0 No

3. Dizziness
   1 Yes
   0 No

4. Blurred vision
   1 Yes
   0 No

5. Bothered by noise
   1 Yes
   0 No

6. Bothered by light
   1 Yes
   0 No

7. Insomnia
   1 Yes
   0 No

8. Memory difficulties
   1 Yes
   0 No

9. Difficulty concentrating
   1 Yes
   0 No

10. Irritability
    1 Yes
    0 No

11. Anxiety
    1 Yes
    0 No

12. Loss of temper easily
    1 Yes
    0 No

Page 14...continue

The Wimbledon Self-Report Scale

The words in capital letters below describe how people sometimes feel. With each word there are four choices that can be used to show how often you have had that feeling. Please indicate how often you have had each feeling in the **past 6-7 days** by circling one of the choices each time.

1. WORTHLESS
0 Most of the time
1 Quite often
2 Only occasionally
3 Not at all

2. RELAXED
0 Most of the time
1 Quite often
2 Only occasionally
3 Not at all

3. DESPERATE
0 Most of the time
1 Quite often
2 Only occasionally
3 Not at all

4. PANICKY
0 Most of the time
1 Quite often
2 Only occasionally
3 Not at all

5. HELPLESS
0 Most of the time
1 Quite often
2 Only occasionally
3 Not at all

6. GUILTY
0 Most of the time
1 Quite often
2 Only occasionally
3 Not at all

7. CONFIDENT
0 Most of the time
1 Quite often
2 Only occasionally
3 Not at all

8. DISCOURAGED
0 Most of the time
1 Quite often
2 Only occasionally
3 Not at all

Page 15...continue

9. MISERABLE

0 Most of the time
1 Quite often
2 Only occasionally
3 Not at all

10. LONELY

0 Most of the time
1 Quite often
2 Only occasionally
3 Not at all

11. IRRITABLE

0 Most of the time
1 Quite often
2 Only occasionally
3 Not at all

12. GLOOMY

0 Most of the time
1 Quite often
2 Only occasionally
3 Not at all

13. NERVOUS

0 Most of the time
1 Quite often
2 Only occasionally
3 Not at all

14. HAPPY

0 Most of the time
1 Quite often
2 Only occasionally
3 Not at all

15. ANNOYED

0 Most of the time
1 Quite often
2 Only occasionally
3 Not at all

16. UNWANTED

0 Most of the time
1 Quite often
2 Only occasionally
3 Not at all

17. TENSE

0 Most of the time
1 Quite often
2 Only occasionally
3 Not at all

18. STUPID

0 Most of the time
1 Quite often
2 Only occasionally
3 Not at all

19. AS IF I'M BEING PUNISHED FOR SOMETHING

0 Most of the time
1 Quite often
2 Only occasionally
3 Not at all

20. IN GOOD SPIRITS

0 Most of the time
1 Quite often
2 Only occasionally
3 Not at all

Page 16...continue

The words in capital letters below describe how people sometimes feel. With each word there are four choices that can be used to show how often you have had that feeling. Please indicate how often you have had each feeling in the **past 6-7 days** by circling one of the choices each time.

21. FULL OF REGRETS

0 Most of the time
1 Quite often
2 Only occasionally
3 Not at all

22. FRIGHTENED

0 Most of the time
1 Quite often
2 Only occasionally
3 Not at all

23. AS IF MY LIFE HAS BEEN RUINED

0 Most of the time
1 Quite often
2 Only occasionally
3 Not at all

24. WORRIED ABOUT MY FUTURE

0 Most of the time
1 Quite often
2 Only occasionally
3 Not at all

25. CHEERFUL

0 Most of the time
1 Quite often
2 Only occasionally
3 Not at all

26. USELESS

0 Most of the time
1 Quite often
2 Only occasionally
3 Not at all

27. FED UP

0 Most of the time
1 Quite often
2 Only occasionally
3 Not at all

28. HOPELESS

0 Most of the time
1 Quite often
2 Only occasionally
3 Not at all

29. ANGRY

0 Most of the time
1 Quite often
2 Only occasionally
3 Not at all

30. CONTENT

0 Most of the time
1 Quite often
2 Only occasionally
3 Not at all

Page 17...continue

Self Assessed Rankin Score

Please read the following questions and circle the score you feel best describes your current wellbeing.

Structured Interview for Modified Rankin Scale	**Rankin Score**
Do you require constant care?	**5**
Is assistance essential for eating, using the toilet, daily hygiene or walking?	**4**
Is assistance essential for preparing a simple meal, doing household chores, looking after money, shopping or travelling locally?	**3**
Has there been a change in your ability to work or look after others if these were roles before the haemorrhage? Has there been a change in your ability to participate in previous social and leisure activities? Have you had problems with relationships or become isolated?	**2**
Do you have difficulty reading or writing, difficulty speaking or finding the right word, problems with balance or co-ordination, visual problems, numbness (face, arms, legs, hands, feet) loss of movement (face, arms, legs, hands, feet) difficulty with swallowing or other symptoms resulting from the haemorrhage?	**1**
No symptoms at all	**0**

Page 18...continue

Stroke-QoL

On the following pages you will find some statements which have been made by people who have suffered with Stroke

Instructions: This questionnaire consists of 30 statements. Please read each statement carefully, and then choose **True** if the statement applies to you and choose **Not True** if it does not apply to you **at the moment**. Circle the appropriate number

1. **I don't like relying on others**
   1 True
   0 Not True

2. **I'm not as strong as I used to be**
   1 True
   0 Not True

3. **It upsets me that I am not as active as I was**
   1 True
   0 Not True

4. **I can't cope as well**
   1 True
   0 Not True

5. **My balance isn't good**
   1 True
   0 Not True

6. **I feel guilty that I can't help others now**
   1 True
   0 Not True

7. **Difficulty climbing stairs limits where I can go**
   1 True
   0 Not True

8. **I can't walk far outside**
   1 True
   0 Not True

9. **I can't stand for long**
   1 True
   0 Not True

10. **I can't bend down very well**
    1 True
    0 Not True

11. **People close to me have been affected**
    1 True
    0 Not True

12. **The stroke occasionally makes me depressed**
    1 True
    0 Not True

13. **I feel useless at times**
    1 True
    0 Not True

14. **I worry that my stroke has affected other people**
    1 True
    0 Not True

Page 19...continue

15. **I cant concentrate for long**
    1 True
    0 Not True

16. **I get embarrassed if I need to ask for help**
    1 True
    0 Not True

17. **I'm bored a lot of the time**
    1 True
    0 Not True

18. **I get fed up when I think about what I have lost**
    1 True
    0 Not True

19. **The stroke has made me accident prone**
    1 True
    0 Not True

20. **I have to concentrate to keep control of my arm**
    1 True
    0 Not True

21. **Pain sometimes keeps me awake**
    1 True
    0 Not True

22. **I feel older than my years**
    1 True
    0 Not True

23. **Its an effort to get up**
    1 True
    0 Not True

24. **I feel stiff all the time**
    1 True
    0 Not True

25. **I become withdrawn more easily**
    1 True
    0 Not True

26. **I don't like eating in public**
    1 True
    0 Not True

27. **My arm is in spasm**
    1 True
    0 Not True

28. **I have pain all the time**
    1 True
    0 Not True

29. **I can't easily face going out**
    1 True
    0 Not True

30. **I am in pain when I lie down**
    1 True
    0 Not True

Page 20...continue

And The Final Questions

What best describes your occupation before your stroke? Please tick ✓ 1 box

Employed /Self –employed/ Part-Time work/ Carer	
Unemployed	

And what about now?

Employed /Self –employed/ Part-time work/ Carer	
Unemployed	

Page 21...continue

And The Final Questions

How did you complete this questionnaire?

Please tick which is the case

By Myself ☐

With Help from someone else ☐

If you needed help, was this with,

Please tick **each aspect** which you needed help with

Turning the pages ☐

Writing ☐

Reading the pages ☐

Understanding the pages ☐

You have now completed the questionnaire. Thank you

If you have any problems or questions about the questionnaire please do not hesitate to contact Ms D Bhargava, Department of Neurosurgery, Leeds General Infirmary Telephone number 07737867840