Diplomarbeit

Influence of acute normovolemic hemodilution on bispectral index monitoring - A clinical study

eingereicht von

Sarah – Maria Rinnhofer

Mat.Nr.: 0210506

zur Erlangung des akademischen Grades

Doktorin der gesamten Heilkunde

(Dr. med. univ.)

an der

Medizinischen Universität Graz

ausgeführt an der

Univ. Klinik für Anästhesiologie und Intensivmedizin

unter der Anleitung von

Univ. Prof. Dr. H. Metzler

Eidesstattliche Erklärung

Ich erkläre ehrenwörtlich, dass ich die vorliegende Arbeit selbstständig und ohne fremde Hilfe verfasst habe, andere als die angegebenen Quellen nicht verwendet habe und die den benutzten Quellen wörtlich oder inhaltlich entnommenen Stellen als solche kenntlich gemacht habe.

TABLE OF CONTENTS

PREFACE

My diploma thesis is based on the clinical study “Influence of acute normovolemic hemodilution on bispectral index monitoring and propofol dose requirements“ as I got part of the research team in 2006. I was very happy getting the chance to do professional scientific work with skilled people directly in clinical practice because all formal prearrangements already had been done in the two years before. Now I want to thank all the people who did this excellent work because no study can be good if the preparations are bad.

As all was prepared we could start our research in the LKH - Univ. Klinikum Graz. Particularly Dr. Dahaba introduced me faithfully to the measurement procedure in the operating room and the arrangements, which must be done before. Consequently I did them for myself. Thus I got to know exactly, which problems appear in such a process, commencing with how equipment can be provided, followed by how to receive eligible patients, how to make statistical analyses of the data or how difficult it is to write a good article, which will get published in a good journal. I never thought that research requires so much effort and time.

During my work at the hospital I spoke with Univ. Prof. Dr. Helfried Metzler if I could write my diploma thesis about this clinical study and he agreed to be my official tutor. He helped me to arrange all approval documents at the university and supported me during the whole process.

SUMMARY

For demonstrating our clinical study “Influence of actue normovolemic hemodilution on bispectral index monitoring and propofol dose requirements” (Dahaba, Rinnhofer et al 2008) in a comprehensible way my diploma thesis is structured into five chapters. The first one deals with the acute normovolemic hemodilution (ANH) which is a blood conservation technique aiming at avoiding allogeneic blood transfusion. The main idea is to reduce the amount of red blood cells and other plasma constituents lost during surgical bleeding through preoperative dilution of the circulating blood volume. An estimated blood loss of 1500 mL or more during surgery is the indication for that process.

The second chapter explains the bispectral index monitoring (BIS), an EEG derived parameter which is widely used in anesthesia for monitoring the effects of anesthetic/hypnotic drugs and the depth of anesthesia. Through four electrodes stuck on the forehead the EEG and also the EMG could be measured. A small box transforms the measured electroencephalographic and myographic activity into one BIS value which varies between 100 and 0. A defined scale allows the correlation between the BIS value and the level of narcosis, i.e. 100 stands for fully awake, 60 to 40 is necessary for surgical tolerance and 0 correlates with a flat line EEG. As ANH is shown to affect cerebral function (Weiskopf et al 2000) it might consequently also result in EEG changes which we wanted to demonstrate with our BIS measurement during induction of anesthesia.

A small part is devoted to the spectral edge frequency (SEF) because it is the precursor value of BIS for assessing the depth of anesthesia and is shown on each BIS monitor but have no relevance for our study.

The fourth part demonstrates the target-controlled-infusion system (TCI), per definition “an infusion system which allows the anesthetist to select the target blood concentration required for a particular effect, and then to control the depth of anesthesia by adjusting the requested target concentration” (AstraZeneca®). Control of patients’ condition still remains part of the anesthetist but the TCI system supports him by adjusting the dose of a narcotic agent to a achieve and maintain the required depth of anesthesia.

The last chapter explains our clinical study in detail. During induction and maintenance of anesthesia we compared the effect of ANH on BIS monitoring in 30 unmedicated patients undergoing ANH (15 patients got air and the others 100% oxygen to breath) to 15 control patients. The narcotic agent propofol (Diprivan®) was infused via the TCI system during the whole process to demonstrate a probable change in propofol dose requirement. The results showed a significant decline of BIS value after ANH but breathing 100% oxygen restored BIS values back to baseline. That ANH enhances the hypnotic effect of propofol was demonstrated by a significantly shorter onset time for loss of consciousness with fewer propofol TCI dose requirements in the ANH groups. The causation of the observed changes is a big discussion. An idea of the BIS decline after ANH is the lower oxygen carrying capacity of the diluted blood followed by lower oxygen transport to the brain because it is restored by breathing oxygen (Weiskopf el al 2002). The enhanced effect of propofol is probably based on changes in the propofol pharmacokinetics which may be caused by the physiological compensation mechanisms like an increase of stroke volume and cardiac output (Ickx et al 2000) because they induce a change in compartment volume and drug delivery (Honan et al 2002).

ABSTRACT

Background: Recently with cognitive function tests was shown that ANH, a blood procurement technique, results in an increased reaction time and memory alterations. This significant impairment of cognitive function can be detected with EEG and consequently with BIS, an EEG derived parameter.

Methods: We explored whether ANH has an effect on BIS monitoring before induction and during maintenance of propofol TCI anesthesia and whether ANH has an influence on the required propofol dose. The 45 unmedicated patients were randomly allocated in one of three groups: the ANH with oxygen insufflation, the ANH with air insufflation and the control group. BIS was recorded during the whole process.

Results: In the ANH groups a significant BIS decline after ANH could be observed but returns to baseline value by breathing 100% oxygen before induction of anesthesia. During maintenance of narcosis no significant differences between the ANH and the control group could be detected. Furthermore in the ANH group a lower dose of propofol was necessary for achieving LOC what was followed by significantly higher BIS values.

Conclusion: The briefly decreased BIS value after ANH could be returned to baseline by breathing oxygen. The transient enhancement of propofol hypnotic potency through ANH during induction of anesthesia can't be observed during maintenance of porpofol narcosis.

ABSTRACT (in German)

Hintergrund: Kürzlich konnte mittels Tests der kognitiven Funktionen gezeigt werden, dass die akute normovolämische Hämodilution (ANH), eine Technik mit der Eigenblut gesammelt werden kann, die Reaktionszeit verlängert und das Erinnerungsvermögen verändert. Die signifikanten Veränderungen der kognitiven Funktionen konnten mittels EEG aufgezeichnet werden und können folglich auch mittels dem Bispectral Index (BIS), einem vom EEG abgeleiteten Parameter, detektiert werden.

Methoden: Wir erforschten, ob ANH einen Effekt auf die BIS-Messungen während der Narkoseeinleitung als auch während der Aufrechterhaltung der Propofolnarkose, die mittels Target controlled infusion – System (TCI) verabreicht wurde, hat. 45 Patienten, die keine Medikamente einnahmen, wurden randomisiert in eine von drei Gruppen zugeteilt: der ANH mit Einatmung von Sauerstoff, der ANH mit Einatmung von Luft sowie der Kontrollgruppe. Die BIS-Werte wurden während des gesamten Prozesses aufgezeichnet.

Resultate: In der ANH Gruppe konnte ein signifikanter Abfall der BIS-Werte nach der Durchführung von ANH beobachtet werden. Diese konnten jedoch mittels Einatmung von 100% Sauerstoff wieder auf ihren Ausgangswert vor Beginn der Narkoseeinleitung angehoben werden. Während der Aufrechterhaltung der Narkose konnten keine signifikanten Unterschiede zwischen den ANH-Patienten und der Kontrollgruppe festgestellt werden. Weiters konnte gezeigt werden, dass in den ANH-Gruppen eine geringere Dosis Propofol notwendig war, um einen Bewusstseinsverlust zu erreichen. Zudem waren die BIS-Werte zum Zeitpunkt des Bewusstseinsverlustes signifikant höher.

Schlussfolgerung: Der kurze Abfall der BIS-Werte nach der Durchführung der ANH kann mittels Einatmung von 100% Sauerstoff wieder ausgeglichen werden. Auch die Erhöhung der hypnotischen Potenz von Propofol durch ANH konnte nur während der Narkoseeinleitung und nicht im folgenden Verlauf beobachtet werden.

SHORTCUTS

ANH …… Acute normovolemic hemodilution
ANOVA …….. Analyses of variance
ASA …… American society of anesthesiologists
BIS …….. Bispectral index monitoring
CNS …… Central nervous system
CONSORT …… Consolidated standards of reporting trials
DES …… Desflurane
DSST …….. Digital symbol substitution test
Dtn …… Deuteronomium
EEG …… Electroencephalography
EMG ……. Electromyographie
ETO …… Etomidate
Hb ……. Hemoglobin
Hct ……...Hematocrit
HES …… Hydroxyethyl starch
HR …….. Heart rate
LOC …… Loss of consciousness
LR ……. Ringer's lactate
MAP …… Mean arterial pressure
MDF..... Mean edge frequency
MP …….. Measuring phase
NCSS …… Number crunching statistical system
PONV ……. Postoperative nausea and vomiting
PTL ……. Platelet
SEF ……. Spectral edge frequency
SMF …… Spectral mean frequency
SR …….. Suppression rate
TCI …….. Target controlled infusion
TIVA …… Total intravenous anesthesia

TABLE OF FIGURES

LIST OF TABLES

1 INTRODUCTION

At the moment the bispectral index monitoring (BIS) is the simplest device in clinical routine which gives us the possibility to measure impairments of cognitive function independent of the cause. For example in the operation theatre it is used for estimating the depth of anesthesia but it could also be used for measuring the level of hepatic encephalopathy. A lot of other factors, like hypoglycemia or hypovolemia, are examined which can alter the BIS value. The idea that also acute normovolemic hemodilution (ANH), an autologous blood procurement technique, might change the BIS value we got from an observation of Weiskopf et al (2000). They examined the effect of ANH on cognitive function tests, especially the horizontal addition and the digital symbol substitution test (DSST). The results demonstrated that with ANH to a hemoglobin concentration of 6 g/dl the reaction time increased and the immediate and delayed memory were altered. In the year 2002 Weiskopf et al did another very interesting study where they showed that all effects evoked by ANH are reversed by breathing oxygen. Thus the question about the consequences of ANH on anesthesia rose.

As Bispectral index monitoring gives us the possibility to estimate objectively the impairment of cognitive function and also the depth of anesthesia in a simple way in the operating room we decided to test the influence of ANH on depth of anesthesia with this device. We defined the aim of our clinical study as whether ANH has a statisticaly significant sustained effect on BIS monitoring prior to induction of anesthesia, during propofol target controlled infusion (TCI) induction and during maintenance of narcosis.

Primary we defined three different groups: an ANH with oxygen insufflation (oxygen group), an ANH with air insufflation (air group) and a control group. With our a priori power analysis of the study of Weiskopf et al (2000) we found out that at least 7 patients in each group are required to get a statistically significant difference between the groups. We doubled the number of patients in each group to ensure meaningful results. After that all of the 45 patients who gave written informed consent were randomized to one of these groups. For obtaining comparable groups with more or less the same patients' characteristics we

defined the following exclusion criteria: body mass index < 18 or > 26 kg/m^2, ASA classification grade higher than ASA 3, medical conditions that might affect the level of consciousness such as stroke, stupor or dementia, and patients treated with cardiovascular or sedative/hypnotic drugs which might alter BIS values. Furthermore we decided to do the process observer-blinded to avoid the influence of the leading anesthetist and in a silent setting for avoiding disturbance of BIS through noise.

For the statistical analysis of our data we used the repeated measures ANOVA to examine the differences between the three groups. The paired t – test was performed for comparing the oxygen and the air group.

The hypothesis that ANH will influence anesthesia seems to have a clinical relevance because the supposable alteration of depth of anesthesia through ANH will possibly also change the required dose of the narcotic agent for achieving the same effect. Furthermore it seems to be important to know if BIS value is altered through ANH or not because BIS changes will no longer allow the anesthetist to interpret the level of narcosis correctly that would result in an enhanced risk of awareness during the surgery.

In the following pages a description of basics is given, which must be known before the significance of our study could be comprehended and after that the whole procedure is explained in detail.

2 ACUTE NORMOVOLEMIC HEMODILUTION

Acute normovolemic hemodilution (ANH) autologous blood procurement technique is recommended by the National Institute of Health Consensus Conference (Consensus Conference 1988) as a cost-effective blood conservation technique (Monk et al 1999). As well as preoperative autologous blood donation or intraoperative cell salvage, ANH aims at avoiding or reducing allogeneic blood transfusion during major surgery in procedures with expected blood loss of more than one liter (Napier et al 1999).

2.1 TECHNIQUE

Immediately before surgery, either before or shortly after induction of anesthesia, ANH is performed. Two venous access lines were used; each is placed in one arm. One is for blood procurement and the other for simultaneous administration of crystalloid or colloid to maintain normovolemia (Monk 2005).

2.1.1 Blood collection

Blood is collected in standard blood collection bags. They contain an anticoagulant agent, i.e. acid citrate-dextrose as we used in our study, to avoid blood coagulation as all collected blood is ideally re-infused towards the end of the operation after the phase of major blood loss has occurred, or sooner if clinically indicated. They are stored at room temperature in the operating room to be available whenever needed but storage should not exceed 8 hours. If more time elapses between collection and transfusion, the blood should be stored in a monitored refrigerator. Very important is to label these blood units properly even though they remain in the operating room with the patient. The label must contain, at a minimum, the patient's full name, medical record number, date, time of collection, and the statement 'For Autologous Use Only' (Goodnough & Monk 2005).

“The approximate volume of blood to be removed (in litres) to achieve the desired hematocrit can be calculated using the formula by Brouke and colleagues” (Napier et al 1999):

$$V = EBV \times (H_0 - H_f / H_{av})$$

V = volume to be removed, EBV = estimated blood volume (usually taken as 70 ml/kg body weight), H_0 = initial hematocrit, H_f = desired hematocrit and H_{av}= average hematocrit (mean of H_0 and H_f)

The result of the formula is only an estimated value and should be adapted to patient’s conditions and surgical extent. But not only this calculation is in use because it “is reported to overestimate estimated blood volume in the adult that may endanger the patient. The new iterative model proposed by Meier and colleagues that predicts estimated blood volume more reliably, is physiologically based, and leads to an improvement in patients safety” (Shander & Rijhwani 2004). Various factors like patient’s height and weight, starting hemoglobin, comorbidity and anticipated surgical blood loss are considered.

2.1.2 Threshold of hemoglobin

Hemodilution is divided in tow types based on hematocrit level. Moderate hemodilution aims for hematocrit target of 25-30 % (Hb 8-10 g/dl) what possibly reduce hemodilution risks. Extreme hemodilution is likely to be more efficacious in reducing allogeneic transfusion requirements but risks are greater because it aims for a hematocrit target of < 20% (Hb < 7g/dl). So this type should be applied only to relatively healthy patients (Napier 1997).

The first time a threshold of hemoglobin concentration during ANH was exhibited by Weiskopf et al (2000). They found out that before systemic oxygen deficit occurs cognitive function is impaired. Nine healthy volunteers, age 29 ± 5 yr were tested with verbal memory and standard, computerized neuropsychological tests [i.e. horizontal addition and digital symbol substitution test (DSST)] before and after ANH with hemoglobin levels of 7, 6 and 5 g/dl. Their results showed no

changes at hemoglobin concentration of 7 g/dl compared with the data at baseline hemoglobin of 14 g/dl. However, at hemoglobin concentration of 6 g/dl reaction time, but not error rate, increased and alterations of immediate and delayed memory were observed. The values declined further at 5g/dl. In another study Weiskopf et al (2002) proved that increasing Pao_2 to 350 mmHg or greater by breathing oxygen reverses all effects observed during acute isovolemic anemia.

Young healthy people with healthy cardiovascular system, allow lower hemoglobin concentration levels. But always should be considered that the central nervous system is the first which is impaired during extreme anemia and also the other systems are more endangered in such a situation. These facts led Shander and Rijhwani (2004) to suggest an endpoint of hemoglobin concentration during ANH of 9 g/dl. But they mentioned also some other possible endpoint indicators:

- Removal of 2 to 3 units of whole blood;
- Vital sings – avoidance of hypotension and/or tachycardia that is unresponsive to fluid resuscitation;
- Monitoring for the onset of coagulopathy

2.1.3 Maintenance of normovolemia

The safety during ANH also depends on the maintenance of normovolemia. Therefore acellular fluid, crystalloid (normal saline, lactated Ringers's) or colloid (albumin, hetastarch, HES) is simultaneously administrated.
For the choice of replacement fluid researches provide some answers. Schierhout & Roberts (1998) found in a review of randomized controlled trials with critically ill patients "that, compared with crystalloids, use of colloids was associated with an increase in absolute risk of mortality of 4%. There was no evidence for differences of effect among different types of injury necessitating fluid resuscitation". Scheingraber et al (1999) compared the effect of rapid saline infusion and lactated Ringer's solution on acid-base status of patients undergoing gynecologic surgery and found hyperchloremic acidosis in the saline group. They

concluded that although this hyperchloremic acidosis is benign, it still should be treated keeping in mind the effect of combining it with the acidotic effect of opiate analgesics in the postoperative phase which can result in pH values much lower than 7.20. Also Wilkes et al (2001) demonstrated the difference between a balanced or saline-based hetastarch and crystalloid solutions. Two-thirds of patients in the saline group developed postoperative hyperchloremic metabolic acidosis. They concluded that the use of balanced crystalloid or colloid solution prevents the development of hyperchloremic acidosis. “Jones et al (2004) randomized patients undergoing ANH during radical retropubic prostatectomy to receive either Ringer’s lactate (LR), 5% albumin, 6% hetastarch (Hespan) to maintain normovolemia. These investigators found that the heart rate and pulmonary capillary wedge pressure were unchanged from baseline in all of the fluid treatment groups, but patients receiving LR or albumin had greater declines in mean arterial blood pressure at the end of the ANH procedure. However, the authors concluded that despite minor differences in the hemodynamic variables among the groups, ANH was well tolerated irrespective of the replacement fluid use”.

Considering all these studies; balanced solutions seem most physiological of all tested fluids for volume resuscitation. For crystalloids only a lower risk of mortality of critically ill patients can be argued. In tested hemodynamic effects barely evidence of differences among crystalloids and colloids could be found. But both should be balanced because saline-based solutions can cause hyperchloremic acidosis. However, the ideal volume replacement strategy is still a big dispute. Thus “crystalloid convinced” and “colloid convinced” users exist. The fluid most frequently used in clinical frame is Voluven®, the colloid hydroxyethyl starch (HES) in saline solution.

The ratio between collected blood and resuscitation volume could be 1:1 or 1:3 depending on used substitution fluid but it’s independent of preoperative volume state and perioperativ fluid requirement. The clinical status determines how much volume is administrated. For example: Old patients, patients suffering from hypertension or coronary heart disease often sustain volume deficit (so more volume can be given) but on the other hand patients with commencing or apparent heart insufficiency can profit from decreased circulation volume (Oberreither n.d).

2.2 SELECTION CRITERIA FOR PATIENTS UNDERGOING ANH

In general in selecting patients for ANH; overall conditions, presence of anemia, presence of comorbid conditions and the type of surgery should be considered. “Particular caution should be exercised in patients more than 45 yr of age in the assessment of the risk of underlying ischemic heart disease and in patients with severe diseases in other systems” (Napier et al 1997). But most important is to put the evaluated medical status in relation to the type of surgery planed. First of all Kreimeier and Messmer (Hahn 1989) described the criteria for selection of patients for perioperative hemodilution including the following:

- Estimated blood loss of 1500 mL
- Preoperative Hb concentration of 12 g per dL after correction of normovolemia
- Normal cardiovascular function (i.e. no ischemic signs, no ST segment changes)
- Absence of restrictive or obstructive lung disease (confirmed by preoperative chest X-ray and possibly lung function tests)
- Absence of renal disease
- Absence of untreated hypertension and liver cirrhosis
- Absence of coagulation abnormalities
- Absence of infection

To decide which surgical procedure requires ANH expected blood loss should be contemplated. Loubser et al (n.d) mentioned some eligible surgeries:

- Cardiac surgery - on of off-pump procedures, minimally invasive techniques
- General surgery - major bowel or cancer resections
- Neurosurgery - major back procedures
- Orthopedic surgery - major back, joint replacement procedures
- Thoracic surgery - lobectomy, pneumonectomy
- Urologic surgery - prostatectomy, cystectomy, nephrectomy
- Vascular surgery - major reconstructive vascular surgery

They also describe few absolute contraindications:

- Presence of severe sepsis
- Respiratory failure
- Myocardial pump failure
- Hemorrhagic shock secondary to trauma
- Severe anemia

2.2.1 Jehovah's Witnesses

Jehovah's Witness patients require special consideration because they belief in the old testaments proposition: "Only beware of this, that thou eat not the blood, for the blood is for the soul: and therefore thou must not eat the soul with the flesh" (Dtn 12, 23), what means that blood sustains life, which should be returned back to the earth and not be eaten aiming in maintenance of life (Schmidt – Kortenbusch 1998). However, most of them accept ANH but only with special modifications. Therefore Loubser (1997) developed a new system called "Closed circuit autologous sequestration reservoir system". The operative point is that the whole blood collection circuit and fluid administration system have to remain continuous with the patient's intravascular compartment. This is possible, when simultaneously with blood collection's and volume resuscitation's ending, the collected blood begins trickling back into patient's blood system, thereby emulating venous blood flow. This form of ANH is more intricate indeed but even contains advantages considering that the continuous flow sustained in this system affords blood sterility and blood bags can't be confused because they are always connected to the patient.

2.3 PHYSIOLOGICAL CHANGES

Acute normovolemic hemodilution enables physiologic compensating mechanisms elicited by acute anemia. Above a critical point of hemoglobin concentration pulmonary blood distribution is improved and hyperventilation is indicated but first of all cardiovascular adaptations are responsible for maintaining

oxygen delivery. These alterations only commence in a normovolemic state and can be limited by cardiovascular or metabolic diseases as well as by drugs. By surveying these changes differences between moderate and extreme hemodilution could be found (Oberreither n.d.).

	Moderat Hemodilution	Extreme Hemodilution
Hb	↓↓	↓↓
CO	↑	↑↑
CaO_2	↓↓	↓↓
DO_2	N	↓
VO_2	N	↓
O_2 Ex	N	↑
CvO_2	↓↓	↓↓
SvO_s	N	↓

Table 1: Physiological changes through ANH

N normal, Hb Hemoglobin, CO Cardiac output, CaO_2 arterial Oxygen concentration, DO_2 Oxygen delivery, VO_2 Oxygen consumption, O_2Ex Oxygen extraction, CvO_2 mixed venous oxygen concentration, SvO_2 mixed venous oxygen saturation (Oberreither n.d.)

Decreased hematocrit increases stroke volume and cardiac output caused by two main mechanisms: the reduction of peripheral resistance resulting from blood viscosity decline and the raised organ's blood circulation aiming at increased venous return and consequently in an accretion of enddiastolic ventricular filling (Oberreither n.d.). As a result of all these changes, the decreased blood oxygen carrying capacity was partially offset and systemic oxygen delivery could be remained above the critical anaerobic threshold (Licker et al 2005).

Ickx, Rigolet and Van der Linden (2000) tested 40 patients undergoing ANH during major abdominal surgery either awake or with fentanyl-nitrous oxid-isoflurane anesthesia. The result showed a significant increase in cardiac index in the 'awake group' related to both an increased heart rate and stroke index. In the 'anesthetized group' ANH resulted in a significantly smaller increase in cardiac index related only to an increase in stroke index. Thus they concluded that anesthesia significantly reduces the cardiac output response associated with ANH probably induced by the effects of anesthetic drugs on the autonomic and cardiovascular system. Also considering the oxygen delivery differences could be

observed. In the ‘awake group’ “oxygen delivery remained unchanged, but oxygen consumption increased significantly, resulting in an increase in oxygen extraction rate”. In the ‘anesthetized group’ on the other hand oxygen delivery decreased that was followed by increased oxygen extraction for maintaining oxygen consumption.

2.4 BENEFITS of ANH

The advantage of such a decreased blood viscosity is the reduction of loss of red blood cells and plasma constituents during patients bleeding. “In case of transfusion need, the patient receives fresh, whole autologous blood containing coagulation factors and platelets (PLTs)” (Shander & Rijhwani 2004). In this way use of allogeneic blood transfusion might be reduced. Whether allogeneic blood is given or not, the reason must be clearly documented in the patient’s notes (Napier et al 1997).

Another benefit of ANH is, compared with alternative blood conservation strategies, it’s the least costly technique because it obviates the need for blood testing and avoids costly blood wastage as all collected blood is ideally re-infused (Monk et al 1999, 2005).

Cardioprotective effects of ANH could be observed at patients undergoing coronary artery bypass surgery. “In this study, the improved intraoperative myocardial preservation in the hemodiluted patients was clearly demonstrated by lower postoperative release of myocardial biomarkers, the reduced need for inotropic support, and the lower incidence of combined arrhythmia and conduction disorders, compared with patients receiving standard care” (Licker et al 2005). These alterations are provoked by reduced blood viscosity and hence improving oxygen delivery within underperfused myocardial areas.

2.4.1 Risks of allogeneic blood transfusion

With the use of allogeneic blood several complications, infectious and noninfectious, should be considered: “Infectious risks include in particular transmission of viral diseases such as hepatitis, cytomegalovirus, and

retroviruses (human immunodeficiency virus-1, human T-cell leukemia virus-1). […] Noninfectious risks include transfusion reaction, immunomodulation, transfusion-associated graft-versus-host disease, and transfusion-related acute lung injury" (Shander & Rijhwani 2004).

But it must be mentioned that in modern blood banking practice, bacterial contamination of red blood cell units is rare and also hemolytic transfusion reactions nearly could be eliminated with modern compatibility testing techniques. Viruses are the greatest concern in transfusion therapy but it is known for the human hepatitis viruses, probably this finding is also true for the other previously mentioned organisms, that the incidence of infection in recipients increases with the number of donor exposures. Nevertheless these risks result in a lot of patients and personal in clinical practice to prefer autologous blood transfusion techniques when they have a choice (Consensus Conference 1988).

2.5 RISKS AND SAFETY of ANH

The main problem of ANH is the occurrence of tissue hypoxia caused by insufficient cardiopulmonary compensatory abilities during or after surgical procedure. Major sings include an increased heart rate, a decrease of blood pressure, alterations of the ST-segment, ventricular extrasystoles and at least a lactatacidosis. When these signs appear hemodilution have to be terminated immediately. For recognizing these changes a lot of variables of the patient must be monitored. Thus vital signs and physiologic compensatory mechanisms monitoring is routine and a standard practice of anesthesia. "Application of standard anesthesia monitoring is required. More invasive monitors can always be added depending on the complexity of the surgical procedure, the patient's comorbidity, and the clinician's discretion" (Shander & Rijhwani 2004).

The acid-base balance is hardly influenced if acute normovolemic hemodilution is performed according to the guidelines (Oberreither n.d.). An acidosis could be caused by volume resuscitation fluid but that could be avoided by administration of a fluid with physiologic characteristics as explained above. Potassium, phosphorus and magnesium can decrease by severe diuresis and alterations in fluid distribution between intra- and extracellular room, thus before hand

administration of potassium is recommended after a control of potassium concentration in blood serum.

The decrease of clotting factors caused by hemodilution should be no problem for global coagulation if maximal dose of colloids is regarded. Caution is solely advised for patients with pre-existing coagulation disorders because the hypocoagulation could be boosted (Oberreither n.d.).

Despite the fact that ANH deals with patient's blood and risks of allogeneic blood transfusion are avoided "the use of predonated autologous blood still carries the risk of clerical error, mistransfusion, and bacterial contamination. Because ANH blood is never stored away from the patient and should be attached to the patient's intravenous line before the patient leaves the operating room, these risks are eliminated" (Monk 2005).

However, in the context of a meta-analysis done by Segal et al 2004, they found that reported adverse events are inconsistent and sparse. Described are mortality, myocardial infarction, cardiac ischemia, left ventricular dysfunction, cerebral infarction venous thromboembolism, hypotension and transfusion reaction but in general few of them occurred in any study. They concluded that the safety of the procedure can't be assessed based on such arguable data. Another meta-analysis done by Bryson et al 1998 also encounter the poor reporting of adverse effects but no increase in mortality or morbidity in patients undergoing ANH could be found. Anyway, they concluded that "the results of this overview cannot be used to establish the safety of this technique".

2.6 EFFICACY

There is considerable controversy about the question: Is it possible to eliminate allogeneic blood transfusion by using ANH? A meta-analysis by Bryson et al 1998 attempted to respond to this question without success. "When all trials of ANH are combined, it seems that ANH is effective in reducing both the likelihood of exposure to allogeneic blood and the volume of blood transfused. However, the presence of substantial and unexplained heterogeneity suggests that the benefit of ANH is inconsistent and cannot be definitively supported by this overview". Also Segal (2004) found no convincing evidences and concluded that widespread adoption of ANH cannot be encouraged. But both Bryson and Segal exhibited

that volume of intraoperative allogeneic transfusion is most extremely reduced all the more autologous blood is withdrawn before surgery. Monk (2005) mentioned that intraoperative ANH reduces allogeneic transfusions in patients undergoing surgery with significant blood loss and also cardiac surgery is associated with decreased allogeneic blood exposure.

Despite the fact that there are lots of publications regarding the efficacy of ANH, still there is large debate over whether ANH is efficacious or not persists.

3 BISPECTRAL INDEX

3.1 HISTORY

Primarily the narcotic state could be estimated only via blood pressure, heart rate, lacrimation, pupil's reaction, pupil's wideness and movement's reactions. For quantifying these parameters a so called "PRST-Score" was created: P = Blood **p**ressure, R = heart **r**ate, S = **s**weating, T = **t**ears. But these surrogate values are inadequate because they are easily adulterated by pharmaceuticals and consequently narcotic state can't be attributed. Therefore three electrical methods for quantifying the degree of hypnosis were developed. One of them works with acoustic evoked potentials, another is based on the entropie – theory and one is called EEG (Metzler et al n.d.). Electroencephalography (EEG) was the first device for measuring the electrical activity produced by the brain by recording the voltage oscillation on the scalp from electrodes (Wikipedia). So derived data are displayed as waves; the EEG power spectrum embrace the Alpha α, Beta β (β_1 and β_2), Delta δ and Theta θ waves and their pattern can be interpreted by skilled people for getting clinical relevant information. By comparing the EEG from a person awake and one in narcotic state could be shown that the electric activity is addicted to the degree of hypnosis.

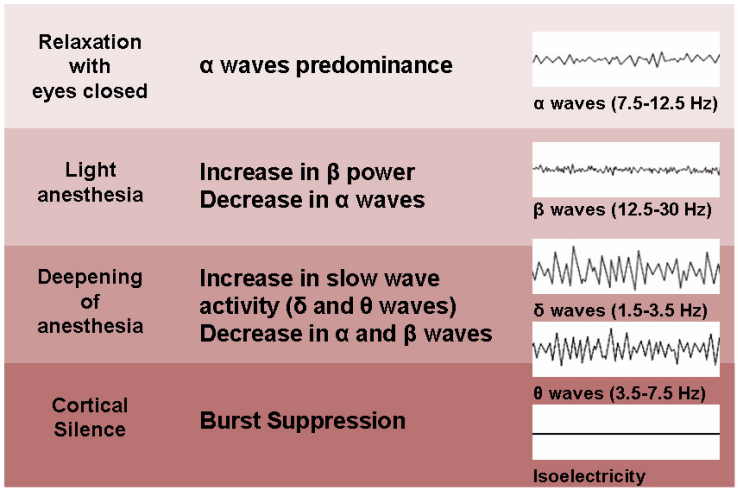


Fig. 1: Correlation of EEG waves and narcotic state (www.anesthesia-research.com)

The posterior alpha waves predominance with normal relaxed eyes closed, with deepening anesthesia frontal/central beta waves increases involving the alpha. With loss of consciousness the slow waves delta and theta become more prominent what represents a decrease in cortical generator activity. A cortical silence is displayed as a horizontal line representing the isoelectricity (Dahaba 2005).

As awareness under general anesthesia could be an unpleasant experience with severe consequences the idea to include EEG measurement in anesthetic routine monitoring during surgery grows up. Advantages of calculating the depth of narcosis are:

- Avoidance of awareness
- Continuous adaptation of the narcotic depth on surgical procedure
- Cost-effective application of anesthetic drugs
- Awaking time and recovery from narcosis can be shortened (Knöpfli n.d.)

However, an electroencephalographer can't describe depth of anesthesia in quantitative terms because there are no identifiable patterns which suggest neither a patient is unconscious and will not react to an incision nor if he is about to waken up. Therefore trends can be discussed only in vague fashion and many parameters derived from the processed EEG vary during relatively narrow portions of the continuum between awake and deeply asleep. The implementation in anesthetic routine monitoring also failed because of the complexity of the EEG device. The EEG machines generate huge amounts of paper what accessorily makes it very difficult to observe trends and interpret the complex waves, especially in the hectic setting of an operating room (Todd 1998). Also time and cost investment isn't efficient (Knöpfli n.d.). Accordingly a new device adequate for clinical routine, i.e. it should be handy and simple to interpret, had to be created.

3.2 BISPECTRAL INDEX

After decades of work a new device was manufactured by Aspect® Medical Systems called the Bispectral index (BIS). Their aim was to produce a new single value changing in linear or monotonic fashion with anesthetic depth. The result was the BIS Index calculated and displayed by a small box with a monitor and based on EEG derived parameters (Todd 1998).

The EEG monitoring unit calculates several different descriptors but none of these descriptors are particular per se. Nevertheless, "Aspect® then collected EEG recordings from thousands of patients undergoing anesthesia with multiple different anesthetic regimens. They also collected clinical information related to anesthetic depth, such as whether patients respond to spoken commands or recalled auditory cues presented via headphones or whether heart rate or blood pressure increased with incision, among others. These recordings were then processed, and a database or library was created of the EEG descriptors and the corresponding clinical states. The descriptors were then ranked by the ability to predict a particular clinical situation, and a statistical analysis was performed to construct combinations of the descriptors that would best correlate with the clinical condition. This statistically based, empirically derived use of combination of descriptors – rather than a single descriptor – is the key to the working of the BIS device (Todd 1998).

It is important to understand that there is no simple mathematic relationship between the EEG data and BIS value because the Bispectral index is a complex parameter composed of three sub-parameters: Relative BetaRatio, SynchFastSlow and Burst Suppression. Realtive BetaRatio is a frequency-domain feature of the EEG. SynchFastSlow is a bispectral-domain feature. Burst Suppression is a time-domain feature combining Burst suppression ratio and QUAZI suppression index. None of these three descriptors is particular per se but everyone has a specific range of anesthetic effect where it performs best (Dahaba 2005).

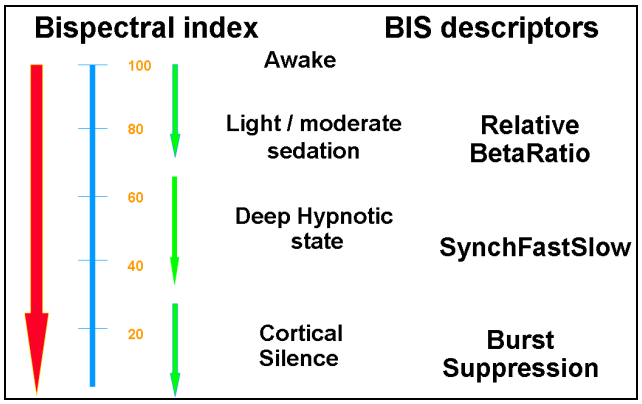


Fig. 2: Correlation of BIS, BIS descriptors and narcotic state (www.anesthesia-research.com)

The algorithm of how the BIS value is exactly calculated from the box is a little known, so we can imagine the process as the following: The master database of Aspect® indicates that, for example, the typical awake patient has an X value of 50, a Y value of 10, and a Z value of 0. Because we want a BIS of 100, by definition, to represent an awake state, we 'define' the combination of 50/10/0 to be equal to 100. In the future, any time the machine 'sees' a data set of 50/10/0, it displays a BIS equal to 100. A sedative drug is then administered, and the processors yield values of 40/18/0. The master database indicates that this combination of values typically is associated with, for example, the loss of response to verbal commands. Someone decides that this state is 20% of the way between awake and deeply asleep – so let us call this a BIS equal to 80. This empiric, reiterative process of calculating the three parameters, of comparing them to the database, and of assigning a BIS value is continued across the entire spectrum between awake and deeply asleep. The BIS numbers themselves are selected to create a linear scale between the two extremes" (Todd 1998), defined as 100 = totally awake and 0 = EEG silence.

Data for calculating the BIS value are collected with a sensor consisting primary of three electrodes. According to the manufacturer, the BIS algorithm (version 3.4) consists of 2 spectral channels; Channel 1 is the difference between electrode 1 and 2; Channel 2 is the difference between electrode 1 and 3; Channel 12 is the resultant of channels 1 and 2 and that is what the monitor displays as the Bispectral Index. In addition, with the new algorithm of the BIS starting from algorithm version 3.0 for the BIS-XP (= BIS 2000) the BIS quarto

sensor consists of 4 electrodes rather than the 3 electrode sensor of the older version of the BIS sensors designed for the use with the older version of the BIS monitor namely the BIS 1000. The new Quarto sensor has an additional electrode; electrode 4, directly above the eye brow, that is designed to exclusively measure the EMG activity in order for the new BIS algorithm (version 3.4) to more efficiently filter the EMG artefacts.

3.3 CLINICAL UTILIZATION

1.) First of all, equipment has to be prepared. A small box with a monitor, a sensor including four electrodes and a cable for connecting the electrodes with the BIS box are necessary.

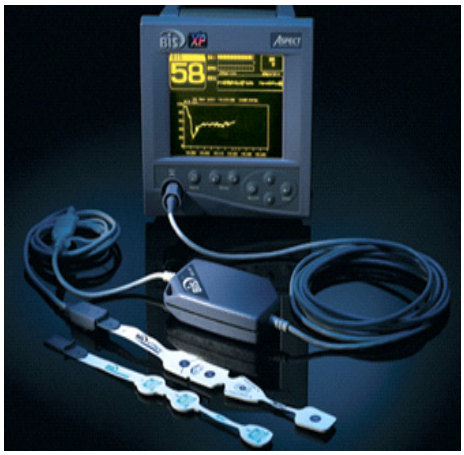
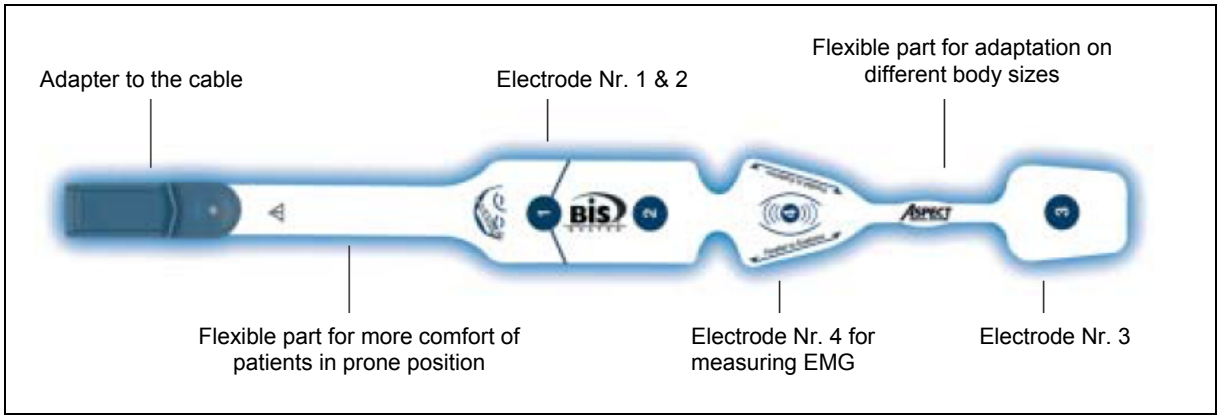


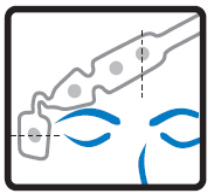
Fig. 3: Bis-Box with Conecting-Cable and Sensor (Aspect® Medical Systems n.d.)

Fig. 4: BIS – Sensor (Aspect® Medical Systems n.d.)



2.) The next step is to adhere these 4 electrodes on patient's forehead like the following description and connect them to the BIS – Box:

Fig. 5: Position of the electrodes on patient's forehead (Aspect® Medical Systems n.d.)



BIS – Electrodes number 1 to 4 have to be adhered in a special angle.

Nr. 1: directly in the middle, 5 cm above the nose.
Nr. 4: above/along the eyebrow
Nr. 3: between the angle of the eye and the hair line on the right or left temple
Nr. 2: position results when the other electrodes are placed correctly

Press the boarder of each electrode, especially the outer area of Nr. 4.

Press each electrode forcefully for 5 seconds with the finger tips

3.) Now BIS recording can be started. If the signal quality is good and a curve appears on the monitor anesthesia can be induced, if not electrodes have to be pressed for a few more seconds.

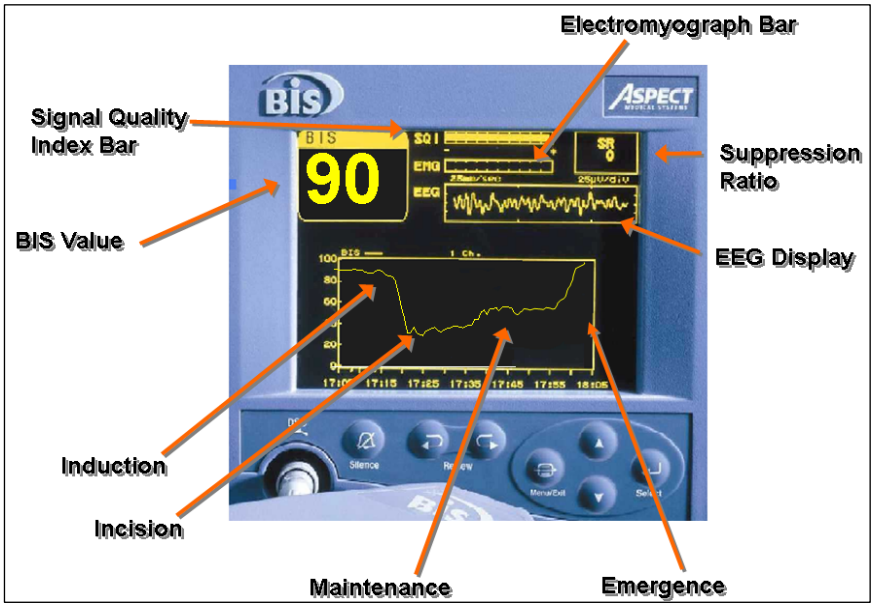


Fig. 6: Monitoring and BIS-Values:
This monitor shows a classical curve of a Bispectral Index during general anesthesia beginning with a value of 90.

On a classical BIS monitor a lot of things are shown. The biggest and most important one is the BIS value, for following the course of the BIS value a curve is displayed which can be compared with the EEG waves. For recognizing BIS artefacts caused by movements EMG can be observed and it's also possible to check the signal quality to avoid a malfunction of the measurement. The suppression rate (SR) is for very deep levels of hypnosis such as in intensive care unit patients who are in an induced pharmacological barbiturate coma, then concentrating only on one of the three BIS descriptors, which could be seen on the BIS screen as SR.

A curve of mean BIS values during general anesthesia is symbolized on this monitor. Special marks should be observed: the quick decline of BIS after induction of narcosis, the incision when intubation occurs, the stationary BIS during maintenance of anesthesia and the increasing part of BIS which signifies the awaking phase.

For getting the correlation between the dimensionless BIS value on the monitor and the hypnotic state in clinical term a BIS – Scale is used which simplifies the attribution. At the beginning of an operation BIS value is between 80 and 100 what is equatable to a light sedation. During induction of anesthesia a decrease of BIS can be observed, the more narcotic agent is administrated the deeper decline BIS. Below BIS of 70 the likelihood that the patient remembers anything is very low. With a BIS decline under 60 loss of consciousness occurs but painful surgical stimulations can awake the patient and an increase of BIS will be observed. So the narcosis has to be deepened until BIS values of 50 or 40 because then a level is reached where all surgical procedures are tolerated by the patient (Knöpfli n.d.).

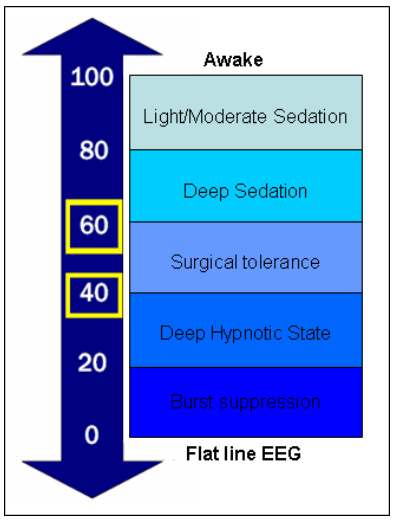


Fig. 7: BIS – Scale

BIS is widely used for monitoring the level of consciousness during general anesthesia because it's very easy to handle and everybody can interpret the simple scale. A clinical advantage is that patients who are afraid of awareness during surgery can be calmed down by explaining that a monitor shows their depth of anesthesia. Also calculating the correct dose of narcotic agents for adipose patients could be supported with BIS because the exact pharmacodynamic of adipose people is not known and prolonged recovery time is the consequence (Knöpfli n.d.).

3.4 POSSIBILITIES OF BIS MEASUREMENT

The most important factor which can be estimated with BIS is the depth of anesthesia (as mentioned above). Sebel et al 1997 tried to support this statement with a multicenter study dealing with the hypothesis that "adjustment of anesthetic dose to achieve lower BIS values would decrease the probability of patient movement in response to skin incision". Three hundred patients from seven study sites were randomized into two groups: The BIS-guided group got anaesthetized till BIS decreased to a value below 60. The other group was only monitored with BIS but not adapted to displayed values; so narcosis was given to reach a level where 50 % of the patients didn't respond with movement to skin incision. The results confirmed their hypothesis of the BIS as a significant predictor of patient response to incision but only when drugs such as propofol or isoflurane are used for the primary anesthetic because with use of opioid analgesics correlation to patients movements became much less significant.

Special clinical conditions causing BIS changes were reviewed by Dahaba 2005. For example blood glucose level is a contributing factor during interpretation of BIS because at hypoglycemic coma patients with blood glucose levels till 21 mg/dl BIS values about 45 were measured; with increasing blood glucose and return of consciousness BIS increased rapidly to a value of 80. Also cerebral ischemia could be detected with BIS because during carotid artery clamping a BIS decline from 40-60 to <10 was observed and returned to normal values with restoration of normal cerebral circulation.

England (1999) supported this statement by publishing a case report of a patient who had a hypovolemic cardiac arrest during tricuspid valve replacement and whose BIS values were recorded during the whole surgery. Induction of anesthesia succeeded without difficulty but during sternotomy the right atrium was lacerated followed by sudden loss of blood volume. “The decrease in BIS lagged behind the decrease in blood volume by approximately 2 min”. Despite infusing phenylephrin blood pressure couldn’t be maintained and the patient sustained a hypovolemic cardiac arrest. During this time neuronal function was low and BIS displayed a high burst suppression ratio but after correction of the blood volume/pressure with a cardiopulmonary bypass also 2 min were necessary for BIS adaptation. BIS returning to normal values was taken as a sign of successful resuscitation. What must be noted is that BIS can’t be used as a predictive monitor but is able to give us additive information about the patient’s condition.

3.5 BIS - FALSIFYING FACTORS

On interpreting BIS value influencing effects should be considered. An ever existing disturbing factor is the noise in the operating room. Kim et al (2001) evaluated the effect of noise on BIS before surgery. Their research was based on the knowledge that noise interfere with the ability to sedate patients before surgery. First of all 30 unpremedicated patients were randomized in two groups. One group got anesthetized with propofol through a stable baseline BIS value of 75, the other one to a BIS value of 80 conducted with TCI. After that an external sound source administrated noise with 50, 80, 110 and 120 dB and alterations in the BIS value were recorded over 1 min interval at each noise level. They concluded that BIS alterations during experimental noise administration are greater during light levels of narcosis and higher dB-values but have no clinical relevance during deeper anesthetic states.

Other factors altering BIS value are EMG activity and neuromuscular blocking drugs. Dahaba (2005) examined this hypothesis and found out that BIS value increases with high EMG activity and decreases with neuromuscular blocking drugs. He concluded that the EMG contaminates the BIS when the EMG activities

occur within the frequency “range of interest” of the bispectrum. Therefore the BIS value could be misinterpreted also considering the fact that high EMG activity let the measured EEG activity seeming higher, so BIS represents a narcotic state which is typically associated with awake or light levels of anesthesia at a patient who is deeply anesthetized. However, the administration of neuromuscular blocking drugs would decrease the BIS value by alleviating the artefact and so the true calculated BIS could be shown. Bruhn et al (2000) supports this results publishing two case reports in which BIS failed to measure depth of anesthesia. “In the first case bispectral index paradoxically increased after increasing propofol concentration, correlating with increasing EMG activity. In the second case the administration of a nondepolarizing muscle relaxant decreased the bispectral index value at constant anesthetic drug concentration”.

As a combination of analgesics, mostly opioids are administrated, with narcotic agents got a proven standard for induction of anesthesia, the question about the influence of opioids on BIS monitoring got important. Lysakowski et al 2001 exhibited the influence of analgesic concentrations of opioids on predicted effect-site concentration of propofol with relation to loss of consciousness (LOC) and BIS values during induction of anesthesia. They compared four opioid groups (fentanyl, alfentanil, remifentanil or sufentanil was administrated) with a placebo group and found out that LOC occurs at a lower effect-site concentration of propofol and consequently at higher BIS values in presence of opioids. This result demonstrated that μ-agonist opioids enhance the hypnotic effect of propofol what is observable by the BIS because BIS only reflects the lower propofol requirement.

4 SPECTRAL EDGE FREQUENCY

The spectral edge frequency is the precursor value of BIS for assessing the depth of anesthesia and the ischemia in the central nervous system. The idea of the development of SEF was to simplify the raw EEG by defining only one numerical descriptor of all the EEG data. That should be more useful for clinical practice because interpretation seems easier and more rapid (Arndt et al n.d.).

SEF can be derived from the powerspectrum of the computer assisted EEG, called the processed EEG. It reflects the frequency below which a defined power of the total power spectrum is situated (Schwarz et al n.d.).

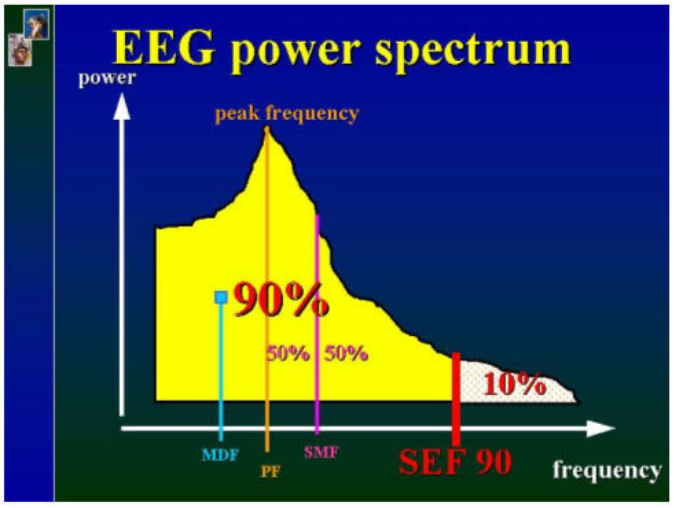


Fig. 8: EEG power spectrum; MDF = median edge frequency; SMF = Spectral mean frequency

For assessing the depth of anesthesia we use SEF 95 and SEF 90, that means 95 or 90 % of the power is situated in lower frequencies. An adequate depth of narcosis is represented by SEF 95 values between 14 and 16 Hz and by SEF 90 values between 10 and 13,5 Hz.

An advantage is that SEF values, as well as BIS values, are independent of preoperative medication and muscle relaxants but it always should be considered that the values are adapted to the narcotic agent administrated. Mostly propofol is

used what allows a standardized recommendation of which SEF values correlate with the state of depth of anesthesia.

Schwarz et al conducted a study about specific problems in interpretation of absolute values of Spectral Edge Frequency (SEF) in comparison with Bispectral Index (BIS) for assessing depth of anesthesia. They randomized 64 patients to receive either sevoflurane or desflurane for maintenance of anesthesia after induction with fentanyl. Four measuring phases were defined for comparing the SEF and BIS values adequately: The first measuring phase (MP1) took place before inducing anesthesia with the patient's eyes closed. The second measuring phase (MP2) was in the ‘excitation phase’ (obtained after equilibration of sevoflurane at 1.2 Vol%et or desflurane at 3.0 Vol%et). The third measuring phase (MP3) was 1 minute after the skin incision, representing the ‘surgical tolerance phase‘. The fourth measuring phase (MP4) took place in the ‘burst-suppression pattern phase’ (measured 10 minutes after the endtidal gas concentrations were doubled respectively).

The results showed a very high interpersonal deviation and also a high intrapersonal instability of SEF values during the awake phase (MP1), which makes the differentiation between the awake and asleep phase difficult. In the ‘excitation phase’ (MP2) they observed that SEF can increase with superficial anesthesia during induction and only decrease with deepening of anesthesia. Therefore, both awake and asleep patients can show similar SEF values. Also in the ‘surgical tolerance phase‘ (MP3) and also during the ‘burst-suppression pattern phase’ (MP4) the increased concentrations of anesthetics are not reflected adequately of the measured SEF values. In comparison to SEF BIS values show a high intrapersonal stability and a very narrow interpersonal deviation. It also reflects the increasing concentration of the narcotic agent and the following decrease in unconsciousness with higher plausibility. The target limit which should be achieved for surgical tolerance can be defined with a BIS value < 60.

They concluded that measurement with BIS allows a secure determination between awake and asleep phases followed by a good control of depth of anesthesia during surgery with high probability to avoid awareness. However they could find no suitable, approximate target limit of SEF for guiding the depth of anesthesia at the present time.

5 TARGET CONTROLLED INFUSION (AstraZeneca® 1999)

By definition 'target controlled infusion' is described as: "When applied to anesthesia, TCI is an infusion system which allows the anesthetist to select the target blood concentration required for a particular effect, and then to control depth of anesthesia by adjusting the requested target concentration". This means that TCI is not a system for the complete computer control of anesthesia; it only supports the anesthetist by adjusting the depth of anesthesia to every clinical condition. Control still remains a part of the anesthetist, who uses clinical sings or more sophisticated means of monitoring to estimate patient's condition during the narcotic phase.

The idea to develop such a delivery system appeared with the implementation of intravenous anesthetics. As it's difficult to maintain optimal narcotic conditions with manual bolus delivery this infusion pump was created for governing the narcotic phase as well as the anesthesia with volatile narcotics administrated via vaporizer. TCI allows a stable infusion of an intravenous narcotic agent, particularly Diprivan®, and a continuous control of the concentration of infused drug in blood or plasma.

5.1 COMPONENTS

The main components of the TCI system are the hardware and the software which are responsible for reaching and maintaining the target blood concentration of a narcotic agent.
The hardware includes a syringe pump for infusion called 'Diprifusor' and a special syringe. The Diprifusor contains a small monitor showing the present setting and buttons for entering patient's age and weight as well as the target blood concentration. The syringe has to be prefilled with a drug, particularly Diprivan®, and contains a recognition tag to be in touch with the infusion pump correctly.

Fig. 9: TCI - system

The software incorporates information about the pharmacokinetic properties of the narcotic agent infused and the appropriate pharmacokinetic model of the human body; both are required for balancing the infusion rate with the process of distribution and elimination. It also includes a specific set of parameters and an algorithm for altering the infusion rate automatically to maintain blood concentration until the anesthetist enters a new target.

The pharmacokinetic model used for TCI is the Marsh-Model (Marsh 1991). However, the properties of anesthetics in the human body can best be described by an open three compartment theory. The following figure shows how the drug will be metabolized and what differences exist between the drug effects in highly and poorly perfused tissues.

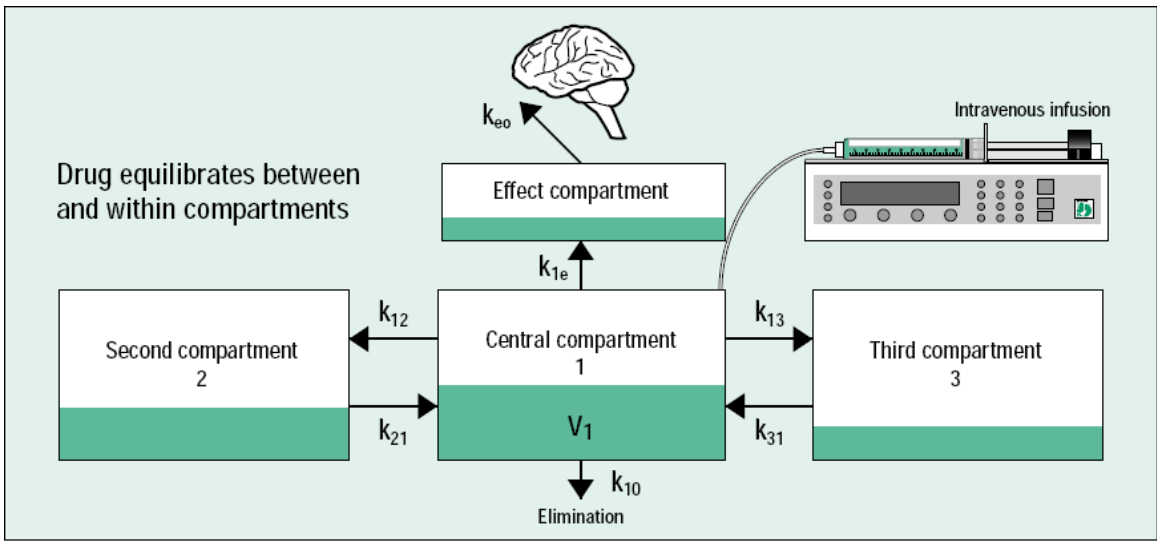


Fig. 10: Three compartment theory of the pharmacokinetic

- Central compartment represents blood or plasma
- Second compartment could represent the highly perfused tissues
- Third compartment could represent the poorly perfused tissues

- k_{10} is the elimination rate constant from the central compartment
- k_{eo} is the rate constant describing drug elimination from the effect site
- k_{21} k_{12} k_{31} k_{13} and k_{1e} are intercompartmental distribution rate constants i.e. they describe the proportions of drug exchanged between compartments per unit time

Primarily after a bolus delivery a rapid, initial distribution phase can be observed which represents distribution to highly perfused organs such as the brain (effect site). The following second phase containing significant metabolism is slower and represents a redistribution to less well perfused tissues such as muscles. The third compartment stands for poorly perfused tissue and is hardly relevant for the effect of narcotics. The recovery from anesthesia is due to extensive redistribution from the brain and to metabolic clearance.
These cognitions make it possible to ensure a correct automatically conducted alteration of infusion rate to maintain required blood concentration.

5.2 CLINICAL RELEVANT ASPECTS

Before commencing the total intravenous anesthesia based on TCI equipment, mentioned above, has to be prepared. The prefilled syringe must be tagged correctly to the Dirpifusor and the air of the infusion line has to be expelled by simultaneous filling with propofol while it is disconnected from the patient. After that a check of the pumps function is recommended concerning the mode, the recognition of 1% or 2% Diprivan® and the reaction on user inputs. The next step is to enter, instead of mg/kg/h needed for the common bolus delivery, the following three main points necessary for an adequate TCI narcosis:

- Body weight of the patient in kilograms
- Age of the patient in years
- Initial target concentration of blood in µg/ml

After that the infusion and the narcotic phase respectively can be started. By pressing the start button the Diprifusor-software initiates a rapid delivery of propofol with an infusion rate of 1.200 ml/h until the pharmacokinetic model calculates that the selected target concentration in blood has been reached. After

that the infusion rates are altered automatically aiming in maintaining the selected target concentration.

Although the pump continues to work automatically often clinical conditions demand an adaptation of the target blood concentration by the anesthetist. Selection of a higher target concentration results in administration of a bolus followed by infusion at an increased rate. A decrease of the target concentration is achieved through a temporary discontinuation of infusion followed by an infusion rate at a lower level. After terminating propofol infusion the blood concentration falls continuously. The awaking time depends on the metabolic clearance of the patient and the level of selected blood concentration.

5.2.1 General benefits and disadvantages of TCI

By comparing the manual and the target-controlled infusion of propofol in clinical practice Russel et al (1995) found out that induction of anesthesia with TCI is more rapid and allows earlier insertion of a laryngeal mask airway. A small disadvantage of TCI is that more propofol is administrated during both induction and maintenance of anesthesia but this gets compensated by a lower tendency of movements in response to surgical stimuli. By examining hemodynamic stability and recovery time no significant differences among manual and TCI controlled group could be found. The research team also asked anesthetists without prior experience which technique they would prefer and came to the conclusion that they got familiar with both, the manual and the target controlled one, quickly but expressed a clear preference for the target-controlled system because of the better predictability of the anesthetic effect.
Especially for anesthesiologists without routine it also seems to be easier to manage the whole anesthesia with only one narcotic agent (getting possible with propofol infused via TCI) compared with the common process, where intravenous induction of anesthesia is given manually and narcotic agent has to be changed after that to a volatile anesthetic to maintain narcosis during surgeries taking hours.

AstraZeneca® (1999) compiled a list of benefits based on a few publications (Engbers & Vujk 1996, Billard V et al 1997, Hitchcock 1997, Kenny GNC & Sutcliffe 1997) and came to similar results. They split the advantages of TCI in two groups:

1.) Convenience of use:
- Simple to operate
- Easy to titrate the level of anesthesia
- Displays calculated blood or plasma concentration
- Compensates for interrupted infusion
- Avoids the need for time-consuming calculations
- Continuous process from induction through to maintenance

2.) Control of anesthesia - Theoretical aspects:
- Good control of depth of anesthesia
- Gives stable anesthesia
- Improved control of cardiovascular and respiratory parameters
- Induction phase can be used to predict maintenance effects

For proving the costs-effectiveness of a total intravenous anesthesia with TCI Suttner et al (1999) compared two standard anesthesia regimes with the TCI controlled narcosis. Group 1 (TIVA/TCI) received total intravenous anesthesia using a propofol-based TCI system and continuous administration of remifentanil. Group 2 (isoflurane) underwent anesthesia based on the volatile narcotics isoflurane and N_2O combined with fentanyl and Group 3 (standard propofol) received fentanyl and propofol for induction and anesthesia was maintained by continuous administration of propofol and N_2O using a regular syringe pump. They found out that the TIVA/TCI group was associated with the largest intraoperative costs but this commercial disadvantage gets compensated by the most rapid recovery time from anesthesia and the fewest incidence of postoperative side effects what allows an earlier discharge from the postanesthetic care unite.
Lehmann et al (2002) compared target-controlled and manually-controlled propofol-based anesthesia at patients undergoing an implantation of a

cardioverter-defibrillator the first time. They demonstrated that the extubation time did not differ significantly between the two groups and also heart rate and mean arterial pressure altered in the same way. By using of remifentanil during anesthesia no differences could be found at any time but in the TCI group significantly more propofol was administrated. Considering the BIS values they were significantly lower in the TCI group after skin incision and first defibrillation but at the end of the surgery they were the same again. Another difference could be found by comparing the costs because target-controlled propofol-based anesthesia is more expensive. They come to the conclusion that both techniques, the manually and the target controlled one, in combination with remifentanil allow good control of anesthesia and BIS helps to avoid intraoperativ awareness and reduces the amount of applied anesthetics.

5.2.2 Clinical benefits of propofol (Diprivan®)

For good control of depth of anesthesia the use of a narcotic agent with rapid onset and short duration of action is recommended. Exactly this qualities were examined for propofol because it undergoes a very rapid distribution and metabolic clearance. Induction characteristics can be described as smooth, rapid and reliable. Duration depends on the rate of infusion which again depends on the clinical response of the individual patient and supplementary used drugs. For example in the study where I was included (Dahaba et al 2008) we chose a rate of infusion of 0,5 µg/ml once every 30 seconds followed by loss of consciousness at a propofol TCI of 2.75 µg/ml after 1.7 min.

The maintenance of anesthesia with propofol is smooth, easy to control and hemodynamic stability is ensured. The use for short and even for major surgeries is possible because doses can be adapted to surgical situations quickly based on the pharmacokinetic profile which enables rapid response of blood concentration to changes in the infusion rate.

A rapid decrease of blood concentration allows a shortening of the recovery phase defined by the time to eye opening and orientation. Also the recovery time including the return of cognitive and psychomotor function as well as the time to discharge could be shortened with Diprivan®. This is important especially for day-case surgeries. Another advantage after a narcosis based on propofol is that the

incidence of postoperative nausea and vomiting (PONV) is low compared with an anesthesia based on volatile narcotics.

This mentioned clinical benefits of Diprivan® are followed by economic advantages: The short time to recover also reduces the saves nursing time in the recovery room. The need of an anti-emetic therapy is limited by the low risk for PONV after narcosis and the short time to discharge allows the patient to return to his work early. All these benefits were considered by deciding that Diprivan® is the best narcotic agent for a TCI-System.

Passot et al (2005) compared the target and manually controlled infusion of propofol and the etomidate/desflurane (ETO/DES) anesthesia in elderly people. The results showed that anesthetic induction time was longer with propofol compared with ETO/DES. Particularly for elderly people propofol TCI ensures better hemodynamic stability than with manual applied propofol boluses. Although ETO/DES ensures the same hemodynamic stability as TCI preferably propofol should be used because it is followed of less postoperativ nausea and vomiting. Recovery times were similar among the three groups.

5.2.3 Contraindications and side effects of propofol (Diprivan®)

As contraindication are mentioned shock, hypovolemia, severe heart insufficiency and severe coronary heart disease because they result from propofol. Also for children younger than three years and during pregnancy and lactation use of propofol is contraindicated because till now no sufficient data could be exhibited.
Always must be anticipated with side effects like hypoventilation till apnoea, irritation of the vein and depression of circulation followed by blood pressure decline and bradycardia. Remarkably is that propofol is no trigger substance for malignant hyperthermia; so it can be applied to patients with high risk for the development of malignant hyperthermia during narcosis.

5.2.4 Interaction of propofol with different anesthetics

Röpcke et al (2001) compared anesthesia induced and maintained with propofol TCI with a narcosis based on propofol in combination with remifentanil both measured with BIS. They came to the conclusion that remifentanil influences the pharmacokinetic of propofol because all from the TCI predicted blood concentrations of propofol in combination with remifentanil overwhelmed the measured concentrations of propofol in arterial blood sampled after a stable BIS value over 20 min.

Wilhelm et al (2003) specified this result in their general article about remifentanil based on a study in which Wilhelm (2002) analyzed the effect of remifentanil or fentanyl in combination with propofol, thiopental or edomidat during narcosis induction. He found that the time till the reflex of the eyelid disappeared was significantly shorter for all narcotics in combination with remifentanil than combined with fentanyl. Simultaneously could be observed that a lower dose of propofol, thiopental or etomidat was necessary for achieving a loss of consciousness with a remifentanil bolus delivered at the beginning. The hemodynamic reactions like an increase of mean arterial pressure or heart rate on the intubation stiumulus were lower with remifentanil. In the article of 2003 they alert that this circulatory degradation of remifentanil combined with propofol can cause complications at patients with chronic cardiovascular disease because the blood pressure and the heart rate decreases to a point where sufficient blood delivery to the myocardial muscle can’t be obtained that will be followed by a heart attack or even a cardiac arrest. By combining remifentanil with etomidate or thiopental hemodynamic stability could be maintained also for high risk patients.

This risk for high risk patients and the fact that in combination with remifentanil a lower propofol concentration achieves the same narcotic effect is considered in every recommendation regarding propofol doses for adequate anesthesia.

5.2.5 Tolerability profile of ‘Diprifusor’ TCI

The tolerability of the TCI system emerges from the side effects of the used drugs, propofol and remifentanil or fentanyl, and the experience of the performing

anaesthesiologist. In summery during the whole process every time the following events mentioned at AstraZeneca®-Homepage can occur:

- Cardiovascular malfunction (e.g. bradycardia, hypotension)
- Respiratory malfunction (e.g. hypoxia, apnoea)
- Local reactions (e.g. pain or discomfort on injection)
- CNS (e.g. mild excitatory phenomena, dreaming)

It's hard to find other publications about disadvantages or even statistically documented adverse events concerning the TCI-system and so I come to the conclusion that this system ensures a well controlled anesthesia without any complications when used according to the manufactory.

6 INFLUENCE OF ACUTE NORMOVOLEMIC HEMODILUTION ON BISPECTRAL INDEX MONITORING AND PROPOFOL DOSE REQUIREMENTS (Dahaba, Rinnhofer 2008)

6.1 SUMMARY

The aim of our study was to explore whether ANH used in clinical practice according to the published guidelines (Napier et al 1997), could be associated with detectable BIS changes in unmedicated patients prior to anesthesia induction, during propofol TCI induction and during maintenance of narcosis. We tested the null hypothesis that ANH will not have a significant sustained effect on BIS monitoring.

For this randomised clinical study we defined three groups: an ANH with oxygen insufflation (oxygen group), an ANH with air insufflation (air group) and a control group. All of the 45 patient who agreed to participate in the study gave written informed consent and were randomly allocated to one of the three groups.

We recorded BIS values over the whole process but we defined the following three different endpoints for comparing the data of the three groups sufficiently: 1. BIS changes before induction of anesthesia, 2. BIS changes and propofol TCI dose requirements during induction, 3. BIS changes and propofol TCI dose requirements during maintenance of anesthesia, all with or without ANH.

After summarizing the data we did a statistical analyses. We used the repeated measures ANOVA to compare the three groups. With the paired t-test we worked out the differences between the oxygen and the air group. We expressed the results as means ± SD and $P < 0.05$ was considered statistically significant.

So we came to the conclusion that a statistical significant decline of BIS value exists after ANH but it returns to baseline by breathing oxygen before induction of anesthesia. The other significant difference we found out was that during induction of narcosis less propofol is necessary with ANH to get the same hypnotic effect than without ANH.

6.2 METHODS

This prospective controlled clinical consecutive randomized observer-blinded study was carried out in conformity with the guidelines of the "Consolidated standards of reporting trials (CONSORT)-statement" (Weiskopf et al 2000). After ethics committee approval, all patients who agreed to take part in the study singed the patient informed consent. Exclusion criteria were body mass index < 18 or > 26 kg/m^2, ASA classification grade higher than ASA 3, medical conditions that might affect the level of consciousness such as stroke, stupor or dementia, and patients treated with cardiovascular or sedative/hypnotic drugs which might alter BIS values (Dahaba 2005). The 45 patients meeting demand and undergoing orthopedic or general surgical procedures with expected blood loss of more than one liter as indication for ANH were included. Stratified for gender and ASA classification they were randomly allocated to the ANH or controlled groups by an assigned nurse using the Number Crunching Statistical System (NCSS Inc., Kaysville, UT, USA) computer generated program.

"Procedures were performed in the anesthesia induction room in a quiet environment with no verbal communications between the induction room personnel because noise transiently provoking BIS response should be averted (Kim et al 2001). Patients were instructed to remain calm but not to fall asleep (Nieuwenhuijs et al 2002). Patients were also instructed to try to keep their facial muscles completely relaxed and avoid making any facial expressions as electromyographic (EMG) activity could spuriously elevate the BIS value (Sleight et al 2001). All tactile or verbal communications with the patients were also avoided".

"BIS 'Quatro' sensors were placed on patients' forehead according to manufacture's guidelines, and connected to a BIS-XP monitor (Aspect Medical Systems, Newton, MA, version 3.4). The BIS monitor was connected to a laptop computer. Recordings were started after verifying a sustained low EMG activity, signal quality index of >95% and electrodes impedance of <5 kΩ. The BIS, spectral edge frequency (SEF) and EMG data were continuously collected and stored every 5 s, whereas the BIS smoothing window was set at 30 s. Patients

were warmed using a forced-hot-air-blanket to maintain skin temperature >32°C. Mean arterial pressure (MAP) and heart rate (HR) were continuously recorded".

Patients in the oxygen and air groups underwent ANH according to published guidelines (Napier et al 1997). Before anesthesia induction a radial artery cannula was placed under local anesthetic for sampling. Additional on each arm a venous cannula were placed for permitting ANH. Approximately 20 ml/kg blood were procured from a cubital vein at an approximate rate of 75 ml/min and stored in an acid citrate-dextrose reservoir bag to be simultaneously replaced by an equal volume of warmed 6% hydroxyethyl starch (HES) 130/0.4 in 0.9% NaCl replacement solution. This replacement fluid was infused constantly at the same rate of blood procurement via the cubital vein cannula in the other arm aiming at reaching a hemoglobin concentration of 9 g/dl (= 5.6 mmol/l).

"All patients were fitted with facemasks through which air at a flow rate of 5 l/min was insufflated. After the conclusion of ANH in the oxygen group and a similar period of time in the control group, 100% oxygen was insufflated at a flow rate of 5 l/min for a 5-min equilibration period, before induction of anesthesia. In the air group, air at a flow rate of 5 l /min was insufflated. Arterial partial oxygen pressure (Pao_2), arterial partial carbon dioxide pressure ($Paco_2$), *p*H as well as arterial oxygen saturation (Spo_2) were recorded before and after ANH, and before anesthesia induction. Patients in the control group were placed in exactly the same ambient conditions with approximately 20 ml/kg lactated Ringer's solution constantly infused via a cubital vein cannula to simulate, as much as possible, the ambient conditions of the oxygen and air groups before induction of anesthesia".

"Because BIS was shown to decrease with sleep (Nieuwenhuijs et al 2002), all patients were interviewed immediately before anesthesia induction, and patients who fell asleep during the recordings were excluded from the study. After the conclusion of blood procurement and HES fluid replacement in the oxygen and air groups and after a similar period of time in the control group, a blinded anesthesiologist unaware of whether the patients underwent ANH, or whether oxygen or air was insufflated, induced anesthesia with propofol TCI using a Diprifusor® infusion pump (AstraZeneca, Cheshire, UK), incorporating a three-

compartment pharmacokinetic algorithm of the Marsh pharmacokinetic model (Marsh 1991). After preoxygenation and entering patients' anthropometric data, propofol TCI was first set to reach a plasma concentration of 1.5 μg/ml, and increased by 0.5 μg/ml once every 30 s until patients lost their eyelash reflex and no longer responded to verbal command". Plasma concentration and not effect site concentration TCI was chosen, as propofol plasma concentration probably requires 10 min time for equilibration with hypothetical effect-site compartment predicted by the Diprifusor® (Marsh 1991). Loss of consciousness (LOC) time, propofol dose requirements for LOC, and the BIS value at LOC were recorded. Anesthesia was then maintained at propofol TCI 4 μg/ml with no further adjustments until a stable BIS level was reached. The maintenance BIS level was recorded and this marked the conclusion of our study period".

After conclusion of the study period, fentanyl 1.5 μg/kg and rocuronium 600 μg/kg were administered for tracheal intubation. The lungs were ventilated mechanically with 40% oxygen in air for the start of surgery.

6.3 STATISTICAL ANALYSES

Because BIS changes during ANH were not previously examined, we based our *a priori* power analysis upon a related observation, namely the effect of ANH on cognitive function tests. A recent study demonstrated that the mean (95% confidence intervals) horizontal addition cognitive function test of 2.811 s (2.405-3.218 s) increased to 3.345 s (2.923-3.767 s) with ANH to a hemoglobin concentration of 6 g/dl (Weiskopf et al 2000). After estimation of standard deviations and logarithmic transformations to accommodate for nonlinear data distribution (of the study mentioned above) our power analysis ($\alpha = 0.05$) showed that a sample size of 7 patients would be required to reveal a statistically significant difference between the two groups with >90% power. The sample size was then doubled to 15 patients to accommodate for the discrepancy between the different natures of cognitive function tests, upon which we based our power analysis, and BIS monitoring. "Repeated measures ANOVA was used to compare the differences between the 3 groups over time". In the oxygen and air groups,

paired comparisons using paired *t*-test were performed to compare the differences in BIS, SEF, HR and MAP before and after ANH. “Data were expressed as means ±SD. *P* <0.05 was considered statistically significant”.

6.4 RESULTS

Primary we had to prove if our two groups are comparable. For that we evaluated the accordance of the main patient characteristics:

Table 2: Patients’ characteristics; Median (range)

	Control group	Oxygen group	Air group
Male/female	11/ 4	11/ 4	11/ 4
Age (years)	51 (37-62)	53 (44-61)	55 (47-66)
Weight (kg)	70 (48-87)	69 (60-74)	67 (58-77)
Height (cm)	168 (157-177)	168 (163-176)	171 (166-181)

The table shows us that the main patients’ characteristics are almost the same in the three different groups, what allows us to go on with our analysis. Only one patient in the oxygen group, who fell asleep during the recording, was excluded from the final analysis and a replacement patient was recruited. EMG values of all recording were below 35 dB, as the EMG activities are artifact signals that occur within the frequency “range of interest” of the bispectrum. The EMG frequency band namely could simulate the BetaRatio, one of the BIS component descriptors, and an increase in EMG activity would be construed by the BIS algorithm as EEG activity and assigned a spuriously (falsely) elevated BIS value (Sleigh et al 2001). To check the general condition of each patient during the whole process we measured and documented the respiratory and laboratory parameters. The following table represents the mean values of the different groups:

Table 3: Respiratory and laboratory parameters of patients

Oxygen group	Before ANH	After ANH	After 100% oxygen
PaO_2 (mm Hg)	81 ±15	84 ±11	357 ±44*
$PaCO_2$ (mm Hg)	44 ±5	43 ±9	41 ±6
SpO_2 (%)	96 ±2	95 ±2	99±1*
pH (units)	7.41 ±0.05	7.38 ±0.04	7.38 ±0.04
Hb (g/dl)	13.4 ±1.6	8.9 ±1.7*	8.8 ±1.8
Hb (mmol/l)	8.3 ±1	5.5 ±1.1*	5.5 ±1.1
Hct (%)	42.7 ±3.6	30.3 ±2.4*	30.2 ±2.5

Air group	Before ANH	After ANH	After 5 min
PaO_2 (mm Hg)	79 ±11	87 ±9	89 ±10
$PaCO_2$ (mm Hg)	45 ±8	42 ±7	40 ±9
SpO_2 (%)	95 ±3	94 ±3	95±2
pH (units)	7.4 ±0.06	7.37 ±0.03	7.38 ±0.03
Hb (g/dl)	12.9 ±2.2	9.0 ±2.5*	9.1 ±2.4
Hb (mmol/l)	8 ±1.4	5.6 ±1.6*	5.6 ±1.5
Hct (%)	44.3 ±4.1	33.4 ±3.5*	32.1 ±2.6

Means ± SD, n = 15 in each group, ANH = acute normovolemic hemodilution, PaO_2 = arterial partial oxygen pressure, $PaCO_2$ = arterial partial carbon dioxide pressure, SpO_2 = arterial oxygen saturation, Hb = hemoglobin, Hct = hematocrit.
Paired *t*-test: *P<0.0001 PaO_2 and SpO_2 before and after 100% oxygen insufflation. *P<0.0001 Hb and Hct before and after ANH.

Our collected BIS and SEF data were normally distributed. At the conclusion of blood procurement and fluid replacement (18±7 min) we found a significant decline in mean BIS value in the oxygen and air groups that was restored to baseline values at the end of the 5 min equilibration period. “Whereas, in the control group there was no significant difference in BIS values at 18 min (95±3) and 23 min (96±2) compared to baseline values (97±2)”. The following figure shows the significant difference in the BIS and SEF values between the oxygen and air groups compared to the control group:

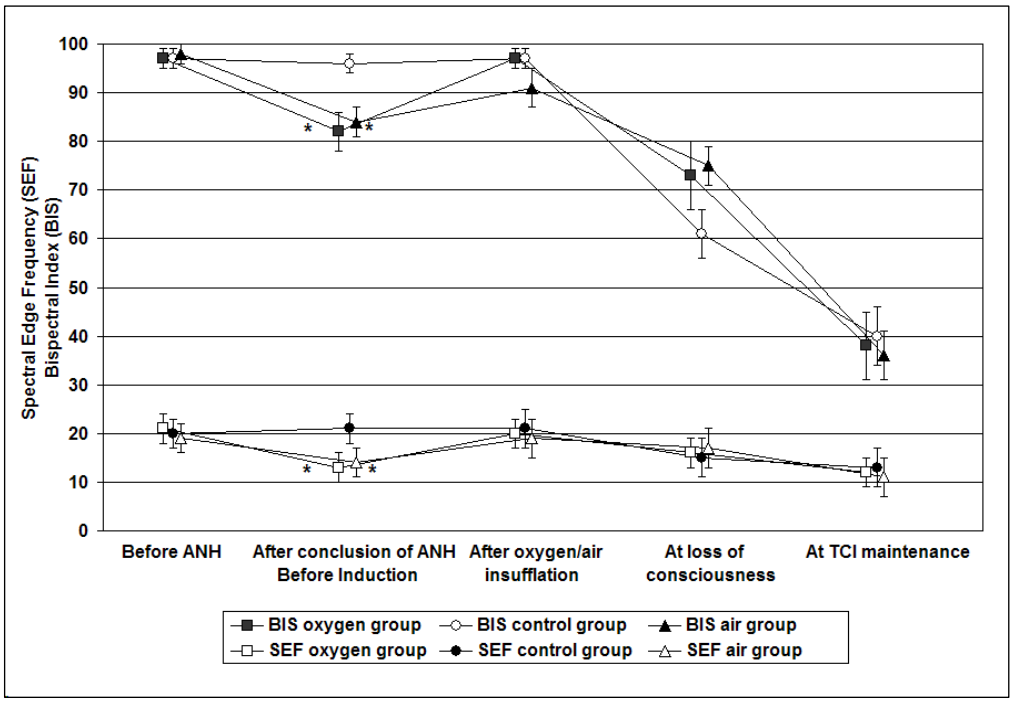


Fig. 11: Difference of BIS and SEF values between the oxygen and air groups; Mean ± SD Bispectral index (BIS) and spectral edge frequency (SEF) before and after acute normovolemic hemodilution (ANH), and after propofol target controlled infusion (TCI) in the oxygen, air and control groups. n = 15. *Significant difference (P< 0.0001) in the oxygen and air groups compared with the control group.

"Loss of consciousness (LOC) time was significantly shorter, with fewer propofol TCI dose requirements and BIS was significantly higher at LOC in the oxygen and air groups compared to the control group. Whereas, there was no significant difference between the 3 groups in BIS values at stable propofol TCI 4 μg/ml anesthesia", represented by this table:

Table 4: BIS and propofol TCI at LOC and anesthesia maintenance

	Control Group	Oxygen group	Air group
Propofol TCI at LOC (μg/ml)	2.75 ±0.17	2.41 ±0.15*	2.44 ±0.17*
BIS at LOC	61 ±5	73 ±7*	75 ±5*
LOC time (min)	1.7 ±0.4	1.3 ±0.5*	1.2 ±0.6†
BIS at TCI 4 μg/ml	40 ±6	38 ±7	36 ±5

Means ± SD, n = 15 in each group. ANH = acute normovolemic hemodilution, BIS = bispectral index, TCI = target controlled infusion, LOC = loss of consciousness.
t-test: *P<0.0001 oxygen and air groups compared to control group. †P<0.05 oxygen and air groups compared to control group.

By examination of the data during ANH we found a significant increase in heart rate (HR) and mean arterial pressure (MAP). The significant difference over time between the oxygen and air groups compared to the control group of MAP and HR is illustrated from the following figure:

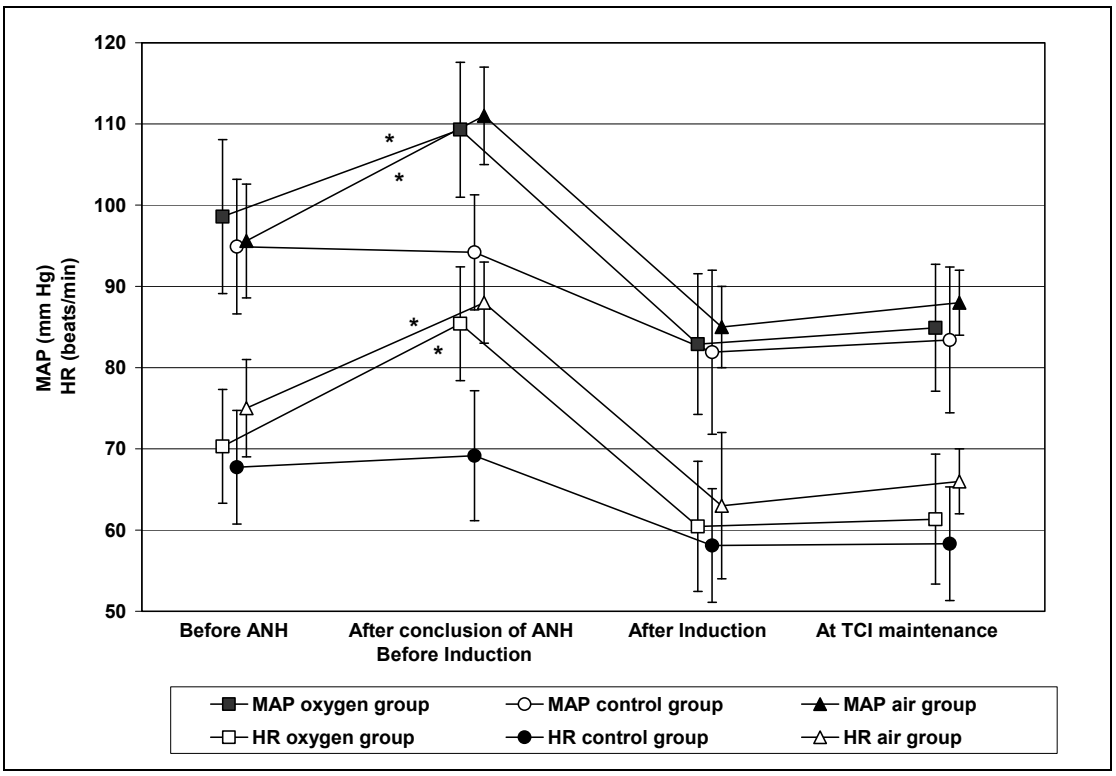


Fig. 12: Difference of MAP and HR between the oxygen and air groups
Mean ± SD mean arterial pressure (MAP) and heart rate (HR) before and after acute normovolemic hemodilution (ANH), and after propofol target controlled infusion (TCI) in the oxygen, air and control groups. n = 15. *Significant difference ($P < 0.0001$) in the oxygen and air groups compared to the control group

6.5 DISCUSSION

Our null hypothesis, of lack of sustained ANH effect on BIS monitoring, was accepted, as there was a transient decline in mean BIS value in the 2 ANH groups after conclusion of ANH which was restored with oxygen as well as air insufflation to baseline values before induction of anesthesia. Furthermore there was no significant difference between the 3 groups in BIS values during induction of narcosis and also at stable propofol TCI 4 μg/ml anesthesia maintenance no BIS changes could be noticed. Although the observed differences in mean BIS

values are statistically significant, they seem to have only a marginal relevance for clinical practice; but the question about the causation still remains.

The first study which demonstrated an impairment of cognitive function during ANH was done by Weiskopf et al (2000). They showed by testing healthy unmedicated patients that ANH to a hemoglobin concentration of 6 g/dl is followed by slowing of reaction time to neuropsychological and memory free recall tests. That these results might be associated with the decreased of cerebral oxygenation Weiskopf et al proved with a study 2002. As the cognitive function deficits reversed by breathing 100% oxygen the authors declared this hypothesis as verified. That our observed BIS decline is also due to a deficit of cerebral oxygenation seems unlikely, although in our oxygen group PaO_2 of 84mmHg with ANH increased to 357mmHg with breathing 100% oxygen, because BIS was only shown to be sensitive to severe cerebral hypoxia i.e. during a complete circulatory failure (England 1999) or in case of a percutaneous cardiopulmonary oxygenator failure (Okawa et al 2001). Also the hemoglobin concentration level of our patients militates against this hypothesis because it only reached a threshold of 9 g/dl what is considerably higher than the 6 g/dl necessary for impairment of cognitive function. Furthermore the physiological compensating mechanisms must be considered because a decreased hematocrit which comes along with a decreased oxygen carrying capacity increases stroke volume and cardiac output followed by hyperventilation for maintaining sufficient oxygenation (Ickx et al 2000). Especially the moderate hemodilution of our patients is probably compensated only with these mechanisms resulting in a physiological systemic oxygen delivery.

A possible causation of our observed BIS decline with ANH are electrolyte shifts associated with acute NaCl administration of our HES in 0.9% NaCl solution for maintaining blood volume after ANH. We came to this idea because two studies, one from Scheingraber et al (1999) and the other one from Wilkes et al (2001), showed the progression of a hyperchloremic metabolic acidosis after saline-based infusions. As it is known that a severe metabolic acidosis, i.e. caused by uremia, diabetes mellitus or drugs can lead in a coma consequently our light acidosis may result in a slight mental confusion and in a cognitive dysfunction respectively what would induce a BIS decline. But as the hyperchloremic acidosis caused by saline-based solution is proved to be a benign self-limiting effect

(Scheingraber et al 1999; Wilkes et al 2001) it is probably compensated during the phase of oxygen administration in our study process and has no relevance for the patient's treatment.

Another BIS influencing factor could be fatigue because Toy et al (2000) examined that patients undergoing ANH declared decreased self-scored energy levels after the process and as proved by Nieuwenhuijs et al (2002) fatigue can decline the BIS value. This fact could play a decisive role in our case because although we instructed the patients not to fall asleep during the experimental process we can't avoid fatigue, also considering the dormicum always given one hour before surgery. The only catch at this fatigue-hypothesis is that it doesn't give us an explanation why the BIS value raises with administration of oxygen.

But not only the BIS value showed significant alterations in our study, also the LOC time was significantly shorter with fewer propofol TCI dose requirements in the oxygen and air groups compared with the control group what led us to the hypothesis that ANH enhances the sedative/hypnotic effect of propofol. This effect is probably based on changes in the propofol pharmacokinetics which may be caused by the physiological compensation mechanisms because we observed a significant increase in heart rate (HR +16%) and mean arterial pressure (MAP +12%) of our patients undergoing ANH associated with the physiological increase of stroke volume and cardiac output (Ickx et al 2000). These mechanisms moreover induce a change in compartment volume and drug delivery to the brain what seems to be the causation of the enhancement of propofol potency (Honan et al 2002). "Furthermore ANH to nadir Hb of 8.5 g/dl, was shown to significantly increase propofol hypnotic potency, as a result of a significant increase in the unbound propofol plasma concentration (+70%) without an alteration in the total propofol concentration (Takizawa et al 2006). The change in the unbound fraction of a drug is only clinically significant for high clearance drugs, such as propofol, that are highly protein bound with narrow therapeutic indices (Takizawa et al 2006; Benet, Hoener 2002)".

"Interestingly, at LOC the mean BIS value was significantly higher in the 2 ANH groups compared to the control group of our study (figure 1, table 4), as BIS only depicts the fewer propofol dose requirements but not the enhanced sedative/hypnotic status (Lysakowski 2001)".

“EMG activities are artifact signals that occur within the frequency ‘range of interest’ of the bispectrum, as the EMG frequency band (30-300 Hz) overlaps the BIS algorithm’s BetaRatio in the 30-47 Hz range. EMG_{30-47} Hz portion could simulate the BetaRatio EEG_{30-47} Hz signal, and an increase in facial EMG activity would be construed by the BIS algorithm as EEG activity and assigned a spuriously elevated BIS value (Sleight et al 2001). Furthermore, some authors consider EMG to be an integral essential part of the BIS algorithm, as neuromuscular blocking drugs administration in awake volunteers was shown to significantly decrease the BIS value (Messner et al 2003). In our study, mean EMG values were below what could be considered as the cut-off point of 35 dB (Mathews et al 2003) indicating that high facial EMG activity probably did not confound our results”.

“Our study has limitations; first, using the standard 130/0.4 in 0.9% NaCl HES solution that we commonly use in our ANH clinical practice did not enable us to explore whether a balanced electrolyte HES preparation with less chloride content, such as Hextend, could have contributed differently (Wilkes et al 2001) to our study results. Second, we did not verify the assumption of cerebral hypoxemia with ANH, as this would have required incorporating in our study design more direct measures of cerebral oxygenation, such as jugular bulb oxygen saturation or near infrared cerebral spectroscopy that was beyond the scope of our current study“.

“In conclusion we demonstrated that, prior to induction of anesthesia, BIS values transiently declined with ANH, but were restored back to baseline with breathing 100% oxygen as well as air insufflation for 5 min. Despite a transient ANH enhancement of propofol sedative/hypnotic effect during induction, there was no significant difference in BIS values with or without ANH during propofol maintenance of anesthesia”.

7 REFERENCES

- Arndt M. Leiter der Arbeitsgruppe der Universität Rostock: Intraoperatives Monitoring der Narkosetiefe; pEEG-Veränderungen unter Propofolanästhesie. http://www.anaesthesie.med.uni-rostock.de/old/Forschung/Narkosetiefe/narkosetiefe.html [5/2008]

- Aspect® Medical Systems: BIS™ mist die Wirkung von Sedativa auf das Gehirn. http://aspectms.com/assets/documents/international/german/ICU_brochure-dui.pdf [3/2008]

- AstraZeneca® Anesthesia: Target controlled infusion (TCI) in anaesthetic practice; New edition 1999. http://www.astrazeneca.no/pdf/dipmon99.pdf

- Benet LZ, Hoener BA: Changes in plasma protein binding have little clinical relevance. Clin Pharmacol Ther 2002; 71:115-21; quoted by AstraZeneca® 1999

- Billard V et al: Ann Fr Anesth Reanim 1997; 16:250

- Bruhn J, Bouillon TW, Shafer SL: Electromyographic activity falsely elevates the bispectral index. Anesthesiology 2000; 92:1485-7

- Bryson GL, Laupacis A, Weils GA: Does acute normovolemic hemodilution reduce perioperative allogenic transfusion? A meta-analysis. Anesth Analg 1998; 86:9-15

- Consensus Conference: Perioperative red blood cell transfusion. JAMA 1988; 260:2700-3

- Dahaba AA: Different conditions that could result in the bispectral index indicating an incorrect hypnotic state. Anesth Analg 2005; 101:765-73

- Dahaba AA, Rinnhofer S, Wang G, Xu X, Liu XY, Wu XM, Rehak PH, Metzler H: Influence of acute normovolemic hemodilution on bispectral index monitoring and propofol dose requirements. Acta Anaesthesiol Scand 2008; 52:815-20

- Dtn = Das Buch Deuteronomium in: Die Bibel. Altes und Neues Testament. Einheitsübersetzung Stuttgard 1980: S.183

- Engbers F & Vujk J: Target controlled infusion. Anaesthesia Rounds, Oxford: Medicine Group (Education) Ltd, 1996; quoted by AstraZeneca® 1999

- England MR: The changes in bispectral index during a hypovolemic cardiac arrest. Anesthesiology 1999; 91:1949-51

- Goodnough LT, Monk TG: Autologous transfusion. In: Miller RD, editor. Miller's anesthesia. 6th edition. Philadelphia: Elsevier/Churchill Livigstone: 2005. p. 1831 – 44; quoted by Monk 2005

- Hahn RG: Estimating allowable blood loss with correction for variations in blood volume. Acta Anaestesiol Scand 1989; 33(6): 508-12; quoted by Shander & Rijhwani 2004

- Hitchcock M. In Millar JM et al: Practical Anaesthesia and Analgesia for Day surgery. Oxford: Bios Scientific Publishers 1997:65; quoted by AstraZeneca® 1999

- Honan DM, Breen PJ, Boylan JF et al: Decrease in bispectral index preceding intraoperative hemodynamic crisis: evidence of acute alteration of propofol pharmacokinetics. Anesthesiology 2002; 97:1303-5

- Ickx BE, Rigolet M, Van der Linden PJ: Cardiovascular and Metabolic response to acute normovolemic anemia. Anesthesiology 2000; 93:1011-6

- Jones SB, Whitten CW, Monk TG: Influence of crystalloid and colloid replacement solutions on hemodynamic variables during acute normovolemic hemodilution. J Clin Anesth 2004; 16:11-7; quoted by Monk 2005

- Kenny GNC & Sutcliffe N. In White PF, Ed.: Textbook of Intravenous Anesthesia. Baltimore: Willams & Wilkins, 1997:527; quoted by AstraZeneca® 1999

- Kim DW, Kil HY, White PF: The effect of noise on the bispectral index during propofol sedation. Anesth Analg 2001; 93:1170-3

- Knöpfli R: Anästhesie unter EEG-Kontrolle. http://www.hirslanden.ch/images/publ_EEG_Kontrolle.pdf [2/2008]

- Licker M, Ellenberger C, Sierra J, Kalangos A, Diaper J, Morel D: Cardioprotective effects of acute normovolemic hemodilution in patients undergoing coronary artery bypass surgery. Chest 2005; 128:838-847

- Loubser P: Closed circuit autologous sequestration reservoir system; US Patent Issued on 1997. http://www.patentstorm.us/patents/5658271-fulltext.html [1/2008]

- Loubser P: No Blood Editorial Team: Acute normovolemic hemodilution. http://wiki.noblood.org/Acute_Normovolemic_Hemodilution [1/2008]

- Lysakowski C, Dumont L, Pellègrini M, Clergue F, Tassonyi E: Effects of fentanyl, alfentanil and sufentanil on loss of consciousness and bispectral index during propofol induction of anaesthesia. British Journal of Anaesthesia 2001; 86(4):523-7

- Marsh B, White M, Morton N, Kenny GNC: Pharmacokinetic model driven infusion of propofol in children. British Journal of Anaesthesia 1991; 67:41-48

- Mathews DM, Kumaran KR, Neuman GG: Bispectral index-derived facial electromyographic-guided fentanyl titration in the opiate-exposed patient. Anesth Analg 2003; 96:1062-4

- Messner M, Beese U, Romstöck J, Dinkel M, Tschaikowsky K: The bispectral index declines during neuromuscular block in fully awake persons. Anesth Analg 2003; 97:488-91

- Metzler H, Schwarz G, Marte W: Moderne Technologie und Technologieentwicklung in der Anästhesiologie. http://vmc.meduni-graz.at/ VMCRepositoryData/0de0af2d-bee4-436f-82f1-36e30876e21a/ifs23p554wss ua55i35ehyus154949463metzler_moderne_technologieentwicklungen.pdf [2/2008]

- Monk TG, Goodnough LT, Brecher ME, Colberg JW, Andriole GL, Catalona WJ: A prospective randomized comparison of three blood conservation strategies for radical prostatectomy. Anesthesiology 1999; 91:24-33

- Monk TG: Acute normovolemic hemodilution. Anesthesiology Clin N Am 2005; 23:271-281

- Napier JA, Bruce M, Chapman J, Duguid JK, Kelsey PR, Knowles SM, Murphy MF, Williamson LM, Wood JK, Lee D, Contreras M, Cross N, Desmond MJ, Gillon J, Lardy A, Williams FG, for the British committee for standards in haematology blood transfusion task force: Guidelines for autologous transfusion. II. Perioperative haemodilution and cell salvage. Br J Anaesth 1997; 78:768-71

- Nieuwenhuijs D, Coleman EL, Douglas NJ, Drummond GB, Dahan A: Bispectral index values and spectral edge frequency at different stages of physiologic sleep. Anesth Analg 2002; 94:125-9

- Oberreither S: Akute normovolämische Hämodilution. http:// www.anesthesia.at/hes/norm_haemodilution.pdf [1/2008]

- Passot S, Servin F, Pascal J, Charret F, Auboyer C, Molliex S: A comparison of target- and manually controlled infusion porpofol and etomidate/desflurane anesthesia in elderly patients undergoing hip fracture surgery. Anesth Analg 2005; 100:1338-42

- Rampil IJ: A primer for EEG signal processing in anesthesia. Anesthesiology 1998; 89:980-1002

- Röpcke H, Könen-Bergmann M, Cuhls M, Bouillon T, Hoeft A: Propofol and remifentanil pharmacodynamic interaction during orthopaedic surgical procedures as measured by effects on bispectral index. Journal of clinical Anesthesia 2001; 13:198-207

- Russel D, Wilkes MP, Hunter SC, Glen JB, Hutton P, Kenny GNC: Manual compared with target-controlled infusion of propofol; British journal of anaesthesia 1995; 75:562-566

- Scheingraber S, Rehm M, Sehmisch C, Finsterer U: Rapid saline infusion produces hyperchloremic acidosis in patients undergoing gynaecologic surgery. Anesthesiology 1999; 90:1247-9

- Schierhout G, Roberts I: Fluid resuscitation with colloid or crystalloid solutions in critically ill patients: a systematic review of randomised trials. BMJ 1998; 316:961-964

- Schmidt-Kortenbusch Martin: “Sekten” – neue Wege zum Heil?. 4.Auflage. Stuttgart: Ernst Klett Verlag GmbH 1998: S. 41-2

- Schwarz G, Voit-Augustin H, Litscher G, Baumgartner A: Specific problems in interpretation of absolute values of Spectral Edge Frequency (SEF) in comparison to Bispectral Index (BIS) for assessing depth of anaesthesia. The Internet Journal of Neuromonitoring ™, ISSN: 1531-300X. http://www.ispub.com/ostia/index.php?xmlFilePath=journals/ijnm/vol3n2/sef.xml [5/2008]

- Sebel PS, Lang E, Rampil IJ, White PF, Cork R, Jopling M, Smith NT, Glass PSA, Manberg P: A multicenter study of bispectral electroencephalogram, analysis for monitoring anesthetic effect. Anesth Analg 1997; 84:891-99

- Segal JB, Blasco-Colmenare E, Norris EJ, Guallar E: Preoperative acute normovolemic hemodilution: a meta-analysis. Transfusion 2004; 44(5):632-44

- Shander A, Rijhwani TS: Acute normovolemic hemodilution. Transfusion 2004; 44:26-34.

- Sleigh JW, Steyn-Ross DA, Steyn-Ross ML, Williams ML, and Smith P: Comparison of changes in electroencephalographic measures during induction of general anaesthesia: influence of the gamma frequency band and electromyogram signal. British Journal of Anaesthesia 2001; 86:50–8

- Suttner S, Boldt J, Schmidt C, Piper S, Kumle B: Costs analysis of target-controlled infusion-based anesthesia compared with standard anesthesia regimes; Anesth Analg 1999; 88:77-82

- Takizawa E, Takizawa D, Hiraoka H, Saito S, Goto F: Disposition and pharmacodynamics of propofol during isovolaemic haemorrhage followed by crystalloid resuscitation in humans. Br J Clin Pharmacol 2006; 61:256-61

- Todd MM: EEGs, EEG processing, and the bispectral index; Anesthesiology 1998; 89:815-7

- Weiskopf RB, Kramer JH, Viele M, Neumann M, Feiner JR, Watson JJ, Hopf HW, Toy P: Acute severe isovolemic anemia impairs cognitive function and memory in humans. Anesthesiology 2000; 92:1646-52

- Weiskopf RB, Feiner J, Hopf HW, Viele MK, Watson JJ, Kramer JH, Ho R, Toy P: Oxygen reverses deficits of cognitive function and memory and increased heart rate induced by acute severe isovolemic anemia. Anesthesiology 2002; 96:871-7

- Wikipedia: http://de.wikipedia.org/wiki/Elektroenzephalografie [3/2008]

- Wilhelm W, Biedler A, Huppert A, Kreuer S, Bücheler O, Ziegenfuß T, Larsen R: A comparison of the effects of remifentanil or fentanyl on anaesthetic induction characteristics of propofol, thiopental or etomidat. Eur J Anaesthesiol 2002; 19:350-356; quoted by Wilhelm et al 2003

- Wilhelm W, Wrobel M, Kreuer S, Larsen R: Remifentanil – Eine Bestandsaufnahmen. Anaesthetist 2003; 52:473-494.

- Wilkes N, Woolf R, Mutch M, Mallett S, Peachey T, Stephens R, Mythen M: The effects of balanced versus saline-based hetastarch and crystalloid solutions on acid-base and electrolyte status and gastric mucosal perfusion in elderly surgical patients. Anesth. Analg. 2001; 93:811-6

8 APPENDIX

8.1 PROJECT SCHEDULE

February 2004:	Application for ethics commission
March 2004:	Vote of ethics commission
January – June 2005:	Pilot study
November 2006 – July 2007:	Clinical study
February 2008:	Letter of acceptance of the publication
July 2008:	Publication in the journal “Acta Anaesthesiologica Scandinavica”

8.2 PATIENT CONSENT

Patienteninformation und Einwilligungserklärung zur Teilnahme an der klinischen Studie: „Einfluss der akut normovolämen Hämodilution auf den Bispectral Index und die erforderliche Propofoldosis“

Patientenname: **Patientennummer:**

Sehr geehrte Patientin, sehr geehrter Patient!

Wir laden Sie ein, an der oben genannten klinischen Studie teilzunehmen. Die Aufklärung darüber erfolgt in einem ausführlichen ärztlichen Gespräch.

Die Teilnahme an einer klinischen Studie ist freiwillig und kann jederzeit ohne Angabe von Gründen durch Sie beendet werden, ohne dass Ihnen hierdurch Nachteile in Ihrer medizinischen Betreuung entstehen.

Klinische Studien sind notwendig, um verlässliche, neue medizinische Forschungsergebnisse zu gewinnen. Unverzichtbare Voraussetzung für die Durchführung einer klinischen Studie ist jedoch, dass Sie Ihr Einverständnis zur Teilnahme an dieser klinischen Studie schriftlich erklären. Bitte lesen Sie den folgenden Text als Ergänzung zum Informationsgespräch mit Ihrem Arzt oder Ihrer Ärztin sorgfältig durch und zögern Sie nicht Fragen zu stellen.

Bitte unterschreiben Sie die Einwilligungserklärung nur,

- wenn Sie Art und Ablauf der klinischen Studie vollständig verstanden haben,
- wenn Sie bereit sind der Teilnahme zuzustimmen, und
- wenn Sie sich über Ihre Rechte als Teilnehmer an dieser klinischen Studie im Klaren sind.

Zu dieser klinischen Studie sowie zur Patienteninformation und Einwilligungserklärung wurde von der zuständigen Ethikkommission eine befürwortende Stellungnahme abgegeben.

Die Funktion einer Ethikkommission ist es sicherzustellen, dass alle Bedingungen zur Beachtung Ihrer Sicherheit und Ihrer Rechte gewährleistet werden. Zusätzlich werden die Vorschriften der „ordnungsgemäßen klinischen Prüfung“ (Good Clinical Practice in Europe, Juni 1991) entsprechend der europäischen Richtlinien eingehalten.

1. Was ist der Zweck der klinischen Studie?

Der Zweck dieser klinischen Studie ist es, den Einfluss der akuten normovolämen Hämodilution (ANH) auf den Bispectral Index (BIS) und die intraoperativ benötigten Propofoldosen zu erforschen. Mittels Aufzeichnung von BIS-Werten auf einem Monitor kann die Narkosetiefe gemessen werden. Propofol ist ein Medikament, das eine narkotisierende Wirkung hat und zur Einleitung, sowie zur Erhaltung der Anästhesie während der Operation intravenös zugeführt wird.

Die oben genannte intraoperative Methode „akut normovoläme Hämodilution“ (ANH) wird folgendermaßen durchgeführt: Zu Beginn der Operation nehmen wir Ihnen 500 ml venöses Blut ab und sammeln es in einem Beutel, wo es vor Gerinnung geschützt ist. Dieser Blutverlust wird durch Gabe von speziellen Infusionen ausgeglichen.

Bei Bedarf oder bei größeren Blutverlusten bekommen Sie diese 500 ml Blut wieder zurück. Sollte der Blutverlust sehr gering sein, bekommen Sie das Blut trotzdem am Ende der Operation zurück.

Diese Methode soll vor allem bei großen Operationen den Blutverlust für den menschlichen Körper leichter tolerabel machen und Fremdblutgaben vermeiden.

Wie läuft die klinische Studie ab?

Diese klinische Studie wird am Univ.-Klinikum Graz durchgeführt, und es werden insgesamt 28 Personen daran teilnehmen.

Ihre Teilnahme an dieser klinischen Studie wird voraussichtlich fünf Stunden dauern. Wie vor jedem operativen Eingriff werden Sie von Ihrem Arzt gründlich untersucht und eine eventuelle Schwangerschaft wird ausgeschlossen.

Wir erheben auch alle Informationen zu Ihrer vergangenen und jetzigen Krankengeschichte und medikamentösen Therapie.

Unmittelbar vor Narkoseeinleitung wird auch ein Gerät zur Überwachung der neuromuskulären Funktion an einen Ihrer Arme angeschlossen. Dieses Gerät gehört zur routinemäßigen Überwachung während einer Allgemeinnarkose.

Nach Einleitung der Narkose wird dann die Funktion Ihrer Muskeln mittels Nervenstimulation überwacht. Zusammenfassend bedeutet das, dass Sie bei der Teilnahme an dieser Studie – wie allgemein üblich - für die Narkose vorbereitet und überwacht werden.

<u>Folgende Maßnahmen werden ausschließlich aus Studiengründen durchgeführt:</u>

Neben unserem Standardmonitoring kommt auch die Überwachung der Narkosetiefe mittels Bispectral Index zum Einsatz. Der Bispectral Index kann durch Messung der Hirnströme (EEG) berechnet werden. Die Hirnströme werden mittels vier an die Stirn geklebten Elektroden abgeleitet und je nach Hirnstromaktivität kann dann auf den Narkosegrad geschlossen werden.

Weiters wird die Narkose mittels einem „Target controlled infusion“ - System (TCI) geführt, um die benötigte Propofoldosis messen zu können.

Falls Sie sich entscheiden sollten, nicht an dieser Studie teilzunehmen, wird die Narkosetiefe ebenfalls überwacht, allerdings mit unseren Routine-Narkosegerätschaften. Das Narkotikum Propofol wird dann ebenfalls intravenös mit einer herkömmlichen Infusionspumpe (Diprifusor) verabreicht.

2. Worin liegt der Nutzen einer Teilnahme an der klinischen Studie?

Es ist nicht zu erwarten, dass Sie aus Ihrer Teilnahme an dieser klinischen Studie gesundheitlichen Nutzen ziehen werden.

Ihre Teilnahme an dieser Studie hilft den Einfluss von ANH auf die Narkosetiefe und die benötigte Propofolmenge besser zu verstehen.

3. Gibt es Risiken, Beschwerden und Begleiterscheinungen?

Wie bei der üblichen Narkose sind durch das Einführen des Tubus (Beatmungsschlauch, der in die Luftröhre eingeführt wird und mit dem Sie beatmet werden) vorübergehende Schwellung, Bluterguss, Rötung, Heiserkeit, Halsschmerzen, Sprachstörungen und Atembeschwerden möglich. Auch kann es durch den venösen Zugang (Plastikschlauch, der in eine Vene am Arm gelegt und über den Medikamente und Infusionen zugeführt werden) zu Rötungen, Blutergüssen und Entzündungen im Bereich der Einstichstelle kommen.

Auch kann es nach dem Aufwachen zu Schmerzen, Übelkeit, Erbrechen, Fieber, Schüttelfrost und Schwindel kommen.

Sollte eine dieser Begleitreaktionen bei Ihnen auftreten, haben wir natürlich die Möglichkeit sofort medikamentös einzuschreiten und Ihre Beschwerden zu lindern.

An Ihrer sonstigen Behandlung wird sich durch die Teilnahme an der Studie nichts ändern.

4. Zusätzliche Einnahme von Arzneimitteln?

Falls sie Antibiotika oder eine medikamentöse Therapie gegen Epilepsie erhalten, teilen sie uns dies bitte mit. Diese Medikamente verändern den Bispectral Index und erlauben somit keine optimale Messung.

5. Hat die Teilnahme an der klinischen Studie sonstige Auswirkungen auf die Lebensführung und welche Verpflichtungen ergeben sich daraus?

Nein, durch Ihre Teilnahme an der Studie ergeben sich für Sie keine weiteren Verpflichtungen. Auch verlängert sich dadurch die Dauer Ihres Krankenhausaufenthaltes **nicht!**

6. Was ist zu tun beim Auftreten von Symptomen, Begleiterscheinungen und/oder Verletzungen?

Sollten im Verlauf der klinischen Studie irgendwelche Symptome, Begleiterscheinungen oder Verletzungen auftreten, müssen Sie diese Ihrem Arzt mitteilen, bei schwerwiegenden Begleiterscheinungen umgehend, ggf. telefonisch (Telefonnummern, etc. siehe unten).

Als Teilnehmer an dieser Studie wurde für Sie eine Versicherung bei der **Wiener Städtischen Versicherung** (Polizzennummer: 08-N 811.957; Kontaktperson: Fr. **Ass. Jur**. **Heike Brandmann**, telefonisch erreichbar unter: 0316/ 7896194) abgeschlossen.

Im Schadensfall können Sie sich auch direkt an Fr. **Brandmann** wenden.

Für Fragen und bei Problemen stehen Ihnen auch zur Verfügung:

Aufwachraum: Anästhesist, Schwester
Station: behandelnder Arzt, Schwester

7. Wann wird die klinische Studie vorzeitig beendet?

Sie können jederzeit vor dem Start der Narkose, auch ohne Angabe von Gründen, Ihre Teilnahmebereitschaft widerrufen und aus der klinischen Studie ausscheiden ohne dass Ihnen dadurch irgendwelche Nachteile für Ihre weitere medizinische Betreuung entstehen.
Auch können Sie ohne Angabe von Gründen die Verwendung Ihrer gesammelten Daten verweigern.

Ihr Prüfarzt wird Sie über alle neuen Erkenntnisse, die in Bezug auf diese klinische Studie bekannt werden, und für Sie wesentlich werden könnten, umgehend informieren. Auf dieser Basis können Sie dann Ihre Entscheidung zur **weiteren** Teilnahme an dieser klinischen Studie neu überdenken.

Es ist aber auch möglich, dass Ihr Prüfarzt entscheidet, Ihre Teilnahme an der klinischen Studie vorzeitig zu beenden, ohne vorher Ihr Einverständnis einzuholen. Die Gründe hierfür können sein:

- Sie können den Erfordernissen der klinischen Studie nicht entsprechen;
- Ihr behandelnder Arzt hat den Eindruck, dass eine weitere Teilnahme an der klinischen Studie nicht in Ihrem Interesse ist;

8. In welcher Weise werden die im Rahmen dieser klinischen Studie gesammelten Daten verwendet?

Sofern gesetzlich nicht etwas anderes vorgesehen ist, haben nur die Prüfer und deren Mitarbeiter Zugang zu den vertraulichen Daten, in denen Sie namentlich genannt werden. Diese Personen unterliegen der Schweigepflicht.
Die Weitergabe der Daten erfolgt ausschließlich zu statistischen Zwecken und Sie werden ausnahmslos darin **nicht namentlich** genannt. Auch in etwaigen

Veröffentlichungen der Daten dieser klinischen Studie werden Sie **nicht namentlich** genannt.

9. Entstehen für die Teilnehmer Kosten? Gibt es einen Kostenersatz oder eine Vergütung?

Durch Ihre Teilnahme an dieser klinischen Studie entstehen für Sie keine zusätzlichen Kosten.

10. Möglichkeit zur Diskussion weiterer Fragen

Für weitere Fragen im Zusammenhang mit dieser klinischen Studie stehen Ihnen Ihr Prüfarzt und seine Mitarbeiter gern zur Verfügung. Auch Fragen, die Ihre Rechte als Patient und Teilnehmer an dieser klinischen Studie betreffen, werden Ihnen gerne beantwortet.

Dr. Ashraf Dahaba unter der Telefonnummer: 0316/385 2829 bzw. 1253 (Piepser)
Handy: 0699/122 34 350

Dr. Georg Wilfinger unter der Telefonnummer: 0316/385 3789
Freeset: 0316/385 81328

11. Sollten andere behandelnde Ärzte von der Teilnahme an der klinischen Studie informiert werden?

Über Ihre Teilnahme werden sämtliche Sie behandelnde Narkoseärzte und Narkoseschwestern informiert.

12. Einwilligungserklärung

Name des Patienten in Druckbuchstaben: .....

Geb.Datum: ..... Code: .....

Ich erkläre mich bereit, an der klinischen Studie „Einfluss der akut normovolämen Hämodilution (ANH) auf das Bispectral Index Monitoring und die erforderliche Propofoldosis“ teilzunehmen.

Ich bin von Herrn *Dr. Ashraf Dahaba* ausführlich und verständlich über sämtliche, mögliche Belastungen und Risiken sowie über Wesen, Bedeutung und Tragweite der klinischen Studie und die sich für mich daraus ergebenden Anforderungen aufgeklärt worden. Ich habe darüber hinaus den Text dieser Patientenaufklärung und Einwilligungserklärung, die insgesamt sechs Seiten umfasst, gelesen. Aufgetretene Fragen wurden mir vom Prüfarzt verständlich und genügend beantwortet. Ich hatte ausreichend Zeit, mich zu entscheiden. Ich habe zurzeit keine weiteren Fragen mehr.

Ich werde den ärztlichen Anordnungen, die für die Durchführung der klinischen Studie erforderlich sind, Folge leisten, behalte mir jedoch das Recht vor, meine freiwillige Mitwirkung jederzeit zu beenden, ohne dass mir daraus Nachteile für meine weitere medizinische Betreuung entstehen.

Ich bin zugleich damit einverstanden, dass meine im Rahmen dieser klinischen Studie ermittelten Daten aufgezeichnet werden. Um die Richtigkeit der Datenaufzeichnung zu überprüfen, dürfen die an der Studie beteiligten Ärzte und die zuständigen Behörden beim Prüfarzt Einblick in meine personenbezogenen Krankheitsdaten nehmen.

Beim Umgang mit den Daten werden die Bestimmungen des Datenschutzgesetzes beachtet.

Eine Kopie dieser Patienteninformation und Einwilligungserklärung habe ich erhalten. Das Original verbleibt beim Prüfarzt.

.....
(Datum und Unterschrift des Patienten)

.....
(Datum, Name und Unterschrift des verantwortlichen Arztes)

(Der Patient erhält eine unterschriebene Kopie der Patienteninformation und Einwilligungserklärung, das Original verbleibt im Studienordner des Prüfarztes.)

8.3 CASE REPORT FORM

Name:	Weight: .....……kg
Height: ……	Date of Birth: ….....
Gender: ….....	Date: …..……
City: …… Hospital: ……	Pt. Number: …..…...

MAP before induction		HR before induction	
Event	**Time**	**BIS**	***Propofol Rate***
TCI start			XXX
TCI 1.5 µg/ml			1.5
30s TCI +0.5 µg/ml			2
30s TCI +0.5 µg/ml			2.5
30s TCI +0.5 µg/ml			3
30s TCI +0.5 µg/ml			3.5
30s TCI +0.5 µg/ml			4
30s TCI +0.5 µg/ml			4.5
LOC			
BIS 40 Maintenance			
Propofol Total Dose	XXX	XXX	…… mg
MAP after induction		HR before induction	

8.4 CURRICULUM VITAE

Name: Sarah-Maria Rinnhofer

Date/Place of birth: 14.2.1984, Leoben / Austria

Education:

- 1990 – 1994 Elementary school Mürzzuschlag
- 1994 – 2002 BG/BRG Mürzzuschlag
- since 2002 medical student on the medical university of Graz

Medical clerkships:

- 4 weeks department of surgery - LKH Mürzzuschlag, 2004
- 3 weeks department of neonatology - LKH-Univ. Klinikum Graz, 2005
- 2 weeks department of anesthesiology - SMZ Ost Wien, 2005
- 2 weeks department of internal medicine - LKH-Univ. Klinikum Graz, 2006
- 2 weeks department of internal medicine - LKH Mürzzuschlag, 2007
- 3 weeks department of anesthesiology - LKH-Univ. Klinikum Graz, 2007
- 4 weeks department of ophthalmology - Morelia / Mexiko, 2007

Work on medical congresses:

- 48. österreichischer chirurgischer Congress in Graz, 2007
- Congress für Religiosität und Psychiatrie in Graz, 2007
- Congress für innere Medizin in Graz, Sept. 2008

Time spent abroad:

- 1 week language course in Eastborn / Great Britain, 2000
- 2 weeks language course in Dublin / Ireland, 2001
- 1 week language course in Madrid / Spain, 2002
- 1 month Australia as backpacker, 2003
- 1 month United States of America as backpacker, 2004
- 1 month Morocco as backpacker, 2006
- 1 month Mexico/Guatemala as backpacker, 2007

Languages I can speak: German, English, Spanish